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QUANTIFIABLE FETAL FIBRONECTIN (FFN) USING 10Q TO ACCURATELY PREDICT PRETERM BIRTH IN TWIN PREGNANCIES.

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Background: Twin pregnancies are associated with spontaneous preterm birth. Cervical length (CL) and qualitative fFN currently used in clinical practice have limited value in prediction of early birth in this group. We have previously shown that quantitative fFN improves prediction in singletons (Kurtzman et al 2009), but has not been evaluated in twins. Mechanism of fFN release is unclear in twin pregnancies and preterm birth associated with uterine stretch. *Methods:* All twins attending a Preterm Surveillance Clinic at St. Thomas Hospital, London (Oct 2010 to Jan 2012) had prospective longitudinal cervicovaginal fFN and CL performed from 18 weeks gestation using a bedside 10qfFN analyzer (HOLOGIC, USA). Appropriate ethical permission was obtained. All first samples were taken before 24 weeks, and used for predictive statistics. These were calculated for 4 ranges; 200ng/ml. to detect spontaneous delivery before 30 and 34 weeks. qfFN was blind to clinicians until post delivery using an embedded code in the analyzer. *Results:* 146 samples were taken in 67 twin pregnancies, with no fetal abnormalities. Preterm delivery rate increased with increasing fFN from 22% (200ng/ml), with significantly shorter CL at time of testing (31mm to 16mm, $p = 0.001$). No woman with levels under 10ng/ml delivered 200ng/ml delivered 200ng/ml and CL < 25mm gave 100% PPV for delivery before 34 weeks. *Conclusion:* This is the first report of 10qfFN in twins, demonstrating that it adds predictive value to the traditional qualitative results. High levels, even in early pregnancy, are associated with very preterm delivery. Management can be targeted to this group; antenatal maternal steroids and proximity to appropriate neonatal facilities can be arranged. Further research should evaluate interventions to prolong pregnancy in this highest risk group, while lower risk women can be reassured.

SPONTANEOUS AND NON-SPONTANEOUS TWINS: A COMPARISON STUDY OF PRETERM LABOR, PRETERM PREMATURE RUPTURE OF MEMBRANES, GESTATIONAL AGE AT DELIVERY, MATERNAL AGE, AND LENGTH OF HOSPITAL STAY

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Objective: To determine the difference between spontaneous versus assisted reproductive technology (ART) twins at a single institution in regards to preterm labor, preterm premature rupture of membranes (PPROM), gestational age at delivery, and length of hospital stay. Study Design: This study is a retrospective review of 348 twin deliveries at a single institution from 2007–2009 examining the morbidities of preterm labor, PPROM, maternal age, gestational age at delivery, and length of maternal hospital stay. Statistical analysis was performed using SPPS version 15 for Windows. Tests performed included descriptive statistics including means and frequencies and inferential statistics including chi square analysis and analysis of variance. A log transformation was performed for days of hospital stay since the data were not normally distributed. Comparisons were made between spontaneous and assisted reproductive technology (ART) twins. *Results:* 348 twin deliveries were documented between 2007 and 2009; twins that were reduced from higher order multiples were excluded. 161 spontaneous twin and 185 ART twin outcomes were compared; 2 twin conception methods were unknown. Of these deliveries, mean maternal age was 29.7 ± 5.3 years for spontaneous twins and

33.8 ± 4.8 years for ART twins (p = <.0005). Mean estimated gestational age at delivery was similar between the groups, with spontaneous twins delivering at 35.0 ± 4.1 days and ART twins at 35.0 ± 4.2 days (p = .955). Preterm labor occurred 37.9% of the time in spontaneous twins and 32.4% of the time in ART twins (p = .310). PPROM occurred 24.2% in spontaneous twins and 23.8% in ART twins (p = 1.000). Hospital stay was highly variable, ranging from 1-97 days, and included antepartum admissions, some for preterm labor, that did not result in delivery. Mean length of hospital stay for the entire sample was 8.7 ± 11.9 days. The mean length for spontaneous twins was 7.4 ± 9.4 days versus ART twins with a mean of 10.0 ± 13.7 days (p = .013). *Conclusion:* In this single institution, there was no significant difference in the percentage of spontaneous and non-spontaneous twins in rates for preterm labour, PPROM, or for estimated age at delivery. There was an expected significance in the difference in maternal age between the two groups, and a statistically significantly higher length of inpatient stay for ART patients. These studies suggest that, while not statistically significant, an ART pregnancy has increased morbidity requiring a longer hospital stay. Future studies are required to further evaluate this difference.

MORPHOMETRIC PARAMETERS OF SHOULDER ROTATOR CUFF: AN ITALIAN TWIN STUDY

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Shoulder rotator cuff consists of four tendons (subscapularis, supraspinatus, subspinatus and little round) that stabilize shoulder joint by centring humerus head into glenoid cavity. Rupture of rotator cuff tendons is an age-related disease with a higher prevalence in women. Risk factors investigated so far include anatomical and physiological parameters (acromial shape, osteophytes, tendon blood supply) as well as life-style determinants (occupational and daily activity). The relative weight of genetic background versus environmental exposures on shoulder anatomical structures has never been quantified. We studied a sample of Italian twin pairs to estimate: i) concordance of shoulder rotator cuff tendon degeneration or lesion in monozygotic (MZ) and dizygotic (DZ) pairs; ii) genetic and environmental contribution to individual differences in measures of shoulder anatomical structures by using quantitative genetic models; iii) the association of acromio-humeral distance with risk of supraspinatus and subspinatus degeneration or lesion by logistic regression model. Through the Italian Twin Registry (ITR), we contacted 50 twin pairs resident in Rome. Of these, 36 agreed to participate and were invited to the Department of Orthopaedics and Traumatology of our University. They underwent clinical and morphological assessment by Constant Score and Simple Shoulder Test on both shoulders, and by Magnetic Resonance evaluation on right shoulder; in particular, we measured acromio-humeral distance, angle of glenoid retroversion and area of the supraspinatus muscle; moreover we evaluated the degree of acromio-clavicular arthropathy, rotator's cuff condition and Goutallier's stage. Data were collected on 15 MZ (10 males) and 14 DZ pairs (4 same gender males, 8 same gender females, 2 opposite gender). Mean age was 63 years (range 53-72). The proportions of twins with degeneration or lesion among males/females were 62/46% for supraspinatus, 31/39% for subspinatus, 6.9/0% for little round and 6.9/7.2% for subscapularis tendons. Proband-wise concordances for degeneration or lesion of supraspinatus tendon were 94% in MZ and 86% in DZ pairs. For the subspinatus tendon, concordances were 91% in MZ and 44% in DZ pairs, suggesting a substantial genetic role in the susceptibility to degeneration or lesion of this tendon. Genetic factors explain 91% of variance for acromio-humeral distance and 56% for glenoid retroversion angle. Individual-specific environmental factors (e.g. life-style and occupational exposures) explain 9 and 24% of the variances of acromio-humeral distance and glenoid retroversion angle, respectively; environmental factors shared between twins account for 20% of the glenoid retroversion variance. Moreover, we found that, adjusting for age, gender and twin-pair clustering, a lower acromio-humeral distance was significantly associated (OR = 1.84; 95%CI: 1.15–2.94; p = 0.01) with risk of degeneration or lesion of the supraspinatus tendon; an increased risk of degeneration or lesion of the subspinatus tendon was also suggested (OR = 1.74; 95% CI: 0.94–3.24; p = 0.079).

TWICE MONTHLY ULTRASOUND EXAMINATION IN MONOCHORIONIC DIAMNIOTIC TWIN PREGNANCIES

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Introduction: Twin-twin transfusion syndrome (TTTS) occurs in 15% of monochorionic diamniotic (MCDA) twin pregnancies. The optimal method and frequency of surveillance for pregnancies complicated with TTTS is still controversial. The objective of this study is to assess that a twice monthly ultrasound examination with fetal growth assessment, evaluation of bladder filling, deepest vertical pocket (DVP) and Doppler velocimetry of the umbilical artery is enough to allow an early diagnosis of TTTS. *Methods:* We retrospectively studied parameters of antenatal surveillance and perinatal outcome of 116 women with a MCDA twin pregnancy cared for 'Twin Clinic' of Maternal-Fetal Medicine Unit of the University of Turin between January 2005 and July 2011. Inclusion criteria were: sonographic diagnosis of monochorionicity in the first trimester, gestational age according to last menstrual period confirmed by a scan in the first trimester, gestational age below 16 completed weeks at the first visit, no signs of TTTS at the first examination, absence of foetal malformation. From 16 weeks until delivery we performed every two weeks in all the MCDA pregnancies an ultra-

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sound examination evaluating: foetal growth, bladder filling, deepest vertical pocket of amniotic fluid for each fetus, end-diastolic flow of the umbilical artery. If amniotic fluid and /or foetal growth discordance was noted, we performed the ultrasound examination weekly or also more frequent, depending on the specific condition. In these cases, we performed also examination of the ductus venosus flow velocity profile and doppler measurements of the middle cerebral artery-peak systolic flow velocity (MCA-PSV). TTTS severity was classified according to Quintero staging. As the Eurofetus has suggested, women with TTTS diagnosed between 15 and 26 weeks were treatated with fetoscopic laser coagulation. Results We diagnosed 17 cases of TTTS, 16 in stage I and II, 1 in III stage. 13 pregnancies underwent laser coagulation at Buzzi hospital in Milan, 1 made a cord occlusion, 2 therapeutic interruptions of pregnancy and 1 spontaneous abortion before any treatment. In the 13 pregnancy treated with lasercoagulation, the mean gestational age at delivery was 33 weeks: in 7 cases both fetuses were born alive, in 1 case both fetuses died and in 5 cases only one fetus was born alive. We analysed pregnancy outcome in 99 MCDA pregnancy not complicated with TTTS. We reported 14 selective IUGR and 1 intrauterine death of one fetus for undetermined reason. The mean gestational age at delivery was 35 weeks. Conclusion 94% (16/17) of TTTS in ourclinic was diagnosed in early stage. We propose twice monthly ultrasound evaluation of fetal growth, bladder filling, deepest vertical pocket of amniotic fluid for each fetus and end-diastolic flow of the umbilical artery in not complicated monochorionic pregnancy.

25-HYDROXY-VITAMIN D, FASTING INSULIN, AND INSULIN RESISTANCE IN A COHORT OF ADOLESCENT TWINS IN RURAL CHINA

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Purpose: To examine the relationship between, and estimate the co-heritability of, 25-hydroxy-vitamin D (25(OH)D) and fasting insulin (FI) and insulin resistance (IR). *Methods:* This report included 1345 adolescent twins, age 13 to 18 years, from the Anqing region of China. Serum 25(OH)D was measured using HPLC tandem mass spectrometry. Insulin resistance was measured using the homeostatic assessment model. Dual-energy X-ray absorptiometry measures included: percent body fat (%BF). Log transformations of 25(OH)D, FI, and HOMA were used to estimate the strength of the association in a linear mixed model and to estimate the co-heritability of 25(OH)D and FI and IR in structural equation models. *Results:* 25(OH)D was inversely associated with fasting insulin and HOMA, and these associations were similar for males and females. The linear associations after adjusting for gender, age, tanner stage, physical activity, occupation, and change %BF: ßFI(se) = -0.11(0.03), p = 0.0002; ßIR(se) = -0.11(0.03), p = 0.0004. Consistent with our previous estimates in this cohort, the heritability of 25(OH)D was greater in males 0.35(95%CI 0.16-0.57), than in females, 0.17(0.05-0.21); the heritability for FI and IR in males was also higher: 0.63(95%CI 0.48) and 0.64 (95%CI 0.49, 0.71), whereas in females it was: 0.47(95%CI 0.20, 0.57) and 0.46 (95%CI 0.18, 0.57). Shared environmental components to the phenotypic variance FI or IR were practically null. As such, the AE model was used to estimate the bivariate heritability between these and 25(OH)D. The genetic correlation, rG, for 25(OH)D and FI or IR specific to males and females were similar; combined genetic correlations were as follows: rG(FI) = -0.29(95%CI -0.48, -0.12) and rG(IR) = -0.27(95%CI -0.46, -0.10). The total phenotypic correlations between 25(OH)D, FI, and IR were quite small: -0.13 and -0.12, respectively. The genetic contribution to this phenotypic correlation was 85% and 92%. *Conclusion:* This analysis demonstrated that fasting insulin and insulin resistance decreases significantly with increasing 25(OH)D levels. Though the phenotypic correlations between 25(OH)D, fasting insulin, and insulin resistance are quite small, this modest correlation is largely driven by genes.

PERINATAL OUTCOME OF 94 MONOCHORIONIC-DIAMNIOTIC PREGNANCIES FOLLOWED IN A REFERRAL HOSPITAL IN SPAIN

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Context: The evolution of twin pregnancies is more uncertain than that of singleton pregnancies and, in adittion, monochorionic pregnancies have more complications than dichorionic. Monochorionicity involves greater risk of fetal death, intrauterine growth retardation and neurodevelopmental disorders. The aim of this study is to reflect the specific complications and management of monochorionic-diamniotic pregnancies at La Paz University Hospital, which is a referral hospital in twin pregnancies. *Materials and Methods:* We performed a retrospective analysis of monochorionic diamniotic pregnancies followed in the High Risk Obstetrics Consultations of the University Hospital La Paz in Madrid, between 2008 and 2010. Ultrasound examination was performed in the first trimester, weeks 15 and 20, and bi-weekly, except indication of closer monitoring. Data were collected on fetal and neonatal complications. *Results:* We collected 94 monochorionic diamniotic pregnancies. Neonatal data were obtained from 82 pregnancies with 159 live newborns. The mean maternal age was 33.6 years (15-41 years). Fetal complications occurred in 23.4% of them: fetofetal transfusion syndrome in 9.57% of cases, selective intrauterine growth retardation in 11.7%, stillbirth in 2.1%, and fetal malformations in 7.4%. 5 fetoscopic ablations of vascular anastomosis, 2 septostomy and 2 selective feticides were performed. Gestational age at delivery had a mean of 34.68 weeks. The delivery occurred

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mainly through cesarean section (65.6%) compared to vaginal delivery (35.4%). The rate of severe neonatal complications was 14.21%, and was higher among pregnancies that had presented fetal complications (39.02%) compared with uncomplicated pregnancies (7.04%). Neonatal survival rate was 95.74%. *Conclusions:* Monochorionic diamniotic twin pregnancies are a type of twin pregnancy of high-risk, as they have been associated with an increased risk of perinatal complications and stillbirth. The mechanism that justifies the development of many complications associated with monochorionic pregnancies implies the presence of vascular anastomosis that connect the circulation of both fetuses. Ultrasound monitoring is recommended for uncomplicated monochorionic pregnancies every 2 weeks from week 16, with the aim of early detection of complications, as complicated pregnancies are associated with fetal and neonatal survival rate significantly lower than that seen in uncomplicated pregnancies. Prospective randomized studies are needed to determine the best strategy for monitoring and treatment of specific complications of these pregnancies.

TWIN PREGNANCY, OBESITY AND IOM GESTATIONAL WEIGHT RECOMMENDATIONS

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This study population included all obese women (BMI >30.0 kg/m^2) living in Missouri who delivered liveborn, twin, term (clinical estimate of gestational age >37 weeks) infants without congenital abnormalities in 2002-2008. Gestational age >37 weeks was used in that the Institute of Medicine (IOM) developed a provisional guideline of 25-42 pounds for term twin pregnancies in obese women that reflected the interquartile range (25th – 75th percentile) of cumulative weight gain among obese women who delivered twins at 37-42 weeks gestation. The patient population of 1,558 twins is initially described. Demographic characteristics, medical/ obstetrical history, and maternal/infant outcomes are described by gestational weight gain. Continuous variables initially were expressed as medians and ranges due to lack of normality of the distributions. Categorical variables were expressed as numbers and percentages. Differences in demographic characteristics, medical/obstetrical history, and maternal/infant outcomes by gestational weight gain were assessed using chi-square test for categorical variables. The nonparametric Kruskal-Wallis test was used for all continuous variables. A p value of <0.05 was used to denote statistical significance. All analyses were performed using SPSS version 18.0 for Windows. The study population of 1.558 twins was born to 743 (47.7%) Class I Obese women, 455 (29.2%) Class II Obese women, and 360 (23.1%) Class III Obese women. Over 70% of the women were non-Hispanic white. Approximately 60% of the women lived in poverty and 16.2% of the mothers were nulliparous. Only 37.2% of the women followed the Institute of Medicine's provisional guideline of weight gain during pregnancy of 25-42 pounds. The percentage of women gaining <25 pounds during pregnancy was 30.2%, while 32.6% of the women gained >42 pounds. Mothers of 18/461 (3.9%) twins in the <25 pound group lost weight during pregnancy, with a range of weight loss of 4-14 pounds and a median weight loss of five pounds. Preeclampsia, cesarean delivery, and instrumental delivery occurred in 9.2%, 72.2%, and 3.5% of the women, respectively. Infant birth weight varied greatly in the twins, with a median of 2,807 grams and a range of 1,559-4,394 grams. Over a fifth of the twins (338/1,558, 21.7%) weighed <2,500 grams. Women who gained >42 pounds during pregnancy were younger and more likely to be non-white and Class I Obese than women who gained <25 pounds or 25-42 pounds. Women who gained <25 pounds were less likely to be nulliparous than women who gained 25-42 pounds or >42 pounds. Significant increasing trends with gestational weight gain were found for preeclampsia (p<0.001) and instrumental delivery (p<0.01). A significant inverse trend with increasing gestational weight gain was found for infants weighing <2500 grams (p<0.01). No significant differences were found for cesarean delivery, infants weighing >4000 grams, or one minute or five minute APGAR scores by gestational weight gain category. *Conclusions:* Obese pregnant women with twins who gain less than the IOM gestational weight recommendations experience significantly less Preeclampsia.

TWIN DELIVERY — QUESTIONS AND ANSWERS

J. Barrett

Introduction: Twins complicate approximately 2-3% of births. Twin fetuses are at higher risk of death and neonatal morbidity than singletons of the same birth weight. In addition, twin B may be at higher risk of a poor outcome compared with twin A if delivery is vaginal birth (VB) versus caesarean section (CS). A Cochrane review has recommended that a large RCT be undertaken. Other important issues in twin delivery include the timing of delivery, the optimal for of monitoring, the use of epidural, and the effect of chorionicity. *Methods of Studies:* We have conducted several studies over the last years to address these issues. The largest called the Twin Birth Study we randomized twins at 32-38 weeks gestation with twin A presenting vertex, and estimated fetal weight 1500-4000g to planned vaginal birth vs LSCS. Other studies we have performed have investigated cohorts of patients delivered by Breech extraction VS External version in second non vertex twins and other studies. In addition we have analysed WHO Birth Cohort studies investigating the outcome of non vertex second twins to Vertex second twins. *Outcomes Reported*: The outcomes in all these studies have been perinatal or neonatal mortality and/or serious neonatal morbidity; Other outcomes such as death

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or poor neurodevelopmental outcome of the children at 2 years of age; ii) problematic maternal urinary or faecal/flatal incontinence at 2 years postpartum were also looked at as well as some outcomes of maternal morbidity. Sample Size: The sample size of our RCT was 2800, the Cohort studies are all large investigating at least 200 sets of twins. *Conclusion:* Our work will provide some definitive answers as to the optimal method of twin delivery. The Cohort studies will provide additional best evidence to the pressing problems of twin delivery.

THE GENETIC AND ENVIRONMENTAL INFLUENCES ON DEPRESSIVE SYMPTOMS IN RUSSIAN 7-9 YEARS OLD TWINS

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The aim of our study was to investigate the genetic and environmental influences on individual differences in depressive symptoms in Russian children of primary school age. The Children"s Depression Inventory (CDI; Kovacs, 1992) was administered to 152 twins aged from 7 to 9 years. The internal consistency of the all-item general depressiveness scale was satisfactory. The analysis of genetic and environmental influences on the variance of depressive symptoms was done using structural equation modeling in 'Mx' program (Neale et al., 2006). Significant gender differences were found for the heritability of depressiveness in children. The results of model-fitting revealed high heritability of depressive symptoms in adolescent boys (additive genetic factors accounted for 46% of variance, with non-shared environment explaining the rest) and low heritability in girls (additive genetic factors accounted for 8% of variance, with 48% of shared and 44% nonshared environment).

TWINS SCHOOL PLACEMENT: DEVELOPMENTAL PERSPECTIVES

H. Birkholm-Buch

Existing studies on the effect of school placement on twins indicates that twins have more academic and internalizing problems in primary school when they go to separate classes. To date there are no studies involving psychological developmental considerations in relation to the question of when twinship can be a resource or a vulnerability for placement in opposite or same class. In order to improve our understanding of the effect on twin's school placement, the importance of twin's mutual attachment, identity and social aspects will be examined with relation to school start. In total, based on the existing empirical data I suggest that twins might form a symmetrical attachment much earlier than singletons which might lead to a misinterpretation of twin s attachment style, where a secure attachment style might be misunderstood as a too dependent twin relationship. Understanding twin's attachment quality, rather than only the quantitative degree of dependency, provides important information about possible psychological developmental consequences of twin's school placement and must be considered in choosing same or separate classes. The implications for twin's identity formation will also be discussed from a postmodern narrative perspective.

A PROSPECTIVE STUDY OF TWINNING RATE AND PERINATAL MORTALITY IN URBAN GUINEA-BISSAU

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Background: Despite twinning being common in Africa, few prospective twin studies have been carried out. We studied twinning rate, perinatal mortality and clinical characteristics of newborn twins in urban Guinea-Bissau. *Methods:* The study was done by the Bandim Health Project (BHP), a health and demographic surveillance site in the capital Bissau. The cohort included all newborn twins delivered at the National Hospital Simão Mendes and in the BHP study area from September 2009 to August 2011 as well as singleton controls from the BHP study area. At the hospital data regarding obstetric history and pregnancy was collected. Live children were examined clinically. For a subset of twin pairs zygosity was established using genetic markers. *Results:* Out of 5271 births among mothers from the BHP study area 95 were twin births, i.e. a community twinning rate of 18/1000. The monozygotic rate was 3.4/1000. Perinatal mortality among twins vs. singletons was 221/1000 vs. 81/1000 (RR = 2.74, 95% CI: 1.97-3.82). Among 13765 hospital births 389 were twin births (28/1000). The hospital perinatal twin mortality was 237/1000. Birth weight<2000g (RR = 4.16, 95% CI: 2.47-7.00) and maternal unawareness of twin pregnancy (1.94, (1.15-3.31)) were significantly associated with perinatal twin death. The association was borderline significant for male sex (1.35, (0.99-1.84)). Sixty-six percent (492/749) of the mothers who delivered at the hospital were unaware of twin pregnancy. *Conclusions:* The community twinning rate was similar to neighboring countries. Twins had very high perinatal mortality. Birth weight<2000g was the strongest risk factors for perinatal death and unrecognized twin pregnancy was common. Urgent interventions are needed to lower perinatal twin mortality in Guinea-Bissau.

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RELATIONS OF OBESITY AND LIVER FAT WITH LIPOPROTEIN SUBCLASS PROFILE: ANALYSES OF HEALTHY TWINS

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Aim: To understand relations between obesity and the lipoprotein subclass profile in young adults. *Methods:* BMI and serum lipoprotein subclass concentrations and size were measured in a large sample of 1497 twin individuals (579 MZ and 918 DZ, complete pairs: 283 MZ and 427 DZ) by proton NMR spectroscopy (age range: 21–33 y, 54% female). In addition, glucose, insulin (OGTT) and body composition (total body, android and gynoid fat by DEXA) were measured in 256 twins (age range: 23-33 y, 44% female, 40% MZ, 128 pairs). A unique sample of obesity-discordant MZ pairs (n = 14, within-pair difference (?) in weight 10–25 kg) was measured for abdominal fat distribution (MRI) and liver fat (MR-spectroscopy). *Results:* Age-adjusted bivariate Cholesky model-fitting analyses in all twins revealed that 54–79% of the phenotypic correlations between BMI and lipoprotein subclasses and size were explained by shared genetic factors and the remaining by non-shared environmental factors. Genetic and non-shared environmental correlations were low to moderate (rg = -0.31–0.29, re = -0.43–0.45). Within the 128 MZ and DZ pairs (?), total body and android (but not gynoid) fat correlated positively with concentrations of non-HDL and small HDL particles (r = 0.19 -“ 0.44; $p<0.05$) and inversely with concentrations of large HDL particles (r = -0.26 -“ -0.28, $p < 0.01$) and HDL particle size (r = -0.29–0.32, $p < 0.001$). In the obesity-discordant MZ sample, 8 pairs had large differences in liver fat (1% in the lean and 6% in the obese co-twins) whereas in the other 6 pairs, both co-twins had low liver fat content (0.5% vs. 0.6%). In the former group, correlations between Dliver fat and DapoB, DLDL particles and Dtotal cholesterol were very high (r = 0.71–0.98; $p < 0.05$), while the correlations were not significant in the latter group. Intra-abdominal fat and serum insulin were associated with an adverse lipoprotein profile, whereas subcutaneous fat and serum glucose were not. *Conclusions:* The covariance between obesity and lipoprotein subclass profile is attributable to genetic and non-shared environmental factors. There is a low to moderate overlap of both genetic and non-shared environmental factors that influence obesity and individual lipoprotein subclasses. Acquired abdominal adiposity and insulin resistance are associated with increased concentrations of pro-atherogenic lipoprotein particles. Liver fat is the most important determinant of an adverse lipoprotein subclass profile.

TWIN PREGNANCY: A MODEL OF PLACENTAL ADAPTATION

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Introduction: The U shaped curve of perinatal mortality rate, showing an increase after 41 weeks of gestational age, is shifted to the left in twin pregnancies, where the increase occurs at 37-38 weeks. This might be due to the fact that placental changes occur earlier compared to those of single pregnancies. The aim of this study was to compare villous patterns of twin and single placentae at 34-37 weeks by morphometric analysis. *Methods:* We examined the placentas from three dichorionic diamniotic uneventful twin pregnancies with normal fetal growth and four age-matched single pregnancies with normal fetal growth. Twin and single placentae were fixed in neutral buffered 4% formaldehyde solution and weighed. Three vertical full-thickness slices (one central, one intermediate and one peripheral) including chorionic and basal plates were excised. Infarctuated areas were excluded. Three villous sections for each placenta were examined to determine structural morphometrical composition (percentage of fibrinoid, intervillous space, and villous tissue) and relative amount of villous type (stem, mature intermediate and terminal villi). *Results:* Twin placentas are characterized by a higher percentage of terminal villi (42.77%) compared to age-matched single placentae (33.89%). No differences were observed in intermediate villi pattern between twin (30.4%) and single (36.6%) placentae. *Discussion:* Our results suggest that maternal hemodynamic changes occurring during multiple pregnancies can't supply to the requirements of two fetuses starting at 35-36 weeks thus inducing an increase in terminal villi in twin dichorionic placentae as previously described in single pregnancies with feto-placental hypoxia.

GENETIC AND ENVIRONMENTAL BASES OF THE INTERPLAY BETWEEN MAGICAL IDEATION AND PERSONALITY: A GENERAL POPULATION TWIN STUDY

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Whereas previous studies investigated the genetic and environmental effects on schizotypy and personality, the interplay between magical ideation, which represents the

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core feature of psychosis-proneness, and specific personality features in the general population is poorly understood. We performed a twin study to explore the relationship between magical ideation and personality, and to unravel its genetic and environmental bases. Subjects were around 270 twin pairs aged 18-65 years, recruited in the population-based Italian Twin Register within a broad survey on health and psychological well-being in adulthood. We assessed magical ideation with the Italian version of the self-report Magical Ideation Scale (MIS), while for personality traits we used the 125-item version of the Temperament and Character Inventory (TCI-125). We estimated phenotypic correlations of MIS total score with individual scores on the seven TCI dimensions (i.e., novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, self-transcendence), as well as cross-twin/within-trait and cross-twin/cross-trait correlations for monozygotic and dizygotic twin pairs separately, which we interpreted under the assumptions of the twin design. Furthermore, we applied a multivariate Cholesky decomposition to derive estimates of heritabilities and genetic correlations of MIS and TCI dimensions. MIS total score was substantially correlated with the score of self-directedness (-0.37) and self-transcendence (0.59), and moderately correlated with the score of novelty seeking (0.22) and cooperativeness (-0.22). The-best fitting Cholesky decomposition included additive genetic and unshared environmental factors, and provided heritability estimates of 0.51 for MIS and from 0.22 (persistence) to 0.50 (self-directedness) for TCI dimensions. Furthermore, estimates of genetic correlations were -0.46 between MIS and self-directedness, and 0.82 between MIS and self-transcendence; genetic correlations of MIS with novelty seeking and cooperativeness were 0.28 and -0.41, respectively. In conclusion, this study shows moderate to substantial genetic effects on MIS and TCI dimensions. Our data also suggest that shared genetic effects may underlie the phenotypic correlation between tendency to magical ideation (i.e. psychosis-proneness) and the personality traits of self-directedness (negative association) and self-transcendence (positive association); in particular, self-directedness relates to individual"s competence toward autonomy, reliability, and maturity, while self-transcendence characterizes the aptitude toward mysticism, religion, and idealism.

DECLARATIVE MEMORY FUNCTION IN TWINS DISCORDANT FOR COMBAT-RELATED POSTTRAUMATIC STRESS DISORDER

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Animal studies show that stress can have long term effects on memory function as well as brain areas involved in memory. Studies in patients with PTSD show smaller hippocampal volume and deficits in memory. Research using twins discordant for PTSD can control for family environment and other confounds than can effect results in cross sectional studies of PTSD. We previously reported 9% smaller hippocampal volume in twins with PTSD compared to their brothers without PTSD. We now report data on neuropsychological testing of memory and cognition, from the same sample of twins, now including 46 pairs of twins discordant for PTSD. Twins with PTSD had a pattern of lower percent retention of a paragraph on the Wechsler Memory Scale, an outcome we have previously associated with PTSD (77 (14 SD) v 82 (15 SD). These findings suggest a pattern of memory deficit in PTSD.

OBSTETRIC AND PERINATAL OUTCOMES OF ART VS SPONTANEOUS TWINS: RESULTS FROM THE MUBICOS COHORT

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Background. Several studies have been looking at obstetric and perinatal outcomes of assisted vs natural twinning and have come to conflicting results. Many of these studies have been performed in a retrospective manner or using registries (i.e. malformation registries) and therefore might experience some biases. The Multiple Births Cohort Study (MUBICOS) is a recent cohort of newborn twins established in Italy enrolling twins newborn in 8 different hospitals. The cohort started in 2010 has now enrolled about 280 twin pairs. Follow-up are planned for 6, 12, 18 and 24 months and possibly further. Aim of the present work is to compare pregnancy and neonatal outcomes between assisted reproductive technique (ART) and naturally conceived twins in our cohort. Methods. Data from 267 twin pairs about pregnancy complications and neonatal outcomes were considered in this analysis. Twin pairs were classified on ART status based on pregnancy medical records. Information was available for: maternal age, corionicity, parity, preeclampsia, prenatal corticosteroids, premature delivery, mode of delivery, apgar score, admission to NICU, birth weight, gender, respiratory distress syndrome, sepsis, SGA, breastfeeding at discharge and length of stay. The analysis was performed only on dichorionic twin pregnancies. A multivariate logistic regression model, adjusting also for hospital of birth, was applied adjusting estimate standard errors for twin data. Results. Out of 534 twins (267 pairs) 174 (31%) were from ART pregnancies. This percentage varies between 18 and 50% of all pregnancies enrolled in this cohort in the different centres. ART twins were significantly more likely to have nulliparous and older mothers. Adjusting for hospital

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of birth, parity and maternal age and gestational age, ART twins were more likely to have administered prenatal corticosteroid (OR = 3.50, 95% CI: 1.7-7.2), have a greater chance of sepsis during the hospital stay (OR = 12.34, 95% CI: 1.1-140.0) and had a longer length of stay (OR = 1.04, 95% CI: 1.0-1.08). Twins conceived using ART were also more likely to be fed with both maternal milk and formula than with exclusive maternal milk (OR = 2.9, 95% CI: 1.4-5.9). Odds ratios for preeclampsia (OR = 2.21, 95% CI: 0.8-6.5) and premature delivery (OR = 1.90, 95% CI: 0.8-4.5) also suggested a higher risk for ART twins but statistical significance was not reached. All other available variables did not show any association. Conclusion. For dichorionic twin pregnancy we found a higher chance of sepsis and use of prenatal corticosteroids. A slightly but not significant risk was found also for preeclampsia and premature delivery. The enrolment is still ongoing, in fact, we will repeat the analysis with a greater sample and will continue to monitor our twins even for later outcomes. A wider sample will also allow us to explore differences in monochorionic twin pairs.

FOLIC ACID SUPPLEMENTATION BEFORE CONCEPTION AND CHANCE OF A TWIN PREGNANCY: PRELIMINARY RESULTS FROM AN ITALIAN CASE-CONTROL STUDY

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Italian physicians recommend, to women who are planning a pregnancy, to assume 400 mcg/day of folic acid (FA) for at least one month before conception and during the 1st trimester of pregnancy in order to prevent neural tube defects in the newborn. There is some evidence, not always confirmed, that FA intake could increase the probability of having a twin pregnancy. Few studies have been performed taking into account vitamin B regulating genes. In 2008, the Italian Twin Registry started a case control study on 500 twin mothers and 500 singleton mothers with the aim of investigating if folic acid supplementation enhances the probability of a twin delivery, taking into account factors such as maternal age at delivery, maternal weight and height before conception, use of assisted reproductive techniques, occurrence of twins in first degree relatives, coffee consumption and smoking before conception. The present analysis was performed on a preliminary sample of 329 cases and 303 controls. The overall prevalence of FA assumption before conception in our sample was 34.6%. In particular, prevalence of FA assumption was 45.6% in twins' mothers and 22.8% in singletons' mothers. Adjusting for maternal age, Assisted Reproduction Techniques (ART) use, coffee consumption and smoking before conception, maternal weight and height, the estimated relative risk of having a twin delivery given preconceptional FA assumption was 2.44 (95%CI: 1.6-3.8)) for dizygotic twins, while a weaker association was detected for monozygotic twins (OR = 1.68, 95%CI: 0.9-3.1). These preliminary data show an increased risk of having a dizygotic twin delivery, given FA assumption before conception and a higher but not significant risk of a monozygotic pregnancy. This result needs to be confirmed and refined when the final complete dataset will be available. The second part of the study will investigate on possible gene-environment interactions between folic acid intake and MTHFR polymorphisms: DNA is up to now available for about 300 cases and 200 controls and sample collection is still undergoing. Furthermore, given the reported high prevalence of AF supplementation in twins' mothers, a study on non-responders is being performed to check for a possible selection bias.

HERITABILITY OF DIURNAL TYPE AMONG FINNISH ADOLESCENT TWINS

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Variability in sleeping rhythm has been shown to be associated with a host of different health and behavioral issues. Diurnal-type refers to relatively stable individual differences in temporal organization for individual sleep/wake behavior and other related biological rhythms. About 10% of adults are clear evening types (they feel most energized in the evening) and 27% clear morning types (they feel most energized in the morning). In adults, heritability estimates of diurnal type have ranged 47% to 50%. We examined the heritability of diurnal type in 17-year old twins from Finland addressing the following research questions: (1) What is the prevalence of diurnal type among Finnish adolescents? (2) What is the effect of genetic and environmental factors on diurnal type among adolescents? (3) Do estimates of the genetic and environmental influences on diurnal type differ between men and women (quantitative sex differences)? The FinnTwin12 population-based study consists of five consecutive birth cohorts of twins. The final study population included 637 MZ, 648 DZ and 613 OSDZ twin pairs aged 17.6 years (SD 0.30). Univariate models of diurnal type were analyzed by using the Mx statistical package. Diurnal type was determined by one question (Koskenvuo et al, J Sleep Res 2007) based on the Diurnal Type Scale of Torsvall and Åkerstedt (1980): 'Will you try to estimate to what extent you are a morning or evening person' The responses were: 1) ('I am clearly a morning person (morning bright and evening sleepy)', 2) ('I am to some extent a morning personâ', 3) 'I am to some extent an evening person (morning sleepy and evening bright' and 4) 'I am clearly an evening person'. Twenty five percent of adolescents (27% of males, 23% of

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females) were classified being clear evening type and six percent (6% of males, 7% of females) as clear morning type. Modelling indicated that there were no sex-specific genetic influences but showed sex differences in heritability estimates. The ICCs for diurnal type are higher for MZ (MMZ 0.40, FMZ 0.52) than DZ pairs (MDZ 0.18, FDZ 0.05, OSDZ 0.10). An ADE model fit the data best for males, such that additive genetic effects accounted for 21% of the variance in diurnal type, genetic effects due to dominance for 26% and unique environment for the remaining 54%. For females, a DE model fit best. The difference with compared to an ADE model was significant ($p < 0.05$). For females, genetic effects due to dominance and unique environment accounted for 53% and 47% respectively. About 11% of 24-29 year old Finnish adults were clear evening types while respective percentage in present study was 25. The difference in evening type percentage may be due to the different time periods (1981 versus 2000-2004) but also due to the different age groups (20-24 versus 17). In both sexes, diurnal type measured at age 17.6 is influenced by genetic and unique environmental factors. While for males, both additive genetic and non-additive genetic factors appear to influence diurnal type in late adolescence, non-additive genetic effects are more important for females.

ANTENATAL CORTICOSTEROID USE IN ELECTIVE LOWER SEGMENT CAESAREAN SECTIONS FOR TWIN PREGNANCIES AND RESPIRATORY DISTRESS SYNDROME

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Background: Antenatal corticosteroids are associated with a significant reduction in rates of neonatal deaths, respiratory distress syndrome (RDS) and intraventricular haemorrhage and are safe for the mother The Royal College of Obstetricians and Gynaecologists (RCOG) advise that they should be administered in all babies delivered by elective lower segment caesarean section (LSCS) prior to 38 + 6 weeks gestation. As elective LSCS for twin pregnancies are often performed prior to 38 + 6 weeks gestation, corticosteroid administration should be considered; however, there is limited data supporting the benefit of their use in twin pregnancies[1]. *Aim*: To identify whether there is a higher incidence of RDS in babies born to those mothers undergoing an elective LSCS for a twin pregnancy, who had not had antenatal corticosteroid administration. *Methods:* Elective LSCS for twin pregnancies (monochorionic, diamniotic and dichorionic, diamniotic) performed between 05/02/2004 and 24/03/2011 were included. This gave a total of 86 mothers and 171 babies. Their gestations ranged from 31 + 2 to 39 + 1 weeks. *Results:* 15 (17.4%) women received antenatal corticosteroids: four as they were undergoing an elective LSCS prior to 38 + 6 weeks gestation and eleven due to risk of iatrogenic or spontaneous pre-term birth. Seven (4.1%) babies required neonatal input due to respiratory problems. One baby was diagnosed with RDS, whose mother had been given antenatal corticosteroids, due to complications. One baby was given no definite diagnosis but received brief IPPV; its mother had received antenatal corticosteroids. The remaining five babies had transient tachypnoea of the newborn. The mother of two of these babies had received antenatal corticosteroids but the other babies' mothers had not. *Conclusion:* The majority of women in the study were not given antenatal corticosteroids. Despite this, there was a low incidence of respiratory pathology. In view of this we would suggest that a blanket policy for the administration of antenatal steroids in women undergoing elective LSCS prior to 38 + 6 weeks gestation, is not applicable to twin pregnancies.

References: [1]Royal College of Obstetricians and Gynaecologists. Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality. Green-top Guideline No. 7. October 2010

THE RELATIVE IMPORTANCE OF GENES AND ENVIRONMENT IN BURNOUT SYMPTOMS: A SWEDISH TWIN COHORT STUDY

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Burnout is a stress-related phenomenon that has received widespread attention as an important problem for the society as well as for the affected individuals, and a large body of scientific publications has treated this subject from various views. Burnout has been found to be prospectively associated with a number of important negative outcomes such as poor job-performance, psychological and physical ill-health, long-term sickness absence, intent to leave the profession, suicidal ideation, and all-cause mortality. Although many contributing factors to burnout have been studied, more knowledge of the underlying causes of burnout is needed, especially of the degree to which burnout is influenced by genetic and early environmental factors. Two previous studies on the topic have been presented and they showed a familial clustering of burnout, and that the clustering was due to genetic factors in men, while for women both genetic and shared environmental factors were of importance. The aim of the study was to estimate the relative importance of genetic influences on burnout in a sample of 20 286 monozygotic (MZ) and dizygotic (DZ) same and opposite sexed (OS) Swedish twins born 1959-1986. These twins participated in the cross-sectional Study of Twin Adults: Genes and Environment (STAGE) in 2005. Burnout was measured with three items from the Pines Burnout Measure (Pines BM), expressed as the adjectives 'Feeling depressed', 'Being emotionally exhausted' and 'Feeling run down'. Answers were given by respondents on a seven point Likert scale ranging from '1 = do not agre to '7 = agree entirely'. Pines BM is a context free measure of

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symptoms of burnout. Within pair correlations and heritability coefficients, i.e. the proportion of the total variance attributable to genetic factors, were calculated using standard biometrical model fitting procedures with raw data using Mx. All six twin groups (MZ female, MZ male, DZ female, DZ male, OS male-female, OS female-male) simultaneously and a series of models were tested. The aim of quantitative genetic analysis is to determine the extent to which genetic and environmental influences are important for variation in a trait, in this case burnout. MZ twins are genetically identical, whereas DZ twins share, on average, 50% of their segregating genes. The results showed that genetic factors explained 33% of the individual differences in burnout symptoms in women and men. The results indicate that the same genes were accounting for genetic effects in burnout in both men and women. The remaining variance (67%) was explained by non-shared environmental variance. Hence, environmental factors explained a substantial part of the variation as well and are thus important to address in rehabilitation and prevention efforts to combat burnout.

THE HEALTH RESEARCH SUPPORT SYSTEM IN THE DANISH TWIN REGISTRY

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The Danish Twin Registry (DTR) is managed by the Health Research Support System. The 5 pillar system assists ongoing research by organizing: 1) Follow-up on all twins and their relatives: vital status, zygosity, participation etc. 2) Projects and keeping track of: progress, status, approvals etc. 3) Survey data and facilitating data export incl. metadata, value labels, code book etc. 4) Storage of biological samples in the bio-bank, withdrawals etc. 5) Genotypes Access. In principle data stored in DTR is accessible to all research areas and it is possible to external researchers to gain access to the data. Prior to access the researcher must submit an application for approval by the DTR scientific board. The DTR databank is protected by extensive security measures. Contents The DTR is hosted by the University of Southern Denmark at the Faculty of Health Sciences. The register was founded in 1953 as the first nationwide twin register in the World. DTR includes almost all twins born in Denmark since 1870. As of January 2011 approximately 87,000 twin-pairs were part of the register and out of these approximately 51,000 were still alive. The purpose of the register is to facilitate research in the influence of nature and nurture on health, disease and human lifespan. The DTR is updated regularly with register data from various national registries which among other data comprises vital status, addresses, hospitalizations, diagnoses and causes of death. In addition the DTR contains data from a large number of surveys that includes objective measures e.g. grip-strength, gait-speed, spirometry, blood pressure, cognitive testing etc. and self reported health, socio-demographic information, life style, mood and personality from thousands of twins. Currently the DTR biobank contains biological samples from approximately 18,000 twins. The material primarily consists of blood, dried blood spots and cheek swabs/saliva for DNA analyses. For subsamples plasma, serum and urine are stored as well. In other projects hair samples, viable cells and samples for extraction of RNA have been collected. The Poster shows how data is organized in the Health Research Support System and the connected slideshow demonstrates details.

INTREPID: AN INTERNATIONAL NETWORK OF TWIN REGISTRIES

D. Buchwald, J. Sung

Under the aegis of ISTS, a working group, comprised of leaders from twin registries (TRs) in Korea, Finland, Norway, Australia, and the United States, was formed in 2010 to facilitate international collaboration among regional and national population-based TRs pertinent to a wide range of phenotypes. More recently, we have also engaged a group of internationally known experts from McGill University in data harmonization. This group has worked with the P^3G Consortium (Public Population Project in Genomics) and been involved in the harmonization of large population-based studies. The organizing group has convened two in-person meetings in Seoul, S. Korea (5/2010) and in Melbourne, Australia (2/2011); this ISTS meeting is the third gathering of the group. A result of this evolving effort is a transformative concept: the International Network of Twin Registries for EPIDemiological (INTREPID) Studies Consortium. INTREPID was established to develop, maintain, and strengthen resources that will be made available to the ISTS community. These resources will support research involving twins and other multiples and foster multi-registry, international, innovative, scientific collaborations. Examples of the types of INTREPID activities that will enhance research collaboration among TRs include:

- Shared resources, including analytical and software tools
- Creation of searchable inventories of available data in TRs
- Harmonization of common methods for assessing or harmonizing phenotypes to facilitate international collaboration
- Harmonization of biobank-related procedures and protocols
- Developing guidelines for conducting international twin studies
- Creating new venues for scholarly exchanges and training
- Highlighting and addressing cross-cultural and cross-national ethical and IRB issues

Since the group mandate was approved by the ISTS board in January 2011, Dr. Joohon Sung obtained funding from the Korean government to conduct pilot work on cardio-

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vascular disease, obesity, and lung function in obesity discordant pairs. In 1/2012, Drs. Dedra Buchwald, Jaakko Kaprio, and Joohon Sung submitted a $7.2 million dollar proposal in response to the NIH Directors Transformative Research Award. To prepare for this proposal, the PIs contacted all 28 active TRs around the globe that contained adults; 26 agreed to participate in the initial activities. This represents over 560,000 twins pairs: 214,295 in Asian TRs; 215,000 in European TRs; 32,000 in Australian TRs, and 66,000 in U.S. TRs.

This proposal has four components. The first two will create the consortium; the last demonstrates our ability to collect primary data together.

1. Data harmonization will involve documentation on a common website of the data available on variables and phenotypes derived from questionnaires and data dictionaries assembled form each TR. Key variable to harmonize include weight, height, selected health conditions, and lifestyle variables.
2. Meta-analytic studies that use summary statistics, not individual data, will focus on obesity as a primary phenotype. Standard methods for analysis of existing data from the 26 TRs participating in INTREPID will be implemented using tools such as DataSHaPER (DataSchema and Harmonization Platform for Epidemiological Research). Since analyses are done locally, issues on data sharing and consents can be readily addressed.
3. A demonstration project will collect detailed epidemiologic and biologic specimens from 150 obesity-discordant MZ twin pairs: 50 from Asia, 50 from Europe, and 50 from Australia and the U.S. We will identify obesity-associated differences in gene expression, genome-wide methylation, and RNA signaling as well as the gut microbiome using a co = twin control design.
4. Explore the feasibility of building new TRs in Latin America and Africa to enhance the diversity of genetic backgrounds, cultures, environments, and economic development.

The symposium will offer the twin research community an opportunity to learn about these and other ongoing and planned related activities pertinent to the INTREPID consortium. As well, this forum will encourage an exchange of ideas that will help to move this agenda forward.

ARABIN VAGINAL PESSARY CERCLAGE IN THE MANAGEMENT OF A TWIN PREGNANCY WITH SONOGRAPHYCALLY SHORTENING CERVIX

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Objective: To present a twin pregnancy in a patient with progressive cervical shortening and the use of Arabin vaginal pessary cerclage. Design: Case report. Patient 42 years old pregnant woman after IVF embryo transfer carrying a bichorionic twin pregnancy with a progressive cervical shortening from the 15 weeks and 5 days of gestational age (GA). After normal results of the 12 week"s aneuploid combined screening and early fetal morphologic ultrasound evaluation, we treated her initially with expectant mangement and Omega 3 and l-Carnitine nutritional support for reduction of oxidative stress as an implicated factor in the triggering of the preterm delivery. Ultrasound surveillance was undertaken with a IC5-9Hz intercavity probe of Voluson 730 Expert General Electric ® with cervical length (CL) measurements every other week. Progressive shortening of the CL was observed since 24.2 mm at the 15 weeks until 6.2mm at the 24 weeks of GA (a CL bellow the 10 th centile according to the reference values). We discussed the treatment options to the patient and chose the pessary use as a less invasive treatment, based on the available evidence that showed some benefit of the cervical pessary use in preventing preterm birth although this evidence comes from nonrandomized trials. There are two ongoing randomized trial conducted in Europe about this topic. *Method:* The facts that there is not yet strong enough evidence that cervical pessary can prevent spontaneous preterm birth on twin pregnancies and the possible side effects were explained to the patient, then she signed a consent application. Before the pessary placement, a bacterial vaginosis, urine culture, PMG-1 (AmniSure®) and PhIGFBP1 (Actim Partus TM®) tests were performed. She recived 12 mg intramuscular betamethasone twice in a 24 hours interval. Twenty four hours before the pessary insertion, at the 25 weeks and 5 days of GA, we used indometacine 100 mg every 12 hours twice, looking for utero inhibition and to lower the amniotic fluid pressure and production. We got a new cervical measuremt of 14 mm of CL al the ultrasound the pessary placement"s day. In a Trendelenburg position and with a full bladder we performed a visual inspection with a vaginal sterile speculum, then an appropriate size pessary (Arabin-cerclage® perforated 65/25/32 ASQ Type) was covered with a 2% clindamicine topic preparation, placed carefully into the vagina and fit it high and tight around the cervix. The smaller inner diameter of the pessary was encompassing the cervix, keeping it closed. An 8 hours observation period of time was established to ensure the patient was able to void and there were not discomfort, vaginal bleeding or uterine activity. We send her home with physical activity restriction indications. Outcome: Last evaluation was performed at 33 weeks and 2 days of GE, seven weeks and five days after the pessary placement, the patient continues without uterine activity, vaginal bleeding or secretion. Ultrasound evaluation every other week has shown fetal growth on 46th and 50th centile, respectively. Normal anatomy, amniotic fluid level and umbilical IP Doppler has been found.

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THE ROLE OF ASSISTED REPRODUCTIVE TECHNOLOGIES IN CURRENT TWIN STUDIES: IMPLICATIONS FOR TWIN STUDY FINDINGS

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Rates of twinning have risen dramatically in the United States over the last 30 years, from 1 in 53 births in 1980 to 1 in 30 births in 2009 (Martin et al., 2012). This increase is largely attributable improvements in Assisted Reproductive Technologies (ART), combined with delays in parenthood. Although this increase means that more twins are available for recruitment into twin studies (a clear advantage for twin researchers), it also has potential consequences for the heritability estimates we obtain form those studies. However, only a few studies have examined these consequences to date. The largest such study, by Goody et al. (2005), compared 101 families with DZ twin pairs conceived via ART to 1,073 DZ twin pairs conceived naturally. Although there was little evidence of mean differences in childhood psychopathology across the two types of twins, they found evidence that DZ twin correlations were often larger in twins conceived naturally as compared to those conceived using ART. Although such results are provocative, there are some limitations. First, the sample of ART twins was admittedly rather small, limiting confidence in their results. Second, they focused exclusively on DZ twins, even though MZ twinning rates also increase (if somewhat inexplicably) with ART. The current study sought to address these limitations, and in this way, provide the most definitive examination of the implications of ART for twin studies conducted to date. We made use of the on-going Michigan Twins Project (MTP), an arm of the Michigan State University Twin Registry. The MTP currently consists of roughly 8,000 families with twins aged 3 to 17 years. We will thus have a far larger sample of twins conceived via ART (roughly 1,000 families) available for analysis. The inclusion of MZ pairs in our analysis also allows us to compute heritability estimates across naturally conceived and ART conceived twins, using methods introduced by Purcell (2002). Implications of our findings will be discussed.

POST-PARTUM HEMORRHAGE AMONG MOTHERS OF TWINS

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The true incidence rate of post-partum hemorrhage (PPH) is not known with certainty, but it is thought that one woman dies every minute of every day from bleeding or other delivery related causes. Mothers of twins are reputed to be at higher risk of PPH than are mothers of singletons, but rates vary enormously from <5% to as much as 20%, with equal or greater variation in the samples from which these data derive. To our knowledge, prior attempts to query mothers of twins directly regarding their experiences with PPH are lacking. Accordingly, the Center for Study of Multiple Birth and the Post-Partum Hemorrhage Foundation collaborated in the development of a survey which was distributed via the ICOMBO group to constituent national organizations throughout the world. Use of internet membership lists, Facebook Postings and Twitter brought the survey to the attention of a large group of women who had had twin deliveries and offered them a chance to participate using Survey Monkey. Responses were voluntary and it is not possible to generate a denominator that represents the number of mothers who received the survey and could have responded. The first analysis was undertaken in mid-January 2012 and included 1605 respondents. In the current analysis we focused on those mothers who had given birth to one set of twins as well as a singleton. Within these 146 mothers, 19 had experienced PPH in their singleton delivery while 111 had suffered from that condition after the delivery of twins; an additional 16 mothers were affected in both pregnancies. Based on these numbers, the relative risk (RR) of PPH in twin pregnancies is 5.8, confirming the suspected higher risk. Next, we fractioned our analysis on the order of singleton/twins pregnancies. As expected, the majority of mothers had their singleton birth first (107 vs. 39); the RR in this group was estimated at 5.1 vs a substantially higher risk in mothers who had delivered twins in their first pregnancy (RR = 10). This difference in RR was not statistically significant, but its magnitude in clinical terms warrants further analysis in larger samples. Overall, this survey is the first study quantifying the relative risk of PPH in twin pregnancies, highlighting the relevance of this topic in terms of care provided to mothers in the labor and delivery settings.

URINARY GONADOTROPINS IN 6-WEEK-OLD TWINS

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Background: Over the past decades a number of findings in adult twins have been attributed to reproductive endocrine environment in early life but hardly any data are available. Examples are behaviour differences between girls with a boy as cotwin and vice versa and higher rates of testicular cancer in dizygotic twin boys. Differences in gonadotropin levels could help to define plausible explanations for such findings. Urinary samples are easy to collect in very young children. We here present a comparison of urinary LH and FSH levels in urine collected from MZ and DZ boys and girls at six weeks after delivery. In a number of boys we also measured testicular volumes. *Materials and Methods:* Between 2004 and 2009 we sampled urinary FSH (IU/L) and LH (IU/L) in 6 weeks old neonates, data were corrected for creatinin concentration. Testicular volumes were measured using a portable Aloka SSD-900 with a 7.5 mHz linear transducer. The

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epididymus is not included in the volume measurement. Testicular volume (cm^3) was calculated using the formula: length x width x height x (π/6). *Results:* Corrected FSH and LH in urine, number of subjects and testicular volumes are reported. *Conclusions:* We provide for the first time comparative data of gonadotropin levels in urine of newborn twins. Our data indicate that there are potential differences in reproductive endocrine environment between MZ and DZ twins and that twins of opposite sex, while in utero, may influence the reproductive status of their cotwin, possibly with permanent consequences.

DINOPROSTONE VAGINAL INSERT IN TWIN PREGNANCY CERVICAL RIPENING

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Introduction: The efficacy of PGE2 in cervical ripening and in reducing the number of cesarean sections due to induction failure has been little studied in twin pregnancies. *Objective:* To evaluate the efficacy and safety of the dinoprostone 10-mg controlled-release vaginal insert (PG) for the elective termination of labour in twin pregnancies with immature cervix. Methodology: A prospective observational study was carried out. A total of 91 twin pregnancies were included with a first foetus in the cephalic position, Bishop Score < 7 (= 3 in 72.2%), gestational age 32 weeks, and confirmed prior foetal wellbeing, subjected to pre-induction with vaginal dinoprostone. Monoamniotic monochorionic twin pregnancies were excluded, as were patients with a history of uterine surgery involving cavity access, the presence of meconial amniotic fluid, maternal or foetal disease contraindicating PG administration, evident signs of pelvic stenosis, and the presence of spontaneous labouring. The main variables analyzed were: Bishop score, time interval between first induction and fetal expulsion, need of a second induction method, and vaginal rate and indication in the case of cesarean delivery. *Results:* Mean patient age was 34.02 years, with assisted reproduction in 65.9%, dichorionic gestation in 92.3%, first pregnancy in 73.6%, nulliparous patients in 92.3%. The mean gestational age at the time of ripening was 37 weeks. The most frequent indications were elective termination (62.6%) and intrauterine growth retardation (8.79%). A total of 52.7% of the patients started labour due to the effect of PG, while the remaining 47.3% required induction with oxytocin (OT) and amniorrhexis. The prior mean Bishop score was 2.83 and 2.47 in the patients with effective PG and in those requiring induction with OT, respectively. In turn, the mean time to vaginal delivery was 1152 versus 2116 min., respectively. Only 8.3% of the patients started labour with a second induction method. The global vaginal delivery rate was 77.1% versus 44.2% in the effective PG and OT induction groups, respectively. The main indication for caesarean section in the PG group was non-progression of delivery (in 45.3%), versus induction failure in the OT group (75%). Eight cases of uterine atonia were detected in the immediate puerperal period: 3 in the PG group and 5 in the OT induction group. All were resolved with conservative management, including uterine massage, intravenous OT perfusion and, in some cases, PG or ergotamines. *Conclusions:* In this study the PGE2 vaginal insert clearly reduced the time to delivery, with manifest improvement in the Bishop score after use, and a reduction of over 50% in the need for cesarean sections versus the delivery induced with oxytocin. The complications associated to its effective use were fewer than with OT induction, though statistical significance was not reached due to the small sample size involved. Cervical ripening with the PGE2 vaginal insert appears to be safe and effective in twin pregnancies with an unfavourable Bishop score, and should be regarded as an alternative for minimizing the cesarean section rate and the associated maternal morbidity in these cases.

ETHICAL CHALLENGES PRESENTED IN THE MANAGEMENT OF MULTIPLE PREGNANCIES

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This presentation will address the essential ethical dimensions of the clinical management of multiple pregnancies:

The Professional Reasonability Model of professional ethics will be presented and the Ethical Principles of Beneficence and Respect for Autonomy defined.The essential role of the fetus as a patient will be elucidated.

Using these ethical concepts three challenging clinical topics in the management of multiple pregnancies will be analyzed: selective termination, twin-to-twin transfusion syndrome, and discordant obligations in multiple gestation.

THE OPTIMAL TREATMENT OF TWIN-TWIN TRANSFUSION SYNDROME

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Twin-twin transfusion syndrome (TTTS) develops from preferential shunting of blood from one monochorionic twin (donor) to the other twin (recipient). These hemodynamic alterations lead to variable degrees of donor twin oligohydramnios, recipient twin polyhydramnios, and characteristic anatomical and arterial/venous flow abnormalities that can be identified by ultrasound. Most studies have shown that selective laser photocoagulation of communicating vessels (SLPCV) is the optimal treatment for TTTS. Several factors may influence perinatal outcomes in laser-treated TTTS patients, including surgical technique and disease severity. In the recent USFetus study of TTTS patients treated with uniform laser surgery techniques, the

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overall perinatal survival rate for at least one twin was 91% and for both twins was 67%. Survival for at least one fetus was independent of Stage. However, dual twin survival differed by Quintero Stage, predominantly because Stage III pregnancies were associated with decreased donor twin survival. Decreased donor twin survival was also observed in patients with donor twin IUGR. A further factor independently affecting perinatal survival was the use of the sequential SLPCV surgical technique. Those patients undergoing the sequential procedure were nearly twice as likely as those who did not to exhibit dual survival at 30 days. Although sequential laser surgery appeared to improve perinatal outcomes, further study is required before this treatment methodology can be advocated. Knowledge of Stage-specific perinatal outcomes after laser surgery may be useful for counseling patients, tailoring treatment, designing future studies, and elucidating potential TTTS sub-types.

SOCIAL INEQUALITY IN HEALTH – A DISCORDANT TWIN PAIR DESIGN

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Background: Social inequalities in health have been consistently demonstrated in various societal contexts, across different social indicators, and for a wide range of different health outcomes. Although well-established, the mechanisms underlying the social patterning of disease and the way contributing factors are inter-related are still poorly understood. We used a discordant twin pair design to test to which degree familial factors such as genetic dispositions and childhood environment influences underlie the association between adult socio-economic position (SEP) and health in Denmark. *Material and Methods:* We investigated mortality, incidence of breast cancer and cardiovascular disease, as well as prescription redemptions in up to 5,000 + monozygotic and 11,000 + dizygotic twin pairs and 5% of all singletons born in Denmark after 1921 and at least 30 years old at baseline in 1980 (or 1995 for redemption medicine) by linking the Danish Twin Registry and Statistics Denmark registers. SEP classification was based on education and income. Unpaired analyses were carried out and compared to the results of the intra-pair analyses of twins. *Results:* In the unpaired analyses, there was an association between SEP and all the outcomes of interest. For all health outcomes but breast cancer, SEP was inversely associated with health. That is, a higher risk among people of low SEP. In the intra-pair analyses, the associations were generally attenuated in MZ twins. In DZ twins the pattern was less clear, except for prescription medicine in which there was a partial attenuation in DZ twins and a larger attenuation in MZ twins. *Conclusion:* The overall findings of an attenuation of effect in the intra-pair analyses suggest that the causal health effect of SEP in adulthood may be overstated in regular cohort studies and that part of the association may be attributed to underlying familial factors such as genetic dispositions and childhood environment. The fact that attenuation was most pronounced in MZ twins, may point in the direction of genetic confounding. In spite of the large sample sizes, many of the intra-pair analyses suffered from limited power, resulting in imprecise point-estimates, making it difficult to identify clear attenuation patterns. Hence, the interpretation of findings ought to be accordingly cautious.

CANCER AND LONGEVITY – IS THERE A TRADE-OFF? A STUDY OF CO-OCCURRENCE IN DANISH TWIN PAIRS BORN 1900-1918

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Background: Animal models and a few human studies have suggested a complex interaction between cancer risk and longevity indicating a trade-off where low cancer risk is associated with accelerating aging phenotypes, and, vice versa, that longevity potential comes with the cost of increased cancer risk. This hypothesis predicts that longevity in one twin is associated with increased cancer risk in the co-twin. *Methods:* A total of 4354 twin pairs born 1900-1918 in Denmark were followed for mortality in the Danish Civil Registration System through 2008, and for cancer incidence in the period 1943-2008 through the Danish Cancer Registry. *Results:* The 8139 twins who provided risk time for cancer occurrence entered the study between ages 24 and 43 (mean 33 years) and each subject were followed up to death, emigration or at least age 90 years. The total follow-up time was 353,410 person-years and 2501 cancers were diagnosed. A negative association between age at death of a twin and cancer incidence in the co-twin was found in the overall analyses as well as in the sub-analysis stratified on sex, zygosity and random selection of one twin from each twin pair. *Conclusion:* This study did not find evidence of a cancer-longevity trade-off in humans. On the contrary, it suggested that longevity in one twin is associated with lower cancer incidence in the co-twin, indicating familial factors associated with both low cancer occurrence and longevity.

A TWIN STUDY OF BREASTFEEDING

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Introduction: Breastfeeding has short- and long-term health benefits to children, mothers and society. Natural breastfeeding has been related to general infant health, disease protection thorough life and child cognitive, psychomotor and emotional development. Breastfeeding appears to facilitate recovery after delivery and it could be related to a decreased frequency of pre-menopausal breast cancer. It is also an important element in mother-child relationship. These are some of the reasons why the WHO/UNICEF (1990) recommends exclusive breastfeed-

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ing up to six months. Breastfeeding is a complex behaviour in which multiple biological, psychological and social factors are involved. However, there is no information about the relative impact of genetic and environmental factors on natural breastfeeding behaviour. Our objective was to analyze the heritability of breastfeeding behaviour in a sample of adult twins. *Methods:* The data comprised 780 adult female twins from the Murcia Twin Register (Spain), when both twins had been mothers (202 MZ and 188 DZ pairs). The mean age was 50.9 years old (range = 41-67). Demographic and retrospective information about breastfeeding behaviour was based in self-reports and collected through telephone interview. Only data related to the first-born child is reported. Breastfeeding length was recorded in months, and dichotomised into two levels: 'less than 6 months' and '6 months or more'. Zygosity was ascertained by questionnaire and DNA analysis. Threshold models for categorical data were fitted to quantify genetic and environmental influences on variation in breastfeeding behavior. *Results:* The mean length of breastfeeding for the first-born child was 4.79 months (SD = 5.1), with a range of 0 -36 months. Women had been mothers for the first time at the age of 24.29 (SD = 43.69, range 14-47). Tetrachoric correlations for having breastfed were higher for MZ twins [rMZ = .509 (IC 95%: .270, .699)] than for DZ twins [rDZ = .218 (IC 95%: -.099, .504)]. The same pattern was found for breastfeeding the baby for more than six months [rMZ = .406 (IC 95%: .148, .622); rDZ = .161 (IC 95%: -.123, .427)]. Model fitting suggested that an AE model offers the best fit to data in both cases [A: .49 (IC 95%: .274, .679); E: .51 (IC 95% .321, .726)] and [A: .38 (IC 95%: .147, .586); E: .62 (IC 95% .414, .853)] respectively. *Conclusion:* Preliminary results suggest that individual differences in breastfeeding behaviour may be moderately but significantly influenced by genetic factors. Heritability estimates for breastfeeding the first baby (yes/no) and keeping it for at least 6 months are around .40. No evidence of shared environment has been found. Genetic factors involved in this behavior may be related to anatomical (e.g., constitution of the breast and nipple), physiological (e.g. levels of certain hormones), or psychological (e.g. attachment) processes. Research funding: Supported by 'Fundación Séneca' Grant (08633/PHCS/08); MICINN (2009/11560)

POST NATAL CARE AND FOLLOW-UP

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Newborns from multiple pregnancies are continuously raising in number and represent about 3% of all newborns but account for about 15% of perinatal mortality. In fact they show a higher risk of morbidity and mortality compared to singletons, which is related to the number of twins, characteristics of placentation, zygosity, intrauterine growth, gestational age and the eventual use of assisted reproduction technologies (ART). Accurate evaluation of prenatal and perinatal risk factors is mandatory to establish the optimal clinical assessment at birth and the adequate follow-up. Twin newborns, infact, represent a major concern for Neonatal Intensive Care Units (NICUs) and their need for health resorces has been showing a raising trend in the last decades. Main clinical issues in twins are prematurity, intrauterine growth restriction (IUGR), malformations and vascular disruptions. Prematurity is six-fold more frequent in twins and ten-fold in triplets compared to singletons. Mean gestational age is 2 weeks lower in twins, 4 weeks lower in triplets and this gap grows increasing the number of twins. Birth weight is significantly lower in twins than in singletons, according to the number of twins, and this gap appears during the last trimester of gestation, when uterine crowding becomes evident. Specific growth charts for multiple pregnancies and specific inclusion criteria for IUGR are needed to optimize the follow-up of these neonates. All neonatal diseases related to prematurity and low birth weight (respiratory, neurological, infectious) are more frequent in twins and require adequate assistance in NICUs. An increased malformation rate at birth have been observed in twin offspring expecially for neural tube defects, hearth defects, gastro-intestinal and uro-genital malformations. Monozygotic (MZ) twins account for most of this higher relative risk, while dizygotic (DZ) twins show a prevalence at birth which is much closer to singletons. Genetic and non-genetic mechanisms may be involved in the genesis of congenital defects, most of which can be considered defects of blastogenesis, whose most evident example are conjoined twins. Therefore, timing of division of MZ twins after conception plays a key role in determining the birth defects. Vascular disruptions are much more frequent in MZ twins and are determined by placental vascular anastomoses. They may be responsible for both fetal and neonatal morbidity and mortality with different clinical presentations depending on the amount, type and timing of anastomosis (fetal loss, fetus amorphus, fetus papiraceus, twin reversed arterial perfusion sequence, twin-twin transfusion sequence). The occurrence of any diseases in twins raises the issue of phenotypic concordance or discordance and the subsequent issue of managing pregnancy, patiens, parents and decision making events. Risk assessment for the apparently healthy twin, genetic counselling and parental psychologic assistance must be part of the clinical follow-up. In addition, the increasing use of ART with embryo and/or gamete manipulation has been demonstrated to determine an increased risk of epigenetic disorders, requiring both adequate preconceptional information and counselling and strict postnatal long-term follow-up.

PERINATAL OUTCOME OF TWIN PREGNANCIES AFTER ASSISTED REPRODUCTIVE TECHNIQUES (ART)

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Objective: To compare obstetrical and perinatal outcomes of twin pregnancies after assisted reproductive techniques (ART) and twins conceived spontaneously. Study design: Retrospective study. *Results:* There were 102 twin deliveries of

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which 52 were conceived after ART. Patients of the ART group were mostly nulliparous. There was no statistically significant difference in the frequency of preterm delivery or mean gestational age at delivery. Elective Caesarean delivery was more frequent in twin pregnancies conceived after ART. There was no difference in the mean birth weight or frequency of neonatal complication between the two groups. There were no other differences in maternal complications. *Conclusion:* In this comparative study, the obstetric and neonatal outcomes between two groups (twins conceived after ART and spontaneosly) are similar except for higher operative deliveries in the twins after ART.

TRYGLICERIDES, LDL, HDL-CHOLESTEROL, SERUM FOLATE, B12 VITAMINE AND HOMOCYSTEINE AFTER SUPPLEMENTATION IN SINGLE VS TWIN PREGNANCIES

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We compare three different groups of patients between the 25th and 27th week of gestation. One group of 46 single pregnancies, one group of 38 spontaneous twin pregnancies that started supplementation right after confirming the gestation and another group of 32 twin pregnancies after assisted reproduction tecniques that started supplementation several months previous to the confirmation of the gestation. We compare the levels of LDL, HDL-cholesterol, tryglicerides, serum folate, B12 Vitamine, homocysteine, Haemoglobine, creatinine and platelets, in order to study the differences and the effect of supplementation with folic acid, B12 Vit. and iron. The levels of tryglicerides were higher in both groups of twin pregnacies (p>0.001), but the levels of cholesterol remain similar. Serum folate concentrations were higher in the groups of twin pregnancies ($p < 0.001$). The rest of levels studied were similar in the 3 gropups. The supplementation following the ACOG and SEGO recommendations seems to be effective in controlling the values of LDL, HDL-cholesterol, serum folate, B12 Vit., homocysteine, Haemoglobine, creatinine and platelets. Only the levels of tryglicerides appear unaffected by the supplementation.

GENETIC FACTORS MAY CONFOUND THE ASSOCIATION BETWEEN SERUM ALANINE AMINOTRANSFERASE AND INSULIN RESISTANCE. A STUDY IN A HEALTHY DANISH TWIN POPULATION

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Non-alcoholic fatty liver disease is related to increased risk of diabetes and cardiovascular disease. Increased concentration of serum liver enzymes is often used as surrogate measures of fatty liver and is associated with increased body mass and insulin resistance. However, also smaller studies among young adult or elderly twins suggest that also genetic factors contribute to the variation in liver enzymes. The aim of this study was to determine whether the liver function enzyme alanine aminotransferase (ALT) was associated with body fat % and insulin resistance and to test whether genetic factors in general confounds the associations. From 2010 to 2012, we re-investigate a Danish twin sub-cohort (n = 756 twin pairs), named GEMINAKAR established in 1999-2001 within the population-based Danish Twin Registry. Using a mobile examination unit we have so far visited more than 800 twins between 28 and 77 years of age. A physical examination, including measures of bodyweight, waist and thigh circumferences has been carried out. Fasting blood samples and various health questionnaires have been collected. Body fat % was estimated using bio-impedance measures (Bodystat Ltd). Plasma levels of glucose (FPG), insulin (FPI), high density and low density lipoprotein cholesterols and serum levels of ALT were all measured in a central laboratory using routine methodology. In this preliminary report, a total of 544 subjects (235 complete pairs) from whom we have complete information on ALT, insulin, body fat %, demographic and anthropometric characteristics were included in the analyses. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) and calculated as FPI × FPG / 22.5. Male twins had significantly higher ALT and lower body fat % ($p < 0.0001$) compared to female twins (median value 31 U/L, 25-75 percentile range [24-41] vs. female, 21U/L [17-27]; male body fat% 21.4% [17.4 - 24.6] vs. female 32.8% [28.3 - 37.4]). HOMA-IR was not different between sexes. The intra-pair correlation of ALT was higher in MZ twin pairs (corr. 0.55 95% CI [0.39; 0.66]) than DZ twin pairs (corr. 0.24 95% CI [0.03; 0.42]). This indicates that genetic factors contribute to the variation of liver enzymes concentrations observed in the population. In multiple regression models both body fat % (ß-coeff. 0.48, 95%CI [0.17 - 0.79]) and HOMA-IR (ß-coeff. 2.84 95%CI [0.76 - 4.92]) were independent of age and sex associated with ALT. We used the fixed twin model to examine whether observations between ALT, body fat % and insulin resistance were influence by genetic factors. Based on the preliminary results, we suggest that the association between ALT and body fat% adjusted for HOMA-IR, age and sex is not determined by genetic factors, whereas the association between ALT and HOMA-IR is genetically determined. However, due to the present low number of participants the conclusion is very cautious and may change when all twins are included.

PERINATAL SWITCH IN TWIN ORDER BETWEEN THE LAST PRENATAL ULTRASOUND AND BIRTH

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Background: It is often assumed by obstetricians, neonatologists and parents alike that the prenatal nomenclature used to identify twins on ultrasound is equally applicable after their delivery. The aim of this study is to use a large

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regional twin ultrasound database to validate the effectiveness of a scan just prior to birth in predicting twin birth order. *Methods:* The twin ultrasound database from the Southwest Thames Obstetric Research Collaborative (STORK) was used to identify all examination carried out within four weeks of birth. The likelihood of a perinatal switch was evaluated by matching discrepancies in ultrasound estimated fetal weight (EFW) with birth weight discordance. The twin perinatal switch rate estimated from twin sizes was confirmed by comparing pre and post-natal order in discordant sex twins. *Results:* 2103 twin pairs with ultrasound EFW and birth weights were assessed. The anticipated birth order according to the ultrasound scan changed in 753 (35.8%) twin deliveries. The perinatal switch in discordant sex twins (42.1%) was not significantly different. *Conclusion:* Approximately one-third of twin pregnancies switch order between the last scan assessment and delivery whether determined by size or sex discordance. The high likelihood for a perinatal switch should be borne in mind not only by parents, but by physicians when delivering twins discordant for anomalies that are not evident on external examination.

TWIN BIRTHWEIGHT DISCORDANCE AND ADVERSE PREGNANCY OUTCOME: THE STORK MULTIPLE PREGNANCY COHORT

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Background: Twin birthweight discordance is considered to be an important determinant factor for poor perinatal outcome. Despite this association, the degree of birthweight discordance that justifies delivery is not yet established. The aim of this study is to ascertain the nature of the relationship between birthweight discordance and adverse perinatal outcome in twin pregnancy. Methodology: A retrospective study of all twin pregnancy births of known chorionicity from a large regional of 9 hospitals over ten year period. Birthweight discordance was related to adverse perinatal outcome obtained from a mandatory national register (CMACE). Birthweight discordance cut-offs to predict adverse perinatal outcome were evaluated through receiver operating characteristic curves (ROC). Logistic regression analysis was performed to evaluate the importance of chorionicity and birthweight discordance in determining adverse perinatal outcome. *Results:* A total of 2972 twin pregnancies (543 monochorionic and 2429 dichorionic) were delivered after 26 weeks' gestation between 2000 and 2009. Birthweight discordance had an area under ROC curve of 0.71 (95% CI = 0.63 to 0.79) in the prediction of stillbirth and early/late neonatal death. Although birthweight discordance was more prevalent in monochorionic twins, chorionicity itself did not significantly influence adverse perinatal outcome after 26 weeks gestation. Birthweight discordance of = 25% occurred in 10% of pregnancies with a 45% sensitivity (95% CI 0.32 to 0.58) for stillbirth and neonatal death. *Conclusion:* Birthweight discordance pays an important role in determining the outcome of twin pregnancies irrespective of the chorionicity. The data supports the use of a 25% birthweight discordance cut-off for the prediction of perinatal and neonatal death.

THE INFLUENCE OF CHORIONICITY ON MISCARRIAGE AND EARLY PERINATAL LOSS IN TWIN PREGNANCIES: THE STORK MULTIPLE PREGNANCY COHORT

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Background: Monochorionic (MC) twins are at increased risk of fetal loss in early pregnancy as a consequence of twin-twin transfusion syndrome (TTTS). Previous small studies estimated that the cumulative MC loss rate was >12% by 24 weeks' gestation in an era prior to routine fetoscopic laser treatment for TTTS. The aim of this study is to compare fetal loss rates between MC and DC twins in an era of invasive treatment of TTTS. *Methods:* A retrospective study of all twin pregnancy births of known chorionicity from a large regional of 9 hospitals over ten year period. Ultrasound data was matched to hospital delivery records and a mandatory national register for perinatal losses (CMACE). Cumulative fetal and perinatal loss rates for MC and DC twins from 14 to 26 weeks gestation were analysed using Kaplan-Meier survival curves. *Results:* 3133 twin pregnancies (599 MC and 2534 DC) were included in the analysis. The total fetal loss rate in MC and DC twins were 6.3% (75/1198) and 0.9% (44/5068), respectively (OR 0.14, 95% CI 0.09 to 0.20). The cumulative rate of loss in MC twins rose significantly from 0.5% at 14 weeks' gestation up to a plateau of 6.3% at 24-26 weeks' gestation, whereas there was no significant change in DC pregnancy loss rate (0.5%) over this period. *Conclusion:* Cumulative fetal loss rate before 26 weeks' gestation in MC twins has almost halved compared to the rates available in the published literature. Early detection and prompt treatment of complications in MC twins is likely to have contributed to this improvement in twin pregnancy outcomes.

PERINATAL OUTCOME OF TWIN PREGNANCIES AFTER ASSSISTED REPRODUCTION AND SPONTANEUS CONCEPTION

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This study was conducted at University Clinic of Obstetrics and Gynecology, Skopje, and its aim was to compare perinatal outcomes of twin pregnancy achieved after IVF and AI on one side, and twin pregnancies after IVF and AI demand greater care than twin pregnancies after spontaneus conceptions. Statistic evaluation of perinatal outcomes between a group of 67 twin pregnancies after asssisted reproduction (10 IVF and 57 AI) and a group of 68 twin pregnancies after spontaneus conception delivered from September 2005 to

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September 2009. The following parameters were investigated: symptoms of imminent abortion and preterm delivery, bleeding during pregnancy, preterm rupture of membranes, performed cerclage, and occurence of preeclampsia and maternal gestational diabetes. We also evaluated pathologic ultrasound findings (fetal growth irregularities and amniotic fluid amount) and analyzed the delivery methods, delivery week, birthweight, Apgar score in newborns, differentiation of birthweight in sublings, and perinatal mortality. There are significant differences in the method of delivery ending between the group of twin pregnancies after IVF and AI and the group with spontaneus conceptions: there were more cesarean sections in the group of twin pregnancies after IVF (100%) and AI (74%) then in the group with spontaneus conception (45%). Besides, it is important to note the difference in cerclage frequency between the studied groups. Among the twin pregnancy after IVF, cerclages were performed in all cases(100%), and in 35 (61%) of AI cases, and 25 (37%) women from the group of twin pregnancies after spontaneus conceptions had cerclage performed. All cerclages, in both studied groups, were performed between 19 and 20 weeks of gestation. Therefore, there were no differences in gestational age at the time of cerclage. Mean Apgar score was 8/9 in IVF/AI group and 7/8 in spontaneous coneption group. *Conclusion:* The retrospective analysis of pregnancies and deliveris and neonatal outcome found a difference in mode of pergnancy ending. The Apgar score was greater in the group of IVF and AI in comparasion to the group of spontaneus conceptions.

OBSTETRIC AND NEONATAL OUTCOMES OF THE SURVIVING TWIN AFTER FETAL DEATH OF THE CO-TWIN

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Introduction: Twin pregnancies are increasing in the last decades mainly due to assisted reproductive techniques. These pregnancies are associated with an increase number of fetal complications as the death of one twin.

The objective of this study was to review the outcome of twin pregnancies complicated by single fetal intrauterine death and how it can increase morbidity to its co-twin.

Patients and Methods: A retrospective analysis of the fifty six twin pregnancies complicated by single fetal intrauterine death in the second or third trimester in La Paz Hospital, Madrid, Spain, from January 1999 to December 2011.

Of the total amount of 2200 twin pregnancies attended in our centre, 56 were complicated by single fetal intrauterine death (2.5%). In 68,7% of the cases we found several maternal complications, such as 12,2% of preeclampsia and 12% of coagulopathies. As for the dead foetus, there was a 47% of malformations, a 19,6% of intrauterine fetal growth restriction and there was a 9,8% of cases complicated by Twin-Twin Transfusion Syndrome. In the group of the surviving co-twin, 9,8% developed intrauterine growth restriction, 9,8% oligohydramnios and 9,8% Doppler alterations. There was a high risk of prematurity with 43,1% of the births under 34 weeks and 13,7% under 30 weeks of pregnancy. The percentage of caesarean was 64,7%. There was 3 cases of co-twin died intra-uterus, and one more died postpartum. The neonatal complications of the surviving co-twin were: 31,3% multifactorial anemia,21% respiratory distress, 17,6% hyaline membrane disease, 7,8% intraventricular hemorrhage, 7,8% patent ductus arteriosus, 7,8% Twin-twin transfusion syndrome anemia, 5,8% retinopathy, 5,8%necrotizing enterocolitis, 5,8% polycythemia, 3,9% perivetricular leukomalacia and 3,9% renal failure. A 10% of the newborns had some kind of neurological disability. A 49,2% of newborns had sequelae resulting from prematurity. Conclusions:It seems that surviving co-twin prognosis is mainly compromised by prematurity and its consequences. There should be more prospective research to inform decision making and evaluate and control the potential maternal and fetal risks.

BIRTH WEIGHT, GESTATIONAL AGE AND ZYGOSITY AWARENESS IN FEMALE TWINS AT REPRODUCTIVE AGE

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Introduction: Twin data are frequently used in research on the fetal origins of adult disease (Barker-hypothesis). Nowadays, a number of studies are looking at the impact of neonatal outcomes on the health status in later life. A large amount of these studies work with self-reported information. In this study we compared self-reported perinatal data of female twins at reproductive age with the objective information registered at birth. Methodology: Since 1964, perinatal data of all twins born in the East Flanders province of Belgium are registered in the East Flanders Prospective Twin Survey (N = 8600). Zygosity of all these twins is assessed by placentation, blood group - and DNA - examination. A questionnaire on demographic variables, reproductive aspects and health in general was sent to all female twins, born in the years 1964, 1965, 1970, 1975, 1980 and 1985 (N = 327 individuals). Of these women, 203 responded to our mail (60%) of which 166 (49%) agreed to participate. Women were asked whether they knew their birth weight, gestational age at birth and their zygosity. We compared the indicated birth weight, gestational age and zygosity with the perinatal data from the twin registry. *Results:* Twelve women (7.2%) stated they did not know their birth weight, 59 women (35.5%) were not sure about their birth weight and 94 women (56.6%) expressed they knew their own birth weight with certainty. Of the latter group, 31 women (19%) indicated a birth weight that was deviant from the birth weight in the

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perinatal registry (range -650 grams- 1000 grams), 10 of the women who were sure about their birth weight confused their own birth weight with that of their brother or sister. For another 10 of these women, self-reported birth weight was more or less in line with birth weight registered in the twin registry; 43 of these women (25.9%) indicated their birth weight exactly. Twenty-three women (13.8%) declared that they were not aware of their mothers duration of gestation, 44 women (26.5%) indicated that they had a rough idea of the gestational age and 78 women (47%) claimed that they knew exactly at which gestational age they were born. Of the latter group, only 27 women indicated a birth weight that was similar to the one registered in the perinatal data registry. Seventeen out of forty-four women who expressed they were not sure about the gestational age, reported a similar gestational age as within the perinatal records. As for zygosity, 95% of women marked a similar zygosity as was registered in the perinatal database. Seven women (4.2%) did not know their zygosity and 2 women were mistaken about their zygosity. *Conclusion:* Even when female twin-members at reproductive age declare to be sure about their birth weight or gestational age at birth, only a minority of these women is aware of their exact birth weight or duration of gestation. Self-reported perinatal parameters are unlikely to be reliable in research. However, this is not the case for zygosity. Ninety-five percent of women were well-informed on their zygosity status.

INTERNALIZING AND EXTERNALIZING SYMPTOMS AND ALCOHOL USE: A STUDY ON ADOLESCENT ITALIAN TWINS.

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During the developmental period of adolescence, defined as age 10-19 years, alcohol is certainly the most frequently used substance. The use and abuse of alcohol among young people has been associated with increased risk of tobacco and drug consumption, academic failure, road accidents, juvenile delinquency, pregnancy and sexually transmitted disease. Across the whole European Union, more than 90% of 15-16 year olds have drunk alcohol at some point of their life and 13% of them have been drunk more than 20 times. The average initiating use for 15-16-year-olds is 12.5 years, and the average amount drunk on a single occasion is more than 60 g of alcohol in northern Europe, and nearly 40 g in southern Europe. The association between internalizing and externalizing symptoms and alcohol use during adolescence has been highlighted in various studies, even thought the causes of this association are not completely clear. The study of internalizing and externalizing symptoms has a long and successful tradition in psychology and clinical psychiatry. Child psychopathology research distinguish between externalizing, or disorders characterized by behavioral disinhibition (disruptive behavior disorders of childhood), and internalizing or disorders characterized by negative mood states and inhibition (depression, anxiety). The purpose of the present work was to study the relationship between the presence of internalizing symptoms and alcohol use as well as between externalizing symptoms and alcohol use in adolescents. Moreover, using a twin study design, we aimed to evaluate the weight of genetic and environmental components on the co-occurrence of these traits. The research was conducted on a group of 278 twins (118 males, 160 females; 60 monozygotic and 79 dizygotic twins pairs) ranging in age from 14 to 18 years old (mean = 15.54; ds = 1.17). The internalizing and externalizing symptoms of twins were assessed via a self-report questionnaire: Youth self-Report 11-18 (Achenbach, 1991, 2001). In the questionnaire, youths rate themselves for how true each item is in the present time or was within the past six months, using a three-point response scale; alcohol abuse was assessed with a self-report questionnaires. The results of our study indicate that both genetic and the environmental factors, particularly those not shared, favor the onset of both internalizing (males: A = .60, E = .28; females: A = .49; E = .45) and externalizing (males: A = .45, E = .29; females: A = .40; E = .48) symptoms. Regarding the behavior of alcohol consumption, , under the best model, genetic component was .38 and non-shared environmental component appears to be the most effective on the occurrence of such conduct (E = .62). Finally, we found a strong genetic component that explains the relationship between externalizing symptoms and alcohol consumption (A = .92) while no significant correlation was detected between internalizing symptoms and alcohol use.

BREAST FEEDING TWINS, TRIPLETS AND MORE

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Breast milk is the best nutrition for all babies and it is particularly important for twins who are more likely to be born preterm and of low birth weight. The practicalities of breastfeeding twins and more can seem overwhelming for mothers and professionals also need to be well informed about the additional support and information they require. The Multiple Births Foundation (MBF) and National Perinatal Epidemiology Unit undertook a project to review the literature on feeding twins, triplets and more and produce guidance for professionals and information for mothers on all aspects of feeding multiple birth babies. There is a paucity of literature on infant feeding of multiple birth babies but there is evidence that the rates and duration of breastfeeding are lower for multiples than singletons. A systematic review looking at how many multiples are breast fed compared with singletons found that between 12% and 64% of multiples were receiving some breast milk and between 1% and 18% were exclusively breastfed at 3–4 months. Evidence from one UK study found that in babies admitted to Neonatal Units 20% of twins compared with 33% of singletons were breastfed at 3 months and of those not admitted 19%

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twins and 40% singletons were being breastfed at 3 months. Studies on techniques for feeding twins are also lacking but those that are available do not always differentiate between feeding directly from the breast and receiving expressed breast milk. A report giving an overview of the care received by mothers of multiples before and after birth using data from national surveys in the UK found that midwives were less likely to discuss infant feeding antenatally (70% compared with 76%) and fewer mothers exclusively breast fed their babies in the first few days (32% compared with 58%). Our experience and anecdotal feedback from mothers at the MBF suggests that many mothers of twins want to breast feed but are often deterred by a negative attitude before birth and a lack of support postnatally. The evidence based guidance for health professionals gives key general principles followed by sections with detailed advice and good practice points which are specific to multiples. All aspects of feeding including expressing milk and breast feeding preterm babies are included. With the parent information reflecting the guidance for professionals mothers should receive accurate, consistent evidence based information from all healthcare professionals. Both booklets were distributed to all maternity units in the UK in 2011 and a survey is in preparation to assess their use and effectiveness.

REDUCING IATROGENIC TWINNING: THE UK EXPERIENCE

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Multiple births are the single biggest risk to the health and welfare of children born following in vitro fertilisation (IVF) and other fertility treatments. The risk of obstetric complications in a multiple pregnancy is increased for the mother and mortality and morbidity is higher for the babies as a result of preterm birth and low birth weight.. In the UK the rate of triplets has significantly decreased since a two embryo transfer policy was introduced in 2001 but the twining rate has been rising. Crucially multiple pregnancy following IVF is a risk that can be avoided by transferring one embryo for those women most likely to get pregnant and therefore most at risk of having twins. A group comprising professional bodies, patient groups and the Human Fertilisation & Embryology Authority (HFEA), the UK regulatory body, published a consensus statement in 2007, and reviewed in 2011, making recommendations about how this problem should be addressed. Limiting the number of embryos transferred in IVF cycles is an effective way to reduce multiple pregnancies and elective single embryo transfer (eSET) is widely considered best practice but the extent to which this is used varies in different countries. Following the Report of the Expert Group on Multiple Births after IVF (2006) the HFEA, implemented a new policy which aims to reduce multiple births after IVF to 10% in stages over a period of years. The HFEA decided to set a maximum multiple birth rates that clinics should not exceed which would be lowered each year. By law all centres offering IVF services must be licensed by the HFEA and they are now required to have a multiple births minimisation strategy setting out how they will succeed in reducing their multiple birth rates to this level. This allows centres the flexibility to develop their own eSET strategy which is appropriate for their patients. On a national level, the change in practice is promoted by a multi –disciplinary stakeholder group which includes representatives from professional and patient organisations and works with the HFEA. The Multiple Births Stakeholder Group has developed tools to improve clinical practice and information for patients and healthcare professionals about the risks of multiple births. A website, www.oneatatime.org, ensures easy access to all these resources including the latest data and research. The multiple pregnancy rate has decreased to around 19.9% and elective single embryo transfers have risen from 4.8% in 2008 to 16.3% in 2011 with the greatest increase in younger women. The overall pregnancy rate has remained steady at around 30%. The HFEA have recently decided to set the next and final maximum multiple births rate target at 10%, to be brought in from October 2012.

THE GENESIS OF MULTIPLE GESTATION: HOW, WHY AND WHEN

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Because of their origin, twins are generally recognized as being a valuable resource for research not only into multiple birth itself, but importantly in understanding the roles of genetics and environment in development. Indeed, comparing monozygotic twins, who are genetically identical, with dizygotic twins who share half of their genes permits the experiment of 'nature versus nurture'. Twins are not a homogeneous group. According to zygosity and chorionicity essential differences exist. Spontaneous dizygotic twinning is clearly associated with multiple ovulation, is heritable and suggested to be an index of high fecundity. On the contrary, causes of monozygotic twinning remain elusive. According to the time of the zygotic division 3 subtypes of monozygotic twins can be recognized: the dichorionic-diamnionic pairs (early, before the 4th day after fertilization), the monochorionic-diamnionic pairs (intermediate, between the 4th and the 7th day post fertilization) and the monochorionic-monoamnionic pairs (late, after the 8 day post fertilization). According to this early embryological event (before and just after implantation of the embryo) differences exist on important biological phenomena's: sex proportion at birth, X-inactivation and other epigenetic mechanisms. As a result of the modern methods of treatment of infertility the rate of twin births has almost doubled in industrialized countries. Zygosity and chorionicity distribution is totally different in spontaneous and iatrogenic twins and, contrary to the common belief, not all iatrogenic twins, whether conceived after assisted

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reproduction technology or artificial induction of ovulation only, are dizygotic. *Methods:* most of the data come from the East Flanders Prospective Twin Survey (more than 8500 twin pairs and 237 triplet sets), a population-based registry of multiples births in the province of East Flanders (Belgium) with known zygosity and placentation.

TIME TRENDS IN THE NATURAL DIZYGOTIC TWINNING RATE

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Background: The natural dizygotic twinning rate has been proposed as a reliable and useful measure of human fecundity, if adjusted for maternal age at twin birth. The aim of this study was to analyse age-adjusted trends in natural dizygotic twinning rates over the past 40 years using data from the 'East Flanders Prospective Twin Survey'. *Methods:* Study of 4835 naturally conceived twin pregnancies between 1969 and 2009 from the population-based Belgian 'East Flanders Prospective Twin Survey'. Age-adjusted trends of the incidence of natural dizygotic twin pregnancies were calculated using a generalized linear model with Poisson distribution. *Results:* Both the natural dizygotic twinning rates and maternal age at twin birth increased in a linear fashion from 1969 to 2009. When age-adjusted we found that the trend in the natural dizygotic twinning rate was stable during the whole time period. *Conclusions:* According to our population-based data and after age-adjustment a stable natural dizygotic twinning rate could be observed in the last four decades. Under the assumption that spontaneous dizygotic twinning rate is a sensor of fecundity, this indicates a stable population 'high' fecundity.

FETAL AND MOTOR DEVELOPMENT IN TWINS

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The second half of the 20st century saw the dominating theory that all prenatal motility was originated from known or unknown stimuli overthrown. Sonographic examination of the fetus in its own intra-uterine environment showed that spontaneous motility emerged as early or earlier than elicited movements in fetuses exteriorized from the uterus. The obtained knowledge on motility and posture in singletons paved the way to look into more detail into developmental aspects in twins. Do fetal twins reach developmental milestones at the same age as singletons? If changes in these milestones can be demonstrated how well do we understand whether they are adaptations to e.g. interfetal tactile stimulation or different spatial environment such as less fixation in pelvic inlet resulting in more frequent positional changes or shorter umbilical cord than in singletons. Another question is whether twin specific intrauterine adaptations to motility and posture are transient or persistent after birth? For clinical practice it is of importance if monitoring is influenced by twinning for example the duration of observation time for sonographic motor evaluation, cardiotocography, biophysical profile. Does maternal information on presence of fetal motility of her twins support the detection of the fetal movements to detect the fetus at risk? An overview is presented to enhance our present knowledge and applicability of fetal motor and postural assessment in twins.

IS THERE A MASCULINIZING OR FEMINIZING EFFECT ON FOOD INTAKE AND BODY SIZE MEASUREMENTS IN OPPOSITE-SEX TWINS?

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Background: Even though sex differences in body weight, body image, eating habits and eating disorders have been attributed to psychosocial factors, biological factors operating in utero may also play a role. Recent studies suggest a masculinizing effect on female intrauterine development in opposite-sex twin pairs, as well permanent effects to the central nervous system. *Objective:* This research aims to assess the influence of prenatal sex hormone exposure on body size and body image, eating habits and eating disorders by comparing dizygotic (DZ) opposite-sex and same-sex twins. *Methods:* Analyses were conducted using a sample from the Quebec Newborn Twin Study; this data was collected from a birth cohort of 675 twin pairs (1350 twins) born between 1996 and 1998. Participants included 190 dizygotic same-sex (SS) girl twins, 362 DZ opposite-sex (OS) twins and 192 DZ same-sex boy twins. Outcomes included food intake (macronutrients), eating behaviours and anthropometric measures from birth to 9 years of age. Intraclass correlation coefficients were first compared between for DZ opposite-sex and same-sex twins. Hierarchal linear models were then used to examine mean differences in outcomes across opposite-sex and same-sex twins. *Results:* Preliminary analyses indicate a potential male intrauterine influence on the female co-twin. For example, the percentage of girls who had a poor body image and were normal or under-weight, based on CDC body mass index reference, was higher in DZ SS twin girls than girls in DZ OS twin. Almost 42% of DZ OS girls who were normal or under-weight body mass index at 9 years old reported that they were dissatisfied with their body image but only 5.6% perceived themselves as overweight or obese. In contrast, the percentages reported by DZ SS twin girls were 46.15% and 7.9%, respectively. *Conclusion:* Investigating differences in body image, food intake patterns, dietary intake, physical activity and anthropometric measures between opposite-sex and same-sex twins may help us to better understand eating disorders and the origins of obesity in childhood.

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GENETIC CONTRIBUTION TO FOOD INTAKE AND OBESITY IN CHILDHOOD: THE QUEBEC NEWBORN TWIN STUDY

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A better understanding of the influence of genetics on food intake, as it relates to body weight in childhood, is essential for the long term prevention of obesity. However, our understanding of genotype-environment interactions in the development of obesity, defined as when the response of a phenotype (e.g. fat mass) to an environmental change (e.g. dietary intervention) is modulated by an individual's genotype, requires further expansion. The Quebec Newborn Twin Study (QNTS) is a population-based birth cohort of 675 twin pairs, followed longitudinally from birth to 15 years of age. At 9 years of age, a nutrition survey was conducted, providing a unique opportunity for the study of the genetic contribution to food intake and its influence on body mass index in childhood. Using data obtained from this cohort, we examined children's energy and macronutrient (carbohydrate, protein, fat) intakes and body size, exploring the etiology of these phenotypes and behaviours with respect to their genetic and environmental components. The analyses were conducted using structural equation modeling techniques, to evaluate the magnitude of the inherited (genetic) versus environmental (shared or unshared) components involved in differences in food intake (for the day and by meals and snacks) and body weight in childhood. The results indicate that the percent of daily energy from lipids is under genetic influences, and the percent of daily energy from carbohydrates and proteins is under environmental influences. A sex-limited model indicates differences between boys and girls for different nutrients at different meals and snacks. This research provides new insights into the influence of the obesogenic environment in childhood. The results of this study will contribute to the development of nutrition recommendations and public health interventions in childhood, adapted to the short- and long-term prevention of obesity at the level of the population.

TRIPLETS: FETAL AND NEONATAL OUTCOMES

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Objective: To review the fetal and perinatal complications in triplet pregnancies. *Methods:* Retrospective study of triplet pregnancies treated in the Obstetrics Department of La Paz Hospital from January 2000 to May 2010. *Results:* Review of 147 triplet pregnancies with a prevalence of 1 in 640 deliveries (0.15%). Mean maternal age was 34.3 years (rank: 26-50 years). Of the pregnancies, 79% were achieved using fertilization techniques, 73% were in vitro fertilization. Trio zygosity: trichorionic triamniotic 85%, bichorionic triamniotic 10% and monochorionic triamniotic 5%. Out of 402 fetuses, 37 had the following complications: 19 (4.7%) growth retardation or oligohydramnios, 14 (3.4%) intrauterine death, 3 (0.6%) major malformations and there was one case of twin to twin transfusion. The majority (88.9%) of these complications appeared in pregnancies achieved using fertilization techniques. The average duration of gestation was 33 weeks: 8% were born before 28 week-gestation, 30% between 28 and 32 weeks and 62% after 32 weeks. The average birth weight was 1906g (470-2730g). In 29 cases (7.3%) arterial pH was less than 7.20. Some form of resuscitation was required by 60% of newborns and 46.5% were admitted to the intensive care unit. There were no significant differences in neonatal outcomes between the immediate first, second and third newborn. *Conclusions:* The number of triplet pregnancies has increased significantly because of reproductive assistance techniques. The risk of neonatal mortality and morbidity is high in triplet pregnancies. Preterm delivery is the most relevant complication. Adverse neonatal outcomes are related to the high prematurity of these gestations.

PROGESTAGENS IN MULTIPLE PREGNANCY: A RE-EVALUATION

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Multiple pregnancies contribute disproportionately to preterm births (PTB) Overall 52.2% of multiple births deliver before 37 weeks and 10,7% before 32 weeks1. In the USA, the rate of PTB among triplet exceeds 92% and the rate of very PTB exceeds 36%2. In the USA, 57% of twins are born with low birth weight, compared to 6% of singletons3. As yet, no treatments have been identified that can prevent PTB in multiple pregnancy. Two large randomised controlled trials examining whether antenatal progesterone (P) could decrease PTB in twins, have been published, one from the USA4 and one from the UK5. Rouse et al. randomised 661 women with twin pregnancy to weekly intramuscular injection of 250 mg 17-hydroxyprogesterone caproate (17-OHPC) or placebo from 16-20 weeks to 34+6 weeks. There was no effect on the primary outcome of delivery or fetal death before 35 completed weeks (RR: 1.1; 95% CI: 0.9-1.3). Norman et al. randomised 500 women with twin pregnancy to 90 mg vaginal P or placebo daily from 24 to 34 weeks' gestation. Again, no effect was seen on the primary outcome of delivery or intrauterine death before 34 weeks' gestation (OR: 1.36; 95% CI: 0.89-2.09). In both trials, a non-significant increase in intrauterine death was seen in the treatment group. There is one published trial examining the effect of P on triplet pregnancy6, including 134 women, and again no reduction in PTB before 35 weeks was found (RR: 1.0; 95% CI: 0.9-1.1). A trial of P in women with short cervix on ultrasound included 24 women with twins7. In this study 24 women with twin pregnancy and cervical length <15 mm at 20-25 weeks

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were randomised to 200 mg micronized vaginal P or placebo daily from 24 weeks to 34 + 6 weeks gestation. This trial found a trend for a reduction in PTB less than 34 weeks (OR: 0.49; 95% CI: 0.09-2.53). This has not been confirmed in larger studies, so it remains uncertain if P may be of benefit in women with multiple pregnancy with a short cervix. Two double-bind randomised clinical trials have now been published. Combs et al randomised 160 women to 17-OHPC and 80 to placebo: prophylactic treatment with 17-OHPC did not prolong gestation or reduce neonatal morbidity3. Klein et al, in the PREDICT study, concluded that in high-risk twin pregnancies, vaginal micronized P treatment does not significantly improve outcome. A subset of patients from a IPD meta-analysis (in press) focused on women with a twin gestation and a short cervix. In this particular group, vaginal progesterone reduced the rate of preterm birth at <33 weeks by 30% and significantly reduced the composite neonatal morbidity/mortality of twins. A confirmatory study using available progestagens is urgently needed to confirm these data.

MONOCHORIONIC TWIN PREGNANCIES COMPLICATED BY SIUGR AND NEONATAL OUTCOME: OUR EXPERIENCE

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Introduction: Selective intrauterine growth restriction (sIUGR) in monochorionic (MC) twins is associated to an important increase in perinatal mortality and morbidity. Classification of sIUGR into 3 types, according to the characteristics of umbilical artery diastolic flow in the IUGR twin, offers the possibility to distinguish between specific clinical and prognostic groups. sIUGR type 1 presents a normal diastolic flow and a generally good outcome. sIUGR type 2 is characterized by persistently absent or reversed end-diastolic flow, and is associated to intrauterine fetal death (IUFD) as well as preterm delivery. sIUGR type 3 is defined by intermittently absent or reversed end-diastolic flow (iAREDF) and is associated to sudden IUFD of the smaller twin and neurological damage in the bigger twin. Materials and *Method:* We analyzed retrospectively the obstetric management and neonatal outcome of our MC biamniotic (BA) twin pregnancies, who were followed by our Twin Pregnancy Ambulatory from June 2010 until December 2011. MC pregnancies with sIUGR were classified into three groups, depending on the umbilical artery (UA) Doppler pattern: type 1, type 2 and type 3 (see introduction). Neonatal outcome data were obtained by consulting the database of the Department of Neonatology. *Results:* We considered 21 MC BA twin pregnancies. In 5 women the course of pregnancy was complicated by sIUGR, thus confirming the prevalence of 23% of this complication reported in the literature. Among these 5 pregnancies with sIUGR, 2 belonged to type 1, 1 to type 2 and 2 to type 3. From the other 16 pregnancies we selected 5 cases which did not show any maternal or fetal complication, thus representing the control group. The average gestational age at which delivery occurred was: 32 weeks for the affected group and 36 weeks for the control group. Among the 10 babies born from mothers of the control group 2 developed a mild distress respiratory syndrome (DRS), 2 had a mild periventricular hyperechogenicity and 4 developed jaundice. No serious neonatal pathology was observed. Among the 4 babies born in the group of MC pregnancies complicated by sIUGR type 1, we registered 1 case of intrauterine fetal death, 2 cases of mild periventricular hyperecogenicity and 2 cases of jaundice. The sIUGR type 2 pregnancy underwent a selective umbilical cord occlusion of the IUGR twin; the co-twin was delivered at 28 weeks and suffered from a severe DRS and intraventricular hemorrhage (IVH). Among the 4 babies born from pregnancies with sIUGR type 3 the following complications were observed: severe DRS (1 case), mild DRS (2 cases), IVH (2 cases), necrotizing enterocolitis (NEC) (1 case) and retinopathy (2 cases). *Conclusion:* Although the sample was quite restricted, our data seem to be in agreement with the literature confirming that newborns with sIUGR have the worst outcome, in particular twins with sIUGR and intermittently absent/reverse end-diastolic flow of umbilical artery (type 3).

A POPULATION-BASED ITALIAN TWIN STUDY ON BODY MASS INDEX

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Body mass index (BMI), the most frequently used measure of adiposity, has been instrumental in documenting the worldwide obesity epidemics during the last decades. Although the increase in the prevalence of overweight and obesity is thought to be mainly explained by environmental factors, particularly lifestyles, twin studies have consistently shown a large genetic contribution to normal variation of BMI, with heritability estimates of around 70-80%. A few twin studies have aimed at elucidating how the genetic end environmental architecture of BMI changes from young to late adulthood, and such studies are even lacking in the Italian population. In this study, we applied the twin design to a population-based cohort of more than 13000 twins, aged 18-65 years and enrolled in the Italian Twin Registry over the period 2003-20011, to estimate genetic and environmental components of BMI, and to investigate heterogeneity of these components by gender, age or geographical area (Northern, Central, Southern Italy). Data on height and weight were self-reported by the twins at the time of enrolment in the Registry. Prior to twin modelling, we log-transformed BMI data to approximate normality in distribution. Then, we estimated twin correlations by zygosity and gender, which we interpreted under the assumptions of the twin design. Furthermore, we applied structural equation models to estimate genetic and envi-

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ronmental components of BMI; we also tested for heterogeneity of these components by gender or geographical area, using stratification models, as well as by age incorporating this variable as a continuous moderator in the model. The prevalence of underweight was higher in females and that of overweight and obesity was higher in males; a higher percentage of obese subjects was observed in Central and Southern compared to Northern Italy, in agreement with previous reports in the Italian general population. Twin correlation estimates were 0.77 in monozygotic male-male and 0.76 in monozygotic female-female pairs, 0.43 in both dizygotic male-male and dizygotic female-female pairs, 0.27 in dizygotic male-female and 0.24 in dizygotic female-male pairs. The best-fitting structural equation model with age as a covariate included additive genetic and unshared environmental factors, which provided a heritability estimate of 0.77 for both males and females. Variance components were heterogeneous by gender, while no significant differences emerged by geographical area. When considering age as a moderator in the model, unshared environmental proportion of variance increased from young to late adulthood, to a lesser extent among females. In conclusion, this study confirms a large contribution of genetic factors and a negligible role of shared environmental influences in normal variation of BMI, and supports the heterogeneity of gene-environment architecture of adiposity across genders. Furthermore, the results are consistent with a cumulative effect of lifestyles from young to late adulthood and with a greater resistance of women to environmental burden.

A TWIN STUDY ON THE RELATIONSHIP BETWEEN AUTISTIC-LIKE TRAITS AND PERSONALITY

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Autistic-like traits refer to a triad of impairments that are characterized by difficulties with social interaction and communication, and by the presence of restricted and repetitive patterns of behaviour, interests, and activities. Although previous twin and family studies have uncovered a substantial heritability for autistic-like traits, it remains to be clarified whether genetic effects on these traits are independent of higher-order personality traits. The aim of this study is to investigate the relationship between autistic-like traits and personality, and to unravel the genetic and environmental origins of this relationship, by using a multivariate twin design. The sample includes around 270 adult twin pairs from the population-based Italian Twin Registry. Data collection was performed by self-administered mailed questionnaires: autistic-like traits were assessed by the Autism Spectrum Quotient (AQ), that encompasses 50 items corresponding to the five dimensions of social skills, attention switching, attention to detail, communication and imagination; personality was assessed with the 125-item version of the Temperament and Character Inventory (TCI-125), which provides information on four temperament dimensions (novelty seeking, harm avoidance, reward dependence, persistence) and three character dimensions (self-directedness, cooperativeness, self-transcendence). Gender- and age-adjusted twin correlations of AQ total and subscales scores with TCI-125 dimensions scores were estimated, and genetic and environmental correlations of these dimensions were derived by multivariate genetic modelling. Cross-twin/within-trait correlations for AQ total score were 0.46 in monozygotic (MZ) and 0.10 in dizygotic (DZ) twin pairs; for AQ subscales scores, the correlations ranged from 0.35 to 0.40 in MZ and from 0.07 to 0.28 in DZ pairs. Correlation estimates for TCI-125 dimensions scores ranged from 0.25 to 0.49 in MZ pairs and from 0.01 to 0.29 in DZ pairs. These estimates suggested that additive genetic and unshared environmental effects explain individual differences in each AQ and TCI-125 dimension. Phenotypic correlations between AQ total and TCI-125 scores were 0.20 (novelty seeking), -0.46 (harm avoidance), 0.29 (reward dependence), -0.04 (persistence), 0.46 (self-directedness), 0.38 (cooperativeness) and -0.08 (self-transcendence). Cross-twin/cross-trait correlations in MZ versus DZ were consistent with genetic effects common to AQ total and TCI-125 dimensions, except persistence and self-transcendence. According to the correlation pattern, the best-fitting Cholesky decomposition included additive genetic and unshared environmental factors. This model provided heritability estimates of 0.45 for AQ total score, and from 0.22 to 0.51 for TCI-125 dimensions scores; furthermore, the estimates of additive genetic correlation between AQ total and TCI-125 dimensions were 0.21 (novelty seeking), -0.49 (harm avoidance), 0.49 (reward dependence), -0.02 (persistence), 0.60 (self-directedness), 0.57 (cooperativeness), -0.17 (self-transcendence). In conclusion, our results draw attention to the phenotypic and genetic relationship of autistic-like behaviour with temperament and character, but at the same time provide support that studies on autistic-like dimensions are not redundant replicates of studies on higher-order personality dimensions, as the overlap between these traits seems to be moderate.

PERINATAL METABOLOMICS

V. Fanos

Metabolomics enables the parallel assessment of the levels of a broad range of metabolites and has been shown to have a great impact in investigation of physiological status, diagnosing diseases, measuring the response to treatment, discovering biomarkers, identifying perturbed pathways due to disease or treatment, functional genomics. Common analytical techniques applied to metabolomics are nuclear magnetic resonance spectroscopy, gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry.

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The most commonly used biological samples for metabolomics studies are urine, blood plasma or serum. Because of its characteristics and simple non-invasive methods of collection, urine is particularly suited for metabolomic analysis even in small babies. The use of non-invasive techniques is an essential requirement in neonatal medicine, especially in very preterm infants. Little is known about the overall metabolic status of the term and preterm neonate, but it can be currently assessed by metabolomic analysis of urine. Other important applications of metabolomic analysis of urine in the newborn could be the monitoring of postnatal metabolic maturation over time, the identification of biomarkers as early predictors of outcome, and the implementation and monitoring of a tailored management of neonatal disorders. The clinical management of neonates could be probably improved if more information about perinatal and neonatal maturation processes and their metabolic background were available. The metabolomics approach, together with transcriptomics and proteomics, will have substantial impact on development of diagnostics, therapeutics and drug development and may be an important new tool in neonatology.

HYPERTENSIVE DISORDERS OF PREGNANCY AND FETAL GROWTH IN TWIN PREGNANCIES: A REVIEW

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Hypertensive disorders are considered one of the most common diseases in pregnancy, being the main cause of maternal, fetal and neonatal morbidity and mortality. Women with twin gestation are at increased risk for the development of hypertensive disorders of pregnancy: the incidence of gestational hypertension and preeclampsia is double (12.9% vs. 6.3%) and three times greater (12.7% vs. 4.9%) respectively, in twin pregnancies compared to singleton ones. The presence of hypertensive disorders is associated with impaired fetal growth, especially in women with preeclampsia. A large study conducted in 2000 in U.S.A. by Sibai et al., comparing normotensive, hypertensive and preeclamptic twin pregnancies, observed that women with gestational hypertension showed the best outcome in terms of week at delivery, birth weight and rate of IUGR, while those with preeclampsia were associated with high rates of preterm birth and IUGR. An Italian study conducted by Ferrazzani et al., analyzing the outcome of twin pregnancies complicated by preeclampsia, showed that there was an higher rate of IUGR and inter-twin weight discordance in preeclamptic twin pregnancies if compared to normotensive ones. The comparison between the two studies shows that in twin pregnancies complicated by preeclampsia, despite a similar incidence of preterm delivery (67% in the USA vs. 62%. in Italy), the incidence of IUGR is greater in the Italian sample (40% vs. 12%). Similar results also arise from a comparison of American and Italian singleton pregnancies complicated by preeclampsia, with an incidence three times greater for preterm delivery (20% vs. 71%) and five times greater for IUGR (10% vs. 51%) in the latter. In conclusion, the frequency and severity of preeclampsia is not the same in the various countries of the world. There is a 'maternal preeclampsia' or 'late-onset preeclampsia', associated with better neonatal outcome (more frequent in USA) and a 'placental preeclampsia' or 'early-onset preeclampsia', associated with a worse neonatal outcome (more frequent in Italy). Italy is one of the countries with the lowest incidence of preeclampsia (1% vs. 7.4% in the USA), but there is an higher rate of IUGR associated (51% vs. 10%).

COGNITIVE AND EMOTIONAL DEVELOPMENT IN PRETERM TWINS

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Objective: To investigate cognitive and emotional-affective development in twins born preterm in order to determine any correlations with factors linked to prematurity (gestational age, birth weight), the influence of sociocultural level of parents on cognitive development and the quality of parent-child interactions and subsequent interpersonal relationships. *Methods:* we enrolled 29 preterm babies. Birth weight ranged from 1050 to 2220 g. Mean age at assessment was 6 years and 10 months. Cognitive and emotional development was evaluated at the start of elementary school. Developmental age and IQ were calculated. Tests Intellectual function was evaluated by the Revised Wechsler Intelligence Scale for Children (WISC-R, 15) which include a verbal scale to test theoretical-abstract ability and a performance scale for practical-concrete capacity. The Machover Human Figure Drawing Test was used to assess representation of the body as a dynamic structure evolving in time. Developmental age was assessed using the parameters of Goodenough. Affective development was evaluated with the Corman Family Drawing Test which examines children's experience of affective relationships and conflicts or fear in the family environment. *Results:* IQ was average in 72.41%, moderately high in 10.35%, high in 10.35% and moderately low in the other 6.89%. The distribution of scores in the verbal and performance scales showed 72.41% of children with verbal IQ higher than performance IQ and 27.59% the other way around. Individual subtests of WISC-R showed difficulty in planning capacity and prediction of events and situations, judgement and visual-motor coordination. The Machover Drawing test showed a mean developmental age of 5 years, which is slightly less than normal for the age group in question. An examination of the development of emotional-affective assessments showed adequacy in terms of graphics, formal and content than chronological age for 93.11% of the sample. The remaining 6.89% is inadequate. Comparison of IQ of children with their twin

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showed equal distribution of cognitive ability in 64.29% of cases and significant differences with respect to cognitive level in 35.71%. *Conclusion:* The present results suggest the need for better and constant support for families with twins. Supporting breastfeeding is the natural initial easier and available approach. Breastfeeding also allows mothers and their babies to get closer - physically and emotionally.

FEATURES OF GROWTH AND DEVELOPMENT OF BUILD, PHYSICAL STRENGTH AND MOVING ABILITY OF JUNIOR HIGH AND HIGH SCHOOL TWINS - ANALYSIS OF 959 STUDENTS OVER 9 YEARS

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Junior high and high school days are the time when development of mind and body is the most remarkable, and it can be said to be the transition period from child to adult. It is said that children grow taller at the highest rate; for girls when they are in the upper grades of elementary schools and for boys when in the junior high schools. They reach almost adults height level during the high school days. When secretion of the somatotrophin becomes active, growth of height is active too and it has a big influence on growth of mind and body. At this time physical strength and moving ability develop most remarkably and the effect of exercise is tremendous. Features of growth and development at the adolescence spurt have been reported by a lot of researchers. Similarities in build and moving ability between the twins have been also reported. However, reports about growth and development of build, physical strength and moving ability concerning twins at the adolescence spurt have been hardly given. Therefore, to make a research on that, based on the data of sports test accumulated over 9 years, I made a comparative analysis on build, physical strength and moving ability with the data of 959 twins, 149,567 junior high and high school students in the same age group and 6,100 T secondary education school students. As a result, for male twins both height and weight tend to be below the national average, while for female twins height is almost the same, and weight tends to be below it. However, physical strength and moving ability tend to be almost the same, or rather above the national average although some difference can be found according to the events for both male and female twins. In this study, the researcher received the Encouragement Award of Japan Society for Twin Studies on November, 2011.

GENES AND ENVIRONMENT IN CERVICAL CANCER: A CLASSIC TWIN STUDY

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Background: Whilst oncogenic HPV is the etiological agent of cervical cancer, neoplasia develops from only a small proportion of infections. Factors causing development of neoplasia are poorly understood. A classic twin study is a powerful approach to investigate potential host and environmental risk factors. Therefore we are studying monozygotic (MZ) and dizygotic (DZ) female twins where at least one of each pair has evidence of persistent HPV infection or a high-grade cervical abnormality (HGA) to compare concordance/discordance for these lesions within MZ and DZ pairs. *Method:* We obtain Pap smear history, HPV DNA from cytology smears, plus environmental and lifestyle factors as determinants for persistent HPV infection or progression to HGA (as a surrogate for cervical cancer) among women recruited via the Australian Twin Registry. Recruitment began in 2007 and is ongoing. Information on twin pairs concordant for persistent HPV infection or HGA will be used to assess heritability of risk by comparing within-pair concordance in MZ and DZ pairs. Twin pairs (both MZ and DZ) who are discordant for persistent infection or HGA will be studied to assess effects of specific environmental risk factors. *Results:* Currently, 1,892 twin pairs have been recruited. Of the 1,372 pairs (73%) with a complete Pap history, 197(14%) had HGA, 394 (29%) low-grade changes, whilst 781 (57%) recorded no abnormal Pap history. Of the 197 HGA pairs, 175 pairs were discordant for HGA (74 DZ, 98 MZ, 3unknown zygosity) and 22 pairs concordant for HGA (7 DZ, 15 MZ). HPV genotyping is in progress. *Conclusions:* This classic twin study has the potential to explain why some women exposed to HPV infection progress to l cancer while many women do not. The findings have important health implications despite the advent of successful HPV vaccines.

TELOMERE LENGTH IN PLACENTAS DECREASES WITH GESTATIONAL AGE AND IS DELAYED BY MULTIPARITY: A STUDY OF THIRD TRIMESTER LIVE-BORN TWINS

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Background: In contrast to the postnatal period, little is known about telomere length (TL) during prenatal life. There is still debate whether TL decreases with gestational age. There appears to be a rapid decline in leukocyte TL

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between 27 and 32 weeks of gestation, followed by a negligible decrease between 33 and 42 weeks. Change in placental TL remains unknown. It has been argued that telomere shortening does not seem to play a role in the senescence of the placenta. However, IUGR and preeclampsia are associated with shorter placental TL. Aim The aim of the present study was to examine whether there is a decline in placental TL during the third trimester of gestation for live-born twins. The contributions of sex, placental factors (including weight and fusion of the placentas) and maternal factors (including age, parity, smoking, alcohol use, hypertension, diabetes and SES) were taken into consideration. *Methods:* The study sample consisted of 336 live-born third trimester twins (209 pairs) from the East Flanders Prospective Twin Survey. DNA was isolated from placental tissue and TL was determined using a multiplex quantitative PCR (Q-PCR) method (Cawthon, 2009) and carried out in triplicate. Reference samples with known telomere length, i.e. 5.5 kB and 14.5 kB, were included into each run to enable estimation of TL in kB. TL was log-transformed to assure normality. Next, multilevel regression analysis was conducted. *Results:* Thirty five percent of the twins were born preterm and 63% twins were born at term. Placental telomeres in preterm twins were longer than in term twins: mean TL (SD) was 13.5 (6.3) kB for preterm and 12.2 (7.4) kB for term births. Median TL (IQR) was 12.0 (9.5 - 15.3) kB for preterm and 10.4 (8.9 - 13.2) kB for term births ($p = 0.002$). TL decreased with 0.2 kB per week of gestation ($p = 0.05$) from 14.6 kB at 25 weeks to 10.6 kB at 42 weeks of gestation. There was no difference in TL between boys and girls. Placental weights below the 10th centile tended to be associated with longer telomeres (13.3 vs. 11.5 kB; $p = 0.07$). Of the maternal factors, TL of a primiparous mother was shorter than TL of a multiparous mother (11.1 vs. 12.2 kB; $p = 0.02$). The lowest SES tended to be associated with longer TL whereas alcohol use during the third trimester tended to be associated with shorter TL (both $p < 0.15$). *Discussion:* We are the first to show that placental TL decreases during the third trimester of pregnancy. Telomere shortening does seem to play a role in the senescence of the placenta and multiparity seems to delay telomere shortening.

EXPLORING THE GENETIC AND ENVIRONMENTAL FACTORS UNDERLYING THE DSM-IV CRITERIA FOR CANNABIS USE, ABUSE AND DEPENDENCE

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To determine the number of genetic factors underlying the DSM-IV criteria for cannabis abuse and dependence we conducted structural equation twin modeling using eight cannabis criteria including a screening question in 1,762 personally interviewed male twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders who reported lifetime cannabis use. Unlike other substances of abuse, the best-fit twin model required one genetic and one unique environmental common factor along with criterion-specific unique environmental risks. Genetic factor scores derived from the single factor were then used to predict patterns of comorbidity, educational status and other historical/clinical features of cannabis use, abuse and dependence. The single dimension of genetic liability is consistent with the human literature based on phenotypic measurement modeling and has implications for gene-finding efforts in cannabis use disorders.

THE POWER OF NUMBERS – RESEARCH CAN MAKE A DIFFERENCE

T. Gillis

National Organization of Mothers of Twins Clubs

As a 501 (c) 3 organization, the National Organization of Mothers of Twins, Inc. (NOMOTC) centers much of its work around the primary goal of research and education projects that benefit multiple birth families. In support of this goal, NOMOTC has completed over 100 research studies focused around a wide array of the physical and psycho-social needs and challenges of multiples and multiple birth-parenting. NOMOTC maintains this culture of continuous research through a department dedicated to developing and completing research surveys as well as partnering with the scientific community so that members can participate in research studies that benefit the population in general as well as multiples and their families. *Purpose:* The purpose of this abstract is to share the organizational structure of the NOMOTC Research team, including job functions, duties, and how members collaborate to determine survey topics that will benefit its members. This session will also demonstrate the power of online tools that take the 'pain' out of tabulating survey results, and the power of social media in survey penetration to NOMOTC membership and to parents of multiples worldwide. Approach: The author will review NOMOTC's research organizational structure and describe the evolution of their research efforts. She will provide examples of various survey topics, including internal and outside research surveys and share results of some recent research, including results of NOMOTC's research on *Multiples and Autism* and *Intervention and Services of Multiple birth Children with Special Needs*. She will demonstrate the power of using surveys for all facets of a multiple-birth organization. Target audience: This abstract will benefit all multiple-birth organizations, as well as medical and research associates who would like to learn how to partner with multiple-birth organizations for future research projects.

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GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO LONG-TERM SICK LEAVE AND DISABILITY PENSION - A POPULATION-BASED STUDY OF YOUNG ADULT NORWEGIAN TWINS

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Exclusion from the work force due to long-term sick leave and disability pensioning (DP) is an emerging problem in many European countries. Until recently, there has been little interest in studying how genetic and environmental factors contribute to long-term sick leave and DP. In the two studies conducted to date, the heritability of DP was .24 and .49. However, the samples in these two studies were born between 1925 and 1958. Information on how genetic and environmental factors contribute to DP in younger samples is therefore lacking to date. The aim of the present study is to investigate genetic and environmental contributions to long-term sick leave and DP in a population-based sample of young adult Norwegian twins. Data for the current analyses comes from the Norwegian Institute of Public Health Twin Panel (NIPHTP), which has been linked to the Historical-Event Database (FD-Trygd) using unique identification numbers. Our sample thus consists of a detailed, longitudinal dataset on 7,710 young adult twins, born between 1967 and 1979, including annual information on long-term sick leave and disability pension from 1998 to 2008. Univariate twin models, allowing for both qualitative and quantitative sex differences will be conducted on both variables, in order to resolve to what extent the variation in the variables is due to genetic and/or environmental factors. Next, we will conduct bivariate analyses in order to determine to what degree genetic and/or environmental factors are shared between the two variables. The prevalence of DP in the period between 1998 to 2008 was 3.3% (253 individuals, of which 67 were males). The prevalence of having had long-term sick leave at all in the period between 1998 to 2008 was 62,3% (4804 individuals, of which 1515 were males). Preliminary results from univariate twin models suggest that DP is highly heritable, whereas long-term sick leave is moderately heritable. More detailed results will be presented at the conference.

PREVENTION OF PREMATURITY IN TWINS WITH ARABIN CERCLAGE PESARY

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Objective: Evaluation of the effectiveness of Arabin cerclage pesary in twin pregnancies. *Background:* Although advances in recent years, prematurity in twins and its complications especially in severe prematurity, remains a problem still today. Evidences from randomized trials have shown that bed rest, tocolisis and progesterone do not improve the prematurity rate in twins. *Methods:* In this study were included 69 twin pregnancies as below. For every three twin pregnancies we selected randomly one with pessary placement and two without. All patients, with or without pessary, were selected at the same gestational age interval (20-27 weeks), regardless of parity, chorionicity, or cervical length. We excluded patients with uterine malformations, placenta praevia, fetal anomalies, twin-to-twin transfusion or ruptured membranes. Both groups have received treatment with tocolytics, progesterone or bed rest, excluding the cervical cerclage suture. The outcomes measured were: gestational age at delivery, fetal birth-weight, Apgar at 5-10 min, day-stay at NICU, RDS morbidity and early neonatal outcome. *Results:* We analyzed 23 cases of twins with pessary cerclage, compared with 46 cases of twins without pessaries. We found a longer gestational age at delivery, in the pessary group, a higher fetal birth-weight, a shorter day stay at NCIU and a better neonatal outcome. The difference was significant ($p < 0.05$). *Conclusion:* Arabin cerclage pessary can be a useful method for prevention of prematurity in twins. Other trials are needed in the future to confirm these results.

EMBRYO/FETAL LOSSES AND INCIDENCE OF SPECIFIC AND NON-SPECIFIC PATHOLOGY INCLUDING SELECTIVE INTRAUTERINE GROWTH RESTRICTION IN TWINS

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Objective: To evaluate the incidence of specific and non-specific pathology in twins accordingly to embryo/fetal losses and chorionicity. *Methods:* In 222 high risk pregnant women with twin gestations, fetal structural malformations (SM) were analyzed according to mode of conception, chorionicity, amnionicity and presence of pathology, specific for twins, such as 'vanishing twin', twin-to twin transfusion syndrome (TTTS), twin reversed arterial perfusion sequence (TRAP) and selective intrauterine growth restriction (SIUGR). Rate of SM was calculated per pregnancy, per amnion and per fetus (after adjustment for embryo/fetal losses). *Results:* Among 188 spontaneous twins, 54.3% were dichorionic diamniotic (DCDA), 34.6% monochorionic diamniotic (MCDA), 6.9% monochorionic monoamniotic (MCMA) and 4,2% of unknown chorionicity (UC). There were 97.1% DCDA and 2.9% MCDA in 34 twin pregnancies after IVF. Embryo losses in the first trimester were presented in 33 (32.4%) of DCDA, in 4 (6.2%) of MCDA, in 1 (7.7%) MCMA and in 7 (21.2%) of IVF DCDA twin pregnancies. After single embryo losses in DCDA pregnancies, SM were diagnosed in 10% of the survivors. Fetal losses in the second and third trimester were: for DCDA 4.9% per pregnancy, for MCDA 13.8%, for MCMA 9.1%, and were absent in MCMA twin pregnancies in the time being under observation. The most common

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anomalies for DCDA twins were central nervous system (CNS) defects – 26.5%, congenital heart diseases (CHD) – 24.9%, urinary tract -18.4% and abdominal wall defects – 12.2%. In IVF DCDA twin pregnancies, share of CHD was 50%. The incidence of conjoined twins among various fetal anomalies in MCMA pregnancies was 50%. Both twins were affected in 20 cases of all DCDA, IVF DCDA, MCDA and MCMA pregnancies. Share of concordant anomalies in the mentioned groups was 20.0%, 0%, 50.0% and 66.7% respectively. TTTS was presented in 24 (36.9%) of 65 MCDA twin pregnancies. There were 17 (35.4%) SM in 48 fetuses with TTTS: 9 (37.5%) in 24 donors and 8 (33.3%) in 24 recipients. Both fetuses had anomalies in 3 cases. From SM found in recipients, 75% were CHD and 25% were CNS defects. Furthermore, from SM found in donors, CNS defects, multiple malformations, CHD and abdominal wall defects presented 33.3%, 33.3%, 22.2% and 11.2%, respectively. Incidence of CHD found in recipients was 3.4 times more than in donors. TRAP sequence was diagnosed in 3 cases of MCMA twin pregnancies. SIUGR occurred in 12 (18.5%) cases of 65 MCMA twin pregnancies. Fetal SM were found in 5 of 12 (41.7%) SIUGR MCDA pregnancies, in 6 of 24 fetuses (25%). Bigger and smaller fetuses were affected in equal shares (3/3). *Conclusions:* Monochorionicity presents the great perinatal risk. Twin pregnancies with specific complications also bear additional risk of fetal structural anomalies. In cases of TTTS, the incidence of CHD in recipient is 3.4 times higher than in donor. Fetal SM were found in 17 from 24 (70.8%) TTTS of MCDA pregnancies, and in 6 of 12 (50.0%) SIUGR MCDA pregnancies.

EPIGENETIC STUDIES OF A NEWBORN TWIN COHORT: INSIGHTS INTO PRE- AND POSTNATAL DEVELOPMENT

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The Peri/postnatal Epigenetic Twins Study (PETS) is a unique cohort of 250 mothers and their twins. Women were recruited from three Melbourne hospitals midway through their second trimester, which enabled measurement of maternal and fetal factors at multiple time points and minimization of recall bias. We collected multiple biological specimens at birth (cord blood, cords, placenta and buccal tissue) and repeat samples of blood and buccals when infants were 18 months of age. The aims of PETS are to study the plasticity of epigenetic marks and the genes they control during the intrauterine period and in early childhood. It also aims to apply the classical twins model to determine the influence of genetic, common and unique environmental factors on the neonatal epigenome. We have measured DNA methylation and gene expression on a genome scale in DNA from three cell types from 22 monozygotic (MZ) and 11 dizygotic (DZ) twin pairs using Illumina arrays. We found that twin pairs exhibited a wide range of within-pair epigenetic discordance, which overlapped with that observed between unrelated individuals. Comparison with similar data sets from older twins yielded no evidence of "epigenetic drift" over time. Using gene-specific analysis we found that that certain gene ontologies are consistently variably methylated within pairs in all three tissues, and that genetic and intrauterine environmental influence on DNA methylation varied throughout the genome. Using regression analysis, we identified genes whose expression and methylation levels correlated with birth weight in MZ pairs, providing a possible mechanistic link between birth weight and complex disease in later life. To our knowledge, this is the first study to demonstrate genome-wide epigenetic differences within newborn and very young twin pairs.

DESCRIPTIVE STUDY ABOUT 8 CASES OF TWIN ANEMIA POLYCYTHEMIA SEQUENCE (TAPS) DIAGNOSED AND TREATED AT THE PAULE DE VIGUIER MATERNITY HOSPITAL BETWEEN DECEMBER 2008 TO DECEMBER 2011

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TAPS and STT are two distinguished pathologies of monochorionic diamniotic twin pregnancies. The frequency of spontaneous TAPS is 5% vs 13% after laser procedure for STT. We report 6 cases with antenatal diagnosis and 2 cases with postnatal diagnosis according to the criteria established by Lopriore in 2010. The prenatal diagnosis is made by Doppler measurement of MCA-PSV in both foetuses. Placenta studies with colored dye allowed to find anastomoses responsible for the syndrome. It is mostlyan arterio-venous anastomoses of less than 1 mm in diameter responsible for a chronic imbalance of the exchanges between foetus. One foetus became anemic and the other polycythemic. We propose, in prenatal, an organization chart for the care of TAPS. Before 28 weeks, the first line treatment is curative with anastomoses coagulation by laser.

OPTIMAL LENGTH OF GESTATION IN MULTIPLES

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Introduction: The optimal gestational period may be shorter for twins than for singletons. Several studies have shown that fetal and neonatal death rates in multifetal pregnancies are lowest at 37-38 weeks of gestation and that the risk of stillbirth at these gestational ages seems equivalent to that of postterm singletons. Term in twin

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pregnancies is often considered to be 36 weeks, with 'post-term' being after 37 weeks. However, these studies did not take chorionicity into account. It is now well established that monochorionic (MC) twin pregnancies carry a higher risk of perinatal mortality and neonatal morbidity than dichorionic (DC) twin pregnancies. Management decisions regarding delivery will be made depending on the maternal and fetal condition. Due to the high incidence of maternal and fetal complications in twin pregnancies (especially in MC twin pregnancies), an early delivery is often necessary. However, the optimum timing for planned delivery of *uncomplicated* MC and DC twin pregnancies often leads to discussion. There are no data from randomized trials on which to base a recommendation for the optimum timing of delivery of a twin. There is currently only one small randomized trial comparing elective induction of labor at 37 weeks of gestation and continued expectant management in uncomplicated twin pregnancies. In that study, no statistical differences in outcome were found. However, the study was underpowered and no distinction was made between MC and DC twins. Currently, a randomized trial assessing the optimal time for delivery of term twins is conducted in South Australia. Dichorionic twin pregnancies: It has been shown that perinatal mortality in twin pregnancies reaches a nadir at around 38 weeks' gestation and rises thereafter, indicating that it may be unwise to prolong a twin pregnancy much beyond 38 weeks. Prolongation of a twin pregnancy after 39 weeks of gestation clearly increases the fetal risk without any anticipated neonatal benefit. A composite measure of perinatal morbidity is seen to fall steadily from 7% at 36 weeks to 1% at 38 weeks. Uncomplicated dichorionic twins therefore have optimal outcomes when delivered at 38-39 weeks of gestation. Elective delivery of uncomplicated DC twins around 37 weeks of gestation does not seem to improve the outcome of these infants. Monochorionic diamniotic twin pregnancies: About half of the MC twin pregnancies have an uncomplicated pregnancy outcome (i.e. two fetal survivors not complicated by twin-to-twin transfusion syndrome (TTTS), severe growth discordance or IUGR, or major congenital malformations). Unfortunately, mortality in these uncomplicated MC pregnancies cannot easily be foreseen. Current antenatal surveillance sometimes fails to predict and prevent such cases. As a consequence, there is controversy in the literature about when to deliver MC twins. Intrauterine fetal death (IUFD) rates after 32 weeks of gestation vary, leading to diverse recommendations on the optimal timing of delivery. The risk of IUFD in MC twin pregnancies has been investigated in twelve studies, ranging from 50-495 pregnancies, in the years 2005 till 2012. IUFD rates in pregnancies ≥ 32 weeks of gestation ranged from 0 to 2.9%, differences that might be due to the relatively small series, inclusion of IUGR or otherwise, and may also be due to a publication bias in the sense that clustering of IUFDs in a hospital might have prompted publication of results. However, the studies show that IUFD may occur without antenatal signs of TTTS or IUGR, with normal Doppler velocimetry wave form patterns preceding fetal death. The majority of these cases were unexpected and no antenatal signs of impaired fetal condition were present. These cases indicate that modern antenatal surveillance of MC twins fails in a substantial number of cases, in contrast to DC twins in which antenatal deaths are rare. It seems logical that authors who experienced a high rate of IUFDs promote early (preterm) delivery, whereas those with favourable results promote a more expectant approach (although they usually terminate pregnancy around 37 weeks of gestation). *Conclusion:* In conclusion, there is controversy about the optimal time of delivery for 'uncomplicated' MC twin pregnancies. The relatively low incidence of fetal death after 32 weeks of gestation, the increased mortality at term, the failure to predict and prevent all cases of excess IUFD by current antenatal care and the increased risk of (neuro) morbidity warrant planned delivery of the MC twins around 37 weeks of gestation. However, in the absence of large conclusive randomised controlled trials, there is insufficient evidence to support a practice of elective preterm delivery for women with an otherwise uncomplicated twin pregnancy. Optimal length of gestation in DC twins is 38-39 weeks. Elective delivery of uncomplicated DC twins at 36-37 weeks of gestation does not seem to improve the outcome of these infants.

DUCTUS VENOSUS DOPPLER AT 11 TO 13 WEEKS OF GESTATION IN THE PREDICTION OF OUTCOME IN TWIN PREGNANCIES

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Methods: This was a prospective study of 516 dichorionic and 179 monochorionic twin pregnancies in which the fetal ductus venosus flow was assessed at 11 to 13 6/7 weeks of gestation. The prevalence of reversed a-wave in the fetal ductus venosus was compared between monochorionic and dichorionic pregnancies and between those with and without pregnancy complications. Comparisons between each of the pregnancy outcomes and the normal outcome group and between monochorionic and dichorionic pregnancies were made using the Mann-Whitney U-test for continuous variables and the chi2 test and Fisher exact test for categorical variables. *Results:* The prevalence of reversed a-wave in at least one of the fetuses was significantly higher in monochorionic than in dichorionic pregnancies (18.4% compared with 8.3%, $P < .001$) and in pregnancies complicated by miscarriage (28.6%, $P = .005$), fetal aneuploidy (70.0%, $P < .001$), and twin-twin transfusion syndrome (38.5%, $P<.001$) compared with the pregnancies with two healthy live births (7.7%). Pregnancy outcome was normal in 33 of the 43 (76.7%) dichorionic and in 14 of the 33 (42.4%) mono-

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chorionic twins with reversed a-wave in at least one of the fetuses. *Conclusion:* In twins, reversed a-wave in the ductus venosus at 11 to 13 weeks of gestation is associated with increased risk for aneuploidies, miscarriage, and development of severe twin-twin transfusion syndrome. However, in about 75% of dichorionic twins and 40% of monochorionic twins with reversed a-wave, the pregnancy outcome is normal.

SURVIVAL AND NEONATAL OUTCOME AFTER FETOSCOPIC GUIDED LASER OCCLUSION (FLOC) OF TWIN-TO-TWIN TRANSFUSION SYNDROME (TTTS) IN SWEDEN

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Aim: To determine infant survival and neonatal outcome after fetoscopic laser treatment of twin-to-twin transfusion syndrome (TTTS). *Results:* In 53/71 (75%) laser-treated TTTS cases, at least one twin was liveborn and in 42/71 (59%) cases at least one twin survived infancy. Fetal survival did not differ between donors (41/71 [58%]) and recipients (46/71 [65%], $p = 0.36$). Among liveborns, infant survival was 29/41 (71%) in donors and 36/46 (78%) in recipients ($p = 0.12$). Infant survival did not correlate to maternal characteristics (age, BMI, smoking or parity), gestational age at treatment or severity of TTTS (Quintero stage). No TTTS infant born before 25 weeks of gestation survived the first week. Among the 87 infant survivors, 26 (30%) had Apgar score <7 at 5, 47 (54%) developed respiratory distress syndrome, 10 (11%) showed signs of severe brain damage, 9 (10%) renal failure, 8 (9%) bronchopulmonary dysplasia, and 5 (6%) infants developed retinopathy of prematurity = stage 3. There was no significant difference in neonatal morbidity between recipients and donors. *Conclusions:* Fetal survival after laser treatment was comparable to that reported by other international centres. There was no significant difference in survival or neonatal morbidity between donors and recipients. Major neonatal morbidity was common, and combined with extremely preterm delivery the prognosis of TTTS is poor.

GENETIC EPIDEMIOLOGY OF CANCER: NEW INSIGHTS AND OPPORTUNITIES FROM TWIN RESEARCH

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Twin data are providing novel insights into the causes and epidemiology of cancer. This symposium features new findings and methodological approaches from the Nordic Twin Cancer (NorTwinCan) collaboration and other twin studies of genetic and environmental contributions to cancer. The Nordic Twin Cancer (NorTwinCan) project is collaboration between Harvard and the four Nordic Twin Registries: Denmark, Finland, Norway and Sweden. It includes data on twins from the four countries, with linked data on cancer incidence and mortality over five decades of follow-up. In addition, we are developing and applying new statistical methods to study factors influencing estimates of cancer risk.

SOCIAL COMPETENCE AND SELF-ASSERTIVENESS OF JAPANESE TWINS AT SCHOOL AGE

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In this study we investigated the social competence and self-assertiveness of Japanese twins at school-age. The purpose of this study was to examine whether birth order in twins will impact their personality. A mailed questionnaire survey was conducted in 958 mothers from a study in 2004, as a follow-up study. As a result, 516 respondents returned the questionnaire (53.9%). In this study, we used only 216 twins aged 6-12 years old (school-age children) for analysis, excluding those with missing values. *Results:* Dizygotic [DZ] same sex male children were more likely to show high self-assertiveness than Monozygotic [MZ] female children (43.8%:26.5%; $p<0.05$). In addition, first born twins were more likely to show high self-assertiveness than second born twins ($p<0.05$). There was not significant association between social competence and birth order. The present results indicate that not only sex difference but also birth order would influence self-assertiveness of Japanese twins at school-age.

CONGENITAL HEART DEFECTS IN TWINS

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Background: Smaller studies and many case reports indicate that congenital heart defects (CHD) may be more common in twins than in singletons. *Material and Methods:* We investigated CHD occurrence in all twins and 5% of all singletons born in Denmark in the period 1977-2001 by linking the Danish Twin Registry and Statistics Denmark registers including the National Birth Register and the Danish National Discharge Register. The latter register has previously been shown to have high predictive power and completeness for identifying CHD cases. Only inpatient diagnoses were considered, and patent ductus arteriosus was not considered a CHD among twins and singletons born preterm. *Results:* Among 41,525 twin individuals, a total of 331 twins (0.80%) had a CHD registered in the Danish National Discharge Register, while the corresponding numbers for singletons were 479/74,473 (0.64%) ($p = 0.004$), i.e. a 24% (95% CI: 7-44%) increased risk for CHD for twins. Adjustment for calendar year and sex in logistic regression analyses changed the estimate to 30% (12-50%). The adjusted relative risk was highest for the rare, severe anomaly coarctation of aorta, which occurred 4.2 times (95% CI: 1.9-9.3) more often in twins than in singletons. We were not able to demonstrate an increased risk for CHD among monozygotic twins alone. *Conclusion:* CHD is more common in twins than in singletons.

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GENETIC INFLUENCE ON PROSTATE CANCER BASED ON THE NORDIC TWIN STUDY OF CANCER (NORTWINCAN) COHORTS

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The disease of prostate cancer taking onset in middle to late life is partly governed by genetic factors that may vary over time. We study how the risk of prostate cancer due to genetic influences varies over time taking into consideration that death is part of the outcome. We combine the population based Nordic cohorts of in total 17.893 MZ and 28.818 DZ male pairs born after 1900, estimate prostate cancer concordance risk, the heritability of liability for disease and its variation over time. Further, we consider genetic heterogeneity suggesting mode of action of genetic variants on risk scale. After adjustment for censoring and taking the competing risk of death into account, we find an overall prevalence of 13% in the Finnish, Norwegian and Swedish cohorts and 7% in the Danish cohort in accordance with population prevalence. The risk of cancer in MZ twins having a co-twin with cancer is consistently higher for all cohorts and ages than for DZ pairs with highest difference for early cancers and the occurrence is closer in time for MZ than for DZ pairs. The cumulative heritability in liability to prostate cancer peaks for early cancers, forty to sixty years of age, and decreases with age to a rather constant overall level of 56% with 95% CI. (49%; 62%) from around age 80 into late life. Considerable interaction effects are present on risk scale through late life for the action of multiple loci in addition to mainly additive effects. These results strongly favors a substantial genetic contribution to prostate cancer taking censored observations and competing risk of death into account. Further, the study adds insight to expected action of genes and timing of genetic effects, in particular that genetic influence do not decrease in late life.

THE LIABILITY THRESHOLD MODEL FOR CENSORED TWIN DATA

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We extend classical methodology for studying genetic influence of a dichotomous trait observed in twin pairs with missing data. It is very often the case in quantifying the within pair dependence in occurrence of events that twins may or may not have experienced the event at time of follow-up. We propose to extend the classical liability threshold model with the technique of inverse probability weighting of complete observations. We show that the method allows for flexible modeling of twin concordance, mean and covariance structures given that we have observed time to event or to follow-up. We apply the method in simulations and in the case of observing prostate cancer occurrence in twins providing cumulative concordance and heritability by age. The method efficiently corrects for a major source of bias and exploit time to event information often present in twin studies of a dichotomous trait.

MISSING HERITABLITY: DID IT EVER EXIST?

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A genome-wide association study (GWAS) aims to detect variants at genomic loci that are associated with complex traits and has been applied, in particular, to try to detect associations between common single-nucleotide polymorphisms (SNPs) and common diseases. In a recent review titled 'Five Years of GWAS Discovery' by Peter Visscher and colleagues published in the American Journal of Human Genetics (Vol 90: pp.7-24, 2012) it was noted that 'GWASs have led to many scientific discoveries, and yet … many people have pointed to various problems and perceived failures of this experimental design'. Critics had raised the possibility that 'GWASs are founded on a flawed assumption that genetics plays an important role in the risk to common diseases'. Visscher and colleagues identified complex traits where the heritability (proportion of phenotypic variance or variance in liability) explained when all GWAS SNPs are considered simultaneously was considerably lower than the 'heritability' typically estimated from twin studies. 'Whole-genome approaches to estimating genetic variation have shown that approximately one-third to one-half of additive genetic variation in the population is being tagged when all GWAS SNPs are considered simultaneously'. For example, for height the former is about 50% whereas the latter has been of the order of 80% or higher. For obesity/BMI, the former is about 20% whereas the latter has been typically in the range 40–60%. The authors consider that this is 'a surprisingly large proportion given that evolutionary theory predicts that most variants affecting disease risk ought to be found at a low frequency in the population if they affect fitness, and such risk variants would not be in sufficient LD with the common SNPs to be detected in [sic] GWASs'. These observations raise serious questions about the validity of the classic twin model and how the way it has been applied. Some potential explanations for this apparent over-estimation of heritability are: (i) the failure of the 'equal environments' assumption, (ii) the 'winner takes all' paradigm in which a lack of a statistically significant effect of environmental factors shared by twins (C) leads to setting C = 0, with consequent maximal estimates of heritability with substantially smaller standard errors than would be derived if C was estimated concurrently (even if the estimate was negative); (iii) misuse of Aikake's information criteria which was never designed to identify causes but instead to derive the best model in terms of prediction; (iv) the tendency of the above to lead to estimates of heritability equal to the correlation within MZ pairs, which imply that the only reason that MZ pairs are

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similar is due to their shared genes - ignoring the way twins help each other shape their personalities, behaviours, skills, and lifestyle; (v) the fact that much lower estimates of heritability typically arise if the correlation in DZ pairs or other relatives are used. There could also be other fundamental problems in the classic twin modelling approach. The twin research community should address the challenges raised by GWAS by critically reviewing and if necessary changing the current paradigm.

INFERENCE ABOUT CAUSATION FROM EXAMINATION OF FAMILIAL CONFOUNDING: APPLICATION TO SIBSHIP DATA ON INFANTILE ECZEMA AND CHILDHOOD HAY FEVER AND/OR ASTHMA

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Inference about Causation from Examination of Familial Confounding (ICE FALCON) is a new approach to analysis of paired sibling data, including twin data. It uses a regression model and permits inference about a causal effect of a familial predictor on an outcome by examining the change in association with the predictor of the co-sibling after adjusting for the predictor status of self. It can be applied to twin data and goes beyond the simplistic models that allow only for overlap in familial factors as an explanation of cross-trait cross-pair familial associations. ICE FALCON has been applied previously to a twin study where the outcome was a continuously distributed variable, using ordinary linear regression. Here we applied this approach to analyse sibship data on a binary predictor and binary outcome using logistic regression. The context is the atopic march hypothesis, which proposes that eczema precedes development of asthma and allergic rhinitis. The causes of these temporal associations are unclear, although there are familial associations within and between eczema, asthma and hay fever. Our aim was to assess if there is evidence for a causal effect of infantile eczema on childhood hay fever and/or asthma. We used parent-reports from the population-based Tasmanian Longitudinal Health Study (TAHS) on infantile eczema, and on childhood asthma and hay fever history, for 3,778 pairs of 7 year olds matched to their sibling closest in age within two years. We analysed the paired sibling data using a logistic regression model fitted using generalised estimating equations to allow for correlation in outcome between siblings: We found that infantile eczema was highly concordant in siblings (tetrachoric correlation 0.40; $p<0.0001$). For having both hay fever and asthma by age 7, the association with eczema of co-sibling was OR = 1.98 (95% CI 1.37-2.86), which reduced by 26% after adjusting for the eczema status of self to OR = 1.65 (95% CI 3.29-5.88). For having hay fever only, the association with eczema of sibling was OR = 1.68 (95% CI 1.22-2.31) before, and OR = 1.59 (95% CI 1.19-2.14) after, adjusting for eczema of self. For having asthma only, there was no association with eczema of co-sibling (OR = 1.00, 95% CI 0.77-1.30). We conclude that eczema in infancy might cause about 30% of hay fever in children with a history of asthma, and perhaps 10% of hay fever in children without a history of asthma. The association of infantile eczema with asthma in children without a history of hay fever is not causal or familial. These findings have implications for the prevention of hay fever. This work also demonstrates the utility and insights that come from the ICE FALCON approach.

A SYSTEMATIC APPROACH TO FIRST TRIMESTER ULTRASOUND ASSESSMENT OF TWINS

C. Hubinont, J. Santolaya-Forgas

The incidence of twin pregnancies has increased for the last twenty years mainly as a result of assisted reproduction technologies and pregnancies occurring in older women. Both maternal and perinatal mortality and morbidity are increased in twin pregnancies when compared with singletons. A systematic and detailed first trimester ultrasound can be a useful tool for an optimal management: 1: to determine chorionicity and amnionicity; 2: to measure the cervical length; 3: to evaluate for fetal growth and its discordance; 4: to rule out specific disorders of monochorionic twin pregnancies; 5: to screen for genetic anomalies; 6: to detect major congenital anomalies. Using this algorithm, prediction of complications can be done at an early stage. This can help with directing future management and counseling of patients.

OUTCOME OF MULTIPLE PREGNANCIES COMPLICATED BY A NEURAL TUBE DEFECT

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Introduction: Multiple pregnancies complicated by a fetus with a neural tube defect (NTD) are a management dilemma. The risk of preterm delivery from polyhydramnios must be balanced with the risks of selective reduction (SR) of the anomalous fetus. SR has been associated with pregnancy loss rates up to 20% depending on the gestation at which the procedure is performed and which twin is presenting. This study investigated the prevalence of the condition and determined the rate of pregnancy complications in our institution. *Materials and Methods:* A search of our electronic ultrasound database was undertaken to identify all twin pregnancies affected by a NTD at the Royal Women's Hospital, Melbourne (RWH) over a seven year period. An experienced Obstetrician with ultrasound expertise reviewed the ultrasounds to confirm the findings. The clinical notes were analysed to determine obstetric, neonatal and subsequent paediatric outcomes. *Results:* Between January 2004 and May 2011 there were 1216 multiple pregnancies managed at RWH. Nine were complicated by

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NTDs: four with anencephaly, three with an encephalocoele and two with spina bifida. Eight of the nine pregnancies were dichorionic diamniotic (DCDA) and one was monochorionic diamniotic (MCDA). The mean gestations at diagnosis were 13.7 weeks (W) (SD 1.3) for anencephaly, 18.1W (SD 0.4) for spina bifida and 20.4W (SD 3.2) for encephalocoeles. Karyotype analysis was performed on four affected twins and two unaffected twins and was normal in all cases. SR was performed in six cases: two for anencephaly, two for encephalocoeles and two for spina bifida. SR of the presenting twin was performed in three of these cases, one of which miscarried at 19W after SR for anencephaly at 14 W. Polyhydramnios complicated one case in the encephalocoele group and required amniodrainage at the time of SR. Two patients in the expectant management group (EM) required tocolysis for premature labour at 28W and 29W respectively. The first subsequently delivered at 29W and the second was complicated by pre-eclampsia and delivered at 30W. The single MCDA pregnancy delivered at 32W following EM. The co-twin that did not have a NTD has subsequently been diagnosed with macrocephaly and periventricular leukomalacia. The mean gestation at delivery in the SR group was 35.1W (SD 7.7) compared to 30.8W (SD 1.7) in the EM group. Delivery was by caesarean section in six of the nine cases. Four infants required admission to the neonatal unit due to prematurity. Growth restriction affected one liveborn infant with anencephaly and the birthweight of all unaffected twins was >10th percentile. *Discussion:* These outcomes highlight that whilst MC twins are usually discordant for NTDs, careful follow-up of the non-affected co-twin is essential to exclude other abnormalities. Our study has confirmed that polyhydramnios and premature labour may complicate multiple pregnancies affected with a NTD but is not universal. Whilst SR is not without risk, it warrants serious consideration to avoid the potential complications to the unaffected co-twin. It may also be the option preferred by parents to avoid the possibility of a liveborn child with a NTD.

DOES PARENTAL EDUCATION MODERATE GENETIC AND ENVIRONMENTAL INFLUENCES ON COGNITIVE ABILITIES IN SOUTH KOREAN CHILDREN?

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There is growing evidence that relative influences of genetic and environmental factors may vary across different social classes. The main goal of the present study was to examine whether parental education has a modifying effect on genetic and environmental influences on cognitive abilities in South Korean twin children. Approximately 400 pairs of South Korean twin children completed the Raven Standard Progressive Matrices and the Mill Hill Vocabulary test. These twins were predominantly from middle and lower social class families in South Korea. We computed monozygotic and dizygotic twin correlations and fit a structural equation model incorporating a moderator effect to the data. Implications of the findings were discussed.

TWIN-SINGLETON DIFFERENCES IN COGNITIVE ABILITIES IN AFRICA

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Previous studies have been inconsistent in demonstrating differences in cognitive abilities between twins and singletons. The primary goal of the present study was to examine whether twins are lower than singletons in cognitive abilities in African population. We administered family environmental measures, the Raven Standard Progressive Matrices test, and the Mill Hill Vocabulary test to adolescent twins and singletons who attend public schools in Nigeria. We analyzed the data using maximum likelihood model-fitting. Although twins (complete pairs and cotwin death cases) and singletons were comparable in family environments and social class indicators, singletons were significantly higher than twins in both Raven and Mill Hill Vocabulary tests. We speculate that severe obstetric, perinatal, and paediatric risk factors common in Africa may explain the lower cognitive development found in twins as compared with singletons.

INTERACTION BETWEEN IN VITRO FERTILIZATION AND ZYGOSITY ON SELECTED PERINATAL OUTCOMES

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It is shown that in vitro fertilization (IVF) twins are born to a higher extend with low birth weight and/or preterm compared to naturally conceived twins. However, very few studies have taken zygosity into account. Although the majority of IVF twins are born as dizygotic, monozygotic IVF twins do occur. We aimed to investigate the effects of zygosity on neonatal outcomes such as low birth weight, preterm delivery and fetal growth restriction (defined as standardized scores for gestational week less than the 10th percentile for gestational week). In a population of 12 657 twins from the Swedish twin register born between 1993-2002, with known zygosity, we have found an increased risk of low birth weight (OR 1,28 95% CI 1.09–1.50), preterm delivery (OR 1,30 95% CI 1.11–1.53) and fetal growth restriction (OR 1,23 95% CI 1.00–1.51) among IVF twins compared to naturally conceived twins. These estimates were adjusted for maternal characteristics (age, height, BMI, smoking, education family situation), sex of the child, calendar period, years of involuntary childlessness and zygosity. Further, there was a significant interaction at the 10% significance level (p-value = 0.09) between IVF and zygosity when it comes to risk for preterm delivery; the relative risk was highest in dizygotic

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IVF twins (OR 1,33 95% CI 1.11–1.59). Even though IVF twins are born to a lesser extend as monozygotic twins, considering zygosity seems to be of importance.

INFANT MORTALITY IN SINGLETONS AND TWINS ACCORDING TO RISK FACTORS IN JAPAN, 1999-2008

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The infant mortality rate (IMR) was analyzed among single and twin births during the period from 1999 to 2008 using Japanese Vital Statistics. The IMR was 5.3-fold higher in twins than in singletons in 1999 and decreased to 3.9-fold in 2008. The reduced risk of the IMR in twins relative to singletons might be related to a part of survival rates improved after fetoscopic laser photocoagulation for twin-twin-transfusion syndrome. Proportions of neonatal deaths among total infant deaths were 54% for singletons and 74% for twins. Thus, to reduce the IMR, intensive care of twin births is likely to be very important during the first month of life. The IMR decreased as gestational age rose in singletons whereas the IMR in twins decreased as gestational age rose until 37 weeks and increased thereafter. The IMR was significantly higher in twins than in singletons from the shortest (<24 weeks) to 28 weeks and 38 weeks and over, whereas the IMR was significantly higher in singletons than in twins from 30 weeks to 36 weeks of gestation. As for maternal age, the early neonatal and neonatal mortality rates and the IMR in singletons were significantly higher in the youngest maternal age group (<20yr) than in the oldest one (40yr), whereas the opposite result was obtained in twins. The lowest IMR in singletons was 1.1 per 1000 live births for the longest gestation (38) and the heaviest birthweight (2000g) and the lowest IMR in twins was 1.8 at 37 weeks of gestation and 2000g.

DOES USING A TWIN-SPECIFIC GROWTH CURVE IMPROVE THE DETECTION OF AT-RISK PREGNANCIES?

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Objective: Sonographic evaluation of fetal growth is routinely performed in twins. As the rate of growth in twins deviates from that of singletons, some advocate the use of twin-specific growth curves. Because a higher proportion of twins exhibit abnormal growth, this may reduce the detection of growth restriction. We sought to determine if use of a twin-specific fetal growth curve improves the detection of fetuses with placental lesions associated with growth restriction. Study Design: A twin-specific growth curve was constructed using ultrasound measurements from 475 twin sets. Individual twin sets were categorized by whether ultrasound revealed an estimated fetal weight (EFW) <25th percentile in one or both twins in (1) a twin-specific growth curve; (2) a singleton growth curve; or (3) normal growth in both twins. Placental pathology was reviewed for the presence of lesions associated with poor growth. Chisquare for trend was used to compare the rates of placental lesions. *Results:* 286 twin pregnancies were included. 51.4% of twin sets had normal fetal growth. In 17.1%, one or both twins had EFWs in the lowest quartile based on a singleton growth curve only. In 31.5%, EFWs of one or both twins were in the lowest quartile by both growth curves. Lesions consistent with malperfusion or abnormal coagulation were present in 45.9% of placentas. Placental lesions increased from pregnancies with normal growth to those with abnormal growth based on the singleton growth curve to those with abnormal growth on both curves ($p = .03$). The differences were more pronounced in twins exhibiting abnormal growth prior to 34 weeks gestation. The rates of placental lesions are seen in Table 1. *Conclusions:* Using a twin-specific growth curve categorizes fewer twins as having abnormal growth. This may identify a subset of fetuses with particularly high rates of placental lesions, especially prior to 34 weeks. Using such a curve would result in missing a significant number of affected cases, however. The best approach may depend on identifying the clinical significance of such lesions and correlating intrauterine growth with long term outcomes.

A COHORT STUDY OF FETAL AND MATERNAL OUTCOME: THE EFFECT OF SEX AND BIRTH WEIGHT DISCORDANCE

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Among twin pregnancies, risk factors for adverse perinatal and maternal outcomes are beginning to emerge. Early studies suggest that discordance by birth weight and sex, are predictors of morbidity and mortality specific to twin gestation. This pilot study aimed at investigating the effect of sex-discordance and birth weight discordance on fetal and maternal outcomes. Twin data was retrieved from British Columbia Perinatal Database from part of year 2004 and 2005 till 2007. Total number of twins retrieved from this database was 2395 sets of twins (n = 4790). There were 806 pairs of opposite-gender twins (cases) and 1589 sets of same-gender twins. Our analysis did not found any significant differences between discordant and concordant groups in terms of fetal or maternal outcomes under study. Feto-maternal outcomes were found to be similar between the two groups of twin sets (with and without 10% discordance). Same result was found for 20% cut off level. Twin pairs with 30% discordance were 3.65 times more likely to have a mother with the history of delivering a baby with congenital abnormalities, and were 1.93 times more likely to have a mother with pregnancy induced hypertension. These mothers were also more likely to be alcohol consumers during pregnancy. The adjusted odd ratio was calculated as 1.9 (95%CI 1.23-

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2.96). Forty sex percent of twin sets had 10% discordance. Results showed that same-sex twins tend to have more similar birth weights (OR = 0.745, 95%CI 0.629-0.883). In conclusion, the effect of sex-discordance and birth weight discordance on fetal and maternal outcomes is a fascinating study that needs further investigation.

OUTCOME OF MULTIPLE GESTATION WITH ADVANCED MATERNAL AGE

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The rate of multiple-gestation pregnancies has grown exponentially over the last few decades. The aim of this study is to present pregnancy and perinatal outcomes of twin gestations with advanced maternal age. We conducted a retrospective study of twin pregnancies in our department. The women were classified into two groups by maternal age: 56 women of age 35 years and older (study group,) and 70 women less than 35 years (control group) Spontaneous conceptions were significantly higher in the control group ($P < 0.001$), while pregnancies after in vitro fertilization (IVF) were significantly higher in study group ($P < 0.001$). The Cesarean rate for study group was significantly greater compared to control group. There were no differences in rates of adverse outcomes including gestational hypertension, pre-eclampsia, gestational diabetes, suspected fetal growth restriction, preterm birth, low birth weight.

GOOD BEGINNING TO PARENTING MULTIPLES PROJECT (2009-2011)

M. Kaihovaara

The underlying reason for the project 'Good Beginning to Parenting Multiples' was the need to obtain up-to-date information from Finnish society on how families with twins/triplets find themselves in Finland and how the well-being of these families can be promoted. The project aimed on (1) renewing a guide for parents preparing for having twins/triplets and (2) on special family training for multiple birth families. The project produced two studies: Hyväluoma (2010) and Vauhkonen (2011). The project is administered by the Finnish Multiple Births Association and funded by non-profit organizations: Finland Slot Machine Association (RAY) and Alli Paasikivi Foundation. The anxiety over the pregnancy and the wellbeing of the babies is stressing and pressing feeling. Having the fear of too early delivery is constantly present. Parents don't' always have the courage to become attached and build their relationship to their babies, because they fear the loss of the children so much. In Finland almost half of the mothers have their multiples as their firstborn children. Twins are born at the weeks 37-38, triplets at 33 on average. The news about becoming a family with multiples can be everything between severe shock to an exceptionally happy surprise. Multiple pregnancies are always a risk both in psychically and mentally for the parents. One target of the project was to renew a Guide for parents preparing for having twins and triplets. This guide is an initial-Information-Guide for parents expecting twins/triplets. Families will receive this free booklet from their Municipal Maternal Care Unit. Some of the topics of this booklet are; expecting the multiple children, delivery, parenthood, supporting the individuality, relationship matters, letting them to differ or to guide them similar? Second target was to have the Public Sector responsible for organizing appropriate training for families expecting twins/triplets. The main objective is that the regional public health care official will carry out the multiple birth family training for families expecting multiples in co-operation with volunteers from the multiple birth association. Family Coaching is already being organized by the government nationwide for parents waiting for one baby. Special training is needed for families for the unique situation the family will face when more than one child is being delivered. When building the training model, three main topics raised up; multiple pregnancy and birth, the everyday life with multiples, and peer meeting of parents after the birth of multiples. The gestation time and delivery topic should be mainly held by a professional nurse or a midwife and the topic how to survive with twins/triplets and everyday life by the peers on Regional Associations for Multiple Families. Very important value was also on the group meetings for mothers and fathers. Main topics on mothers group are how to breastfeed twins/triplets and how to help mother to manage. In fathers groups, the topics are siblings relationships and relations towards twins/triplets.

HERITABILITY OF SALT INTAKE USING HALF-DAY URINE SAMPLES: THE HEALTHY TWIN STUDY

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Salt is essential for both life and diet, but excess consumption of salt is an established risk factor of hypertension. Historically, salt intake has increased along with civilization, and the traditional Korean diet, although generally considered to be healthier than westernized one, has been reported to contain high level of salt. Whether there is a genetic predisposition toward sodium intake level is a basic but interesting question to ponder in the Korean population. A half-day urine (HU) samples were collected for all participants of the Healthy Twin Study. HU collection starts around 7 pm of the day before visit, after completely voiding when time record starts. All the urine after then was collected in a bag until the next day visit for health examination. On site, in the morning, remaining urine was further voided and the time was recorded as final. The duration of collection ranged 2
24 hours, and we selected samples collected more than 8 hours. Among 3079 participants of the Healthy Twin Study, 1312 (143 pairs of MZ twins, 31 pairs of DZ twins and 961 singletons) were

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included in the analyses. Heritability of 24 hour sodium intake was estimated using a variance components model (SOLAR). After adjustment for age, sex, income and province effects, the heritability was 0.30±0.1. Shared environments did not account significant contribution. We concluded that although salt intake is mediated through diet and meals are shared among families, genetic predisposition will play an important role in controlling salt intake.

ANTENATAL CARE FOR TWIN AND TRIPLET PREGNANCIES: SUMMARY OF NICE GUIDANCE IN THE UNITED KINGDOM

M. D. Kilby

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice.

The National Guidance published in September 2011[1] for the UK includes recommendations on care to:
Determine gestational age and chorionicity.

Screening for fetal anomalies and chromosomal anomalies.

Screening for TTTS and management of monochorionic twin and monochorionic/dichorionic triplet pregnancies.

Monitoring for preterm birth and intrauterine growth restriction.

Indications for referral to a tertiary Fetal Medicine Centre.

Timing of Birth.

[1]Visintin, C., et al. (2011). Antenatal care for twin and triplet pregnancies: summary of NICE guidance. BMJ, 343, d5714.

CO-TWIN PROGNOSIS AFTER SINGLE FETAL DEATH: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: To perform a systematic review and meta-analysis of the effects on the surviving twin of single fetal death comparing monochorionic to dichorionic twins to report the rates of co-twin death, preterm delivery, and neurologic morbidity in the surviving fetus.Data Sources: MEDLINE (inception-December 2010), EMBASE (inception-December 2010), The Cochrane library (inception-December 2010), Web of Science (inception-December 2010), and British Nursing Index (inception-December 2010) were searched electronically. Methods of Study Selection: Selected studies had more than five cases of single fetal death with reports of co-twin death, neurologic morbidity, or both co-twin death and neurologic morbidity. They also must have defined the gestational age of single fetal death and chorionicity. Tabulation, integration and *Results:* The search yielded 1,386 citations. Full manuscripts were retrieved for 204 and 22 were included in the review and meta-analysis. Twenty manuscripts were used to calculate overall summary statistics for monochorionic and dichorionic twins showing rates of co-twin death after single fetal death (15% compared with 3%), rates of preterm delivery after single fetal death (68% compared with 54%), the rate of abnormal postnatal cranial imaging after single fetal death (34% compared with 16%), and the rate of neurodevelopmental impairment after single fetal death (26% compared with 2%). Odds ratios (ORs) were calculated from 16 manuscripts. There was no significant difference reported between preterm delivery of monochorionic or dichorionic twins (OR 1.1, 95% confidence interval [CI] 0.34–3.51, P = .9). After single fetal death, monochorionic twins had higher odds of an abnormal cranial imaging after delivery, this was not significant (OR 3.25, 95% CI 0.66-16.1, P = .12). After single fetal death, monochorionic twins were 4.81-times more likely to have neurodevelopmental morbidity (95% CI 1.39-16.6, P<.05). *Conclusion:* Monochorionic twins are at significantly increased odds of co-twin demise and neurodevelopmental morbidity after single fetal death.

LINKAGE DISEQUILIBRIUM INFORMATION WITHIN MONOZYGOTIC TWIN PAIRS - A RATIONALE FOR GENOTYPING TWINS

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Recently genome-wide association studies have become a standard gene mapping method, but MZs have been either considered to be redundant or treated as unrelated individuals after randomly selecting one cotwin. It has been a common sense in academia that monozygotic twin (MZ) pairs, although they have unique strengths in detecting non-genomic etiology, do not contribute to gene mapping studies. It is indeed true for linkage analysis, but resemblance of phenotypes between MZ cotwins does include information about linkage disequilibrium (LD) between the genetic markers and postulated disease-susceptibility loci (DSL) when the concordance/discordance rates are compared across genotypes. The authors attempted to formulate a method to detect association and suggest several ways of applying the information using triglyceride and hypertriglyceridemia as a model phenotype. Genome-wide association test findings from the Healthy Twin Study, Korea which do not utilize MZ concordance information were compared with the tests of MZ concordance only from 493 MZs with genetic markers It is natural to assume that if allele D (wild type allele is +) is in LD with true DSL, MZ twins with genotype DD or D+ should have more diseases, and thus concordance rate than those with ++ genotype. Numerically, the observed concordance rate of MZ twins will exceed the expected concordance rate under null hypothesis of non-association (Equation 1) where "A*A"—the proportion of MZ with both affected, "U*U"—the proportion of MZ with both unaffected,

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"Obs()"—observed rate, "prevalence"—prevalence rate among general population or study participants This can be further formulated by a trend test assuming additive model, or reduced tests assuming dominant model. Extended models can be constructed such as a logistic regression model allowing covariate adjustment or multiple linear regression calculating the sum of covariance between the cotwins for continuous traits. Formula : logit[p(A*A)] = a×covariates + ß × num(allele D) + e : additive model logit[p(A*A)] = a × covariates + ß×I(allele D exists) + e : dominant model where ß×num(allele D)+E numbers of allele D, ß × (allele D exists) + E1 if allele D exists, else 0. When we applied the multiple logistic regression test with 5.83 mmol/L as a cut-off for hypertriglyceridemia, 10 markers out of 26523 SNPs in chromosome 11 which exceeded p<10-3 showed p-value of 0.0003
>0.001. When we consider p-value of 0.05, 0.1, 0.15, 0.2 and 0.3 as cut-off for the MZ test and p-value of 10–3 and 10–4 as cut-off for GWAS results, the sensitivity/specificity of the MZ tests ranged 0.26
>0.56 for sensitivity and 0.69
>0.95 for specificity. Our findings show a way to extract LD information from MZ concordance or resemblance when one of cotwin was genotyped. Because the MZ resemblance is independent of other information conventionally used for GWAS, it can be combined with other results. The test can be also used to screen markers to alleviate the burden of multiple testing with appropriate threshold. Given that the MZ will be ever popularly applied for various omics studies, the addition of genomic information will facilitate multi-omics study in twin research.

THE RELATIONSHIP BETWEEN THE INTERPREGNANCY INTERVAL AND THE CHANCE OF NATURAL DIZYGOTIC TWINNING

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Background: The role of high parity on a higher rate of dizygotic twins, even when corrected for maternal age, is not understood. One consequence of higher parity is a shorter interpregnancy interval. Our study aims to investigate if interpregnancy interval is related to dizygotic twinning rate. *Methods:* For the purpose of this study, we extracted information about interpregnancy intervals from the database of the Perinatal Registry of the Netherlands over the years 2000-2006 about the reported natural conception pregnancies of all multiparous singleton. We took male/female twins to ensure dizygosity. The interpregnancy intervals were divided in periods of three months (0-<3, 3-<6, until 33-<36 months). For each category the frequency of opposite sex twin pairs was computed. *Results:* From a total of 331.279 deliveries, 328.399 were singleton pregnancies and 2.880 women had a natural conception dizygotic twin pair pregnancy. The lowest rate of opposite sex twin pairs (0,57%) was found with an interpregnancy interval of 6-9 months and it increased significantly to the highest rate (1,06%) with an interpregnancy interval of 18-<21 months followed by some decline. *Conclusions:* Opposite sex twin pair rates seem to relate to interpregnancy interval with a relatively high chance shortly after delivery followed by a progressive decline and a subsequent rise. We suggest that lactation and contraceptive behavior during this period may be of importance. Absence of such information in the data base limits the possibility to confirm this.

ASSOCIATION BETWEEN NICOTINE DEPENDENCE AND MAJOR DEPRESSION: ROLE OF DOPAMINE RECEPTOR GENE VARIANTS

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Modifying genetic influence on the association between major depressive disorder (MDD) and nicotine dependence (ND) has been investigated in a limited number of studies. The aims of this study were to investigate (1) association between lifetime DSM-IV diagnoses of ND and MDD among Finnish adult ever smoking twins; (2) magnitude of shared genetic factors influencing this co-morbidity; and (3) association of dopamine receptor genes with these phenotypes. The study sample was ascertained from the Finnish Twin Cohort study. Twin pairs born 1938-1957 and concordant for cigarette smoking history were recruited along with their family members, as part of the Nicotine Addiction Genetics consortium. Phenotype analysis was based on 1296 twins with data on both ND and MDD diagnoses. Individual level multiple logistic regressions were applied for the affected/non-affected phenotypes adjusted for sex, age, and alcohol use. As pair wise analysis we examined the cross-twin cross-trait correlations showing preliminary evidence on common genetic vulnerability. Further, we conducted bivariate Mx models for ND and MDD in 112 monozygotic and 410 dizygotic pairs. The genetic study sample consisted of 1428 individuals from 735 families (mean age 55.6 years). A total of 70 tagging SNPs within the dopamine receptor genes (DRD1-5) were genotyped and analyzed for association for MDD diagnosis, number of DSM-IV depression symptoms, ND, as well as the co-morbidity of MDD and ND. Individuals with ND diagnosis had significantly higher likelihood for lifetime MDD (OR = 2.51, 95% CI 1.83-3.46, p = 7.6e-09). High genetic correlation (rA = 0.70) derived from a bivariate twin model suggested that shared genetic influences might underlie this association. We detected a significant association between the rs2399496 at the 5' end of DRD3 gene and the

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co-morbidity of MDD and ND (p = 7.9e-05). However, when analyzing nicotine dependent and non-dependent individuals separately, the association signal for MDD originated solely from the nicotine dependent persons. Nicotine dependence may potentiate the association of DRD3 with MDD. To the best of our knowledge, this is a novel finding and needs to be replicated in independent samples.

IATROGENIC LATE PRETERM, SPONTANEUS LATE PRETERM VERSUS TERM TWINS -A COMPARISON OF NEONATAL OUTCOMES

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Objective: To compare neonatal mortality and morbidity in twin pregnancies following iatrogenic late preterm, spontaneous late preterm and term birth. Material and *Methods:* 253 twin pregnancies, hospitalized at the First Department of Obstetrics and Gynecology, Medical University of Warsaw, between 2005-2011, were put into retrospective analysis. Late preterm birth was defined as between 34 + 0 and 36 + 6 wks of pregnancy. Spontaneous birth was a result of primary uterus contractions and iatrogenic late preterm birth was due to perinatal indications for pregnancy termination. Primary outcome was: admission to Neonatal Intensive Care Unit (NICU), respiratory disorders (RD), intraventricular hemorrhage (IVH), sepsis, NEC, pneumonia or phototherapy. *Results:* Spontaneous late preterm birth (SLPB) rate was 26.9%, iatrogenic late preterm birth (ILPB) - 15.8% and term birth (TB) - 34%. There was one case of perinatal death of one twin in ILPB group. The average birthweight in the ILPB group was 2347g, 2433g in the SLPB group, and significantly greater in the TB group - 2741g (p<0.01). In the ILPB group the percentage of admission to NICU and RD was significantly higher than in the SLPB group (NICU: 42.5% vs 20.6%; RD: 32.5% vs 16.2%, p<0.05). The incidence of IVH, pneumonia and phototherapy did not differ. Neonatal outcome was significantly better in the TB group (NICU 3.5%, RD 3.5%, IVH 10.5%, pneumonia 2.3%, phototherapy 16.3%; p<0.05). There were no cases of sepsis and one of NEC in the SLPB group. *Conclusions:* Late prematurity in twin pregnancies is associated with higher risk of neonatal morbidity. Iatrogenic late preterm birth increases the risk of respiratory disorders in neonates.

PERINATAL REPRODUCTIVE ENDOCRINOLOGY IN TWINS

E. Kuijper

Introduction: In many twin studies hormone related cancers (testis, mammae), gender related behaviour and fertility problems are allegedly related to reproductive hormone exposure during pregnancy. Remarkably very little is known about these reproductive hormone levels of twin pregnancies during gestation and immediately after delivery. Aim of our study was to collect in a prospective manner a detailed inventory of reproductive hormone status in twin pregnancies of various nature and for comparison also in singleton pregnancies. *Materials and Methods:* We have collected data from over 500 (257 women pregnant with a singleton and 257 women pregnant with a twin (48 MZ, 209 DZ)) pregnant women for hormone measurements. Serum samples have been taken around 20 weeks of gestation from the mother, at birth from the mother as well as from the umbilical cord and urine has been collected from the neonates around 6 weeks of age. We have measured the following hormones: Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Oestrone (E1), Oestradiol (E2), Oestriol (E3), Testosterone (T), androstendione (Adion), Sex Hormone Binding Globulin (SHBG), Anti Mullerian Hormone (AMH) and progesterone (P). Results:

Normative data, including means and standard errors of all measured hormones will be presented as well as comparisons between singletons and different types of twins controlled for gestational age, age of the mother, parity, ethnicity, smoking and BMI. *Conclusion:* This work fills an important gap in knowledge around perinatal reproductive hormone status of the twin pregnancy. The measured hormone levels during gestation in mothers and at birth in maternal serum and umbilical blood, as well as post partum in neonates will be discussed and put into the perspective of current insight with respect to reproductive hormone status and certain physiological and pathological conditions.

CEREBRAL PALSY IN MULTIPLES - CAN WE DETECT IT ANTENATALLY?

A. Kurjak, U. Honemeyer

Simultaneous visualization of intrauterine dynamics of fetal behavior and appearance, together with reliable quantitative information about fetal movements, became reality only with the advent of four-dimensional ultrasound (4D US). In the case of twins, real time observation of the entire fetuses in three dimensions , with visualization of isolated spontaneous activity of one twin became possible, as well as observation of stimulated activity of the co-twin. The improved visualization of inter-twin contacts allows distinction of behavioral categories such as contact with the head, contact with the body, contact with the hand, and contact with the leg (B. Arabin et al). The incidence of cerebral palsy (CP) is 0.2% in singletons, 1.5% in twins (25% in monochorionic (MC) twins, 3% in dichorionic (DC) twins), 8% in triplets, and 43% in quadruplets remains a permanent challenge for obstetricians. Known risk factors for CP in multiples are discordant growth, vanishing twin, and mono-chorionicity. Cerebral palsy (CP) is the most serious handicap of infancy and is the major cause of medico-legal disputes in obstetrics (Lynch et al, 1996). CP is a syndrome since the etiologies are various. It is not a single nosological entity

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but a collection of motor disorders due to cerebral impairment that may have occurred during either fetal or early child development. Diagnosis of cerebral palsy is typically made at age 2-3 years, and few studies are willing to wait this length of time for a definitive diagnosis. The study of behavior-related phenomena should provide insight in the developmental pathway of fetal CNS and lead to the development of an intrauterine neurological examination sensitive enough to predict fetuses at risk and preventing or at least reducing cerebral handicaps acquired in fetal life. With 4D sonography it is now possible to produce reproducible parameters for the assessment of normal neurobehavioral development. As a long awaited response to the question of antenatal causes for CP, Kurjak and coworkers discovered and developed 4D US and its potential for prenatal observation of abnormal fetal behavior. They created the KANET scoring test which uses a system of eight fetal structural and behavioral parameters to evaluate the status of fetal neurodevelopment. There is urgent need for further multicentric studies applying KANET in singleton- and multiple pregnancies until a sufficient degree of normative data is available and the predictive validity of specific aspects of fetal neurobehavior to child developmental outcome is better established.

THE ASSESSMENT OF NEURODEVELOPMENT OF TWINS BY A NEW TEST BASED ON 3D-4D SONOGRAPHY

A. Kurjak, U. Honemeyer

There is now ample evidence that fetal behavioral patterns are directly reflecting developmental and maturational processes of the fetal central nervous system (CNS). Advances of four dimensional ultrasound (4D US) technology created conditions to develop a new sonographic antenatal neuro-developmental test (KANET). 4D US offers a practical means to assess both the fetal brain function and structure, thereby permitting distinction between normal and abnormal patterns of fetal activity, and offering early recognition of fetal brain impairment in utero. The KANET scoring test uses a system of 8 fetal structural and behavioral parameters to evaluate the status of fetal neurodevelopment. The score for abnormal fetuses is 0 to 5, borderline score is from 6 to 9, and normal score is 10 and above. Antenatal 4D ultrasonographic studies of twins contain the potential to provide valuable information in regards to twin-specific intrauterine conditions of neurodevelopment (inter-twin stimulation), and the augmented risk for neurological impairment especially in monochorionic (MC) twins. The discussion of whether multiple pregnancy with sensory stimulation by intertwin contacts, show accelerated process of neurological maturation, is still controversial. However the need for diagnostic tools in the prenatal assessment of neuro-development in twins is voiced unanimously, mainly because an increased risk for neuromorbidity of MC twins is evident. The authors present the results of n twin- and n triplet pregnancies tested with KANET between April 2010 and Jan 2012, and compare the KANET scores with individual postnatal neurological outcome. To evaluate the question of differences in neuro-development of singleton- and multiple pregnancies reflected by different fetal behavior, KANET scores of multiple pregnancies and of a singleton control group are compared at certain gestational ages.

MONO TWINS ARE BETTER IN STEREO: EFFECTS OF BIOLOGICAL MATERNAL SOUNDS ON CARDIORESPIRATORY AND GROWTH OUTCOMES IN EXTREMELY PRETERM TWINS

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This study examined the effects of recorded maternal sounds on respiratory outcomes in preterm twins born between 25-32 weeks gestation. The underlying hypothesis was that the infant's immature capacity for breathing and self-regulation can be enhanced by providing the biological auditory stimulation which would otherwise be available in utero. Twin infants were assigned in pairs to receive either maternal sounds (Treatment group; T-twins) or standard care (Control group; C-twins). T-twins were exposed to audio recording of their own mother's voice and heartbeat 4x/24 hour period. Treatment was initiated within the first week of life and continued throughout the entire NICU hospitalization. Sounds were delivered via a micro audio system installed inside the infant's isolette/crib. Results show that the T-twins required less days of respiratory support on high/low flow nasal cannula as compared to C-Twins. There were no differences between the groups in the number of days on mechanical ventilation and CPAP. We have additionally compared the T-twins with a group of singletons matched for illness severity and length of stay (T-singletons). Results indicate that T-twins required notably less time of CPAP support than T-singletons who received the same type of maternal sounds treatment. Future studies are needed to determine whether infants of multiple gestation pregnancies might be more inclined to benefit from maternal sounds treatment due to the socially-enriched sensory environment they experience in the womb.

THE BIOLOGY OF MULTIPLE IMPLANTATION IN TWINNING

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Multiple pregnancy implies multiple embryos present followed by multiple implantation. Multiple embryos result from either multiple follicle growth followed by multiple fertilization or early splicing of a single embryo. One could question if women that developed a multiple pregnancy implant better then women that deliver singletons. It is very hard to answer such a question based on data from the general population since it is mostly completely unknown whether a singleton pregnancy followed after presence of only one embryo. On the other hand a multiple pregnancy is unmistakingly associated with the presentation of more than on embryo. The clinical situation of In Vitro

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Fertilization (IVF) allows strict control for the number of presented embryos. In the past this was a common practice with IVF to transfer 2 or more embryos. So, comparison of patients that develop a multiple pregnancy after multiple embryo transfer will yield information about factors that contribute to multiple implantation. According to this principle we recently performed a number of studies. First we found that no more women who delivered a twin after double embryo transfer (DET) with the IVF had twins in their family compared to singleton mothers indicating that with familial dizygotic twinning implantation does not play a dominant role. Next, by comparing blood levels of compounds that are involved in new blood vessel formation, which is thought to play a role with implantation, we found that, prior to any treatment, mothers who carried a twin after DET had much higher Vascular Endothelial Growth Factor (VEGF) compared to the singleton mothers. The IVF twin mothers in this small study had a higher body mass index indicating that in part the body composition as a possible derivative of altered growth factor activity. Data from a much larger Dutch cohort of IVF patients showed that twin mothers after DET are taller then the singleton mothers after the DET. It is concluded that pregnancy and delivery of a dizygotic twin is associated with certain features of body composition which may be related to growth and improved implantation. And as such, it could contribute to natural DZ twinning in addition to the multiple follicle development which is indispensable for this condition.

GESTATIONAL AGE AT DELIVERY IS THE ONLY PREDICTOR OF NEONATAL OUTCOMES IN TRIPLETS

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Background: The optimal timing of delivery for triplet pregnancies is unclear. Obstetricians incorporate maternal and fetal factors, as well as gestational age (GA), in their decision to deliver triplets. *Objective:* Explore short term neonatal outcomes in triplets according to GA and to maternal and fetal conditions. *Design/Methods:* A historical cohort of triplets, born in a tertiary centre between January 1999 and December 2010, was analysed, using logistic regression model analyses. Triplets delivered <20 wks of GA were excluded. Regression models including maternal/neonatal demographics and antenatal factors as covariates were compared to a simple model with GA as independent predictor for the following outcomes: neonatal death (NND), respiratory distress syndrome requiring continuous positive airway pressure (RDS-CPAP), RDS requiring surfactant (RDS-S), intubation/ventilation, bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), sepsis, jaundice, hypoglycemia, parenteral nutrition and a composite neonatal outcome. *Results:* There were 52 sets of triplets, of which 145 babies were live-born. One set of triplets born at a GA of 22.6 wks was not resuscitated but was included in the eight (5.5%) NND. The mean GA at birth of viable triplets was 31.9 wks (SD±3.1; range 24.1 to 38). Crude odds ratios (ORc) were calculated per one week decrement in GA at birth. The ORc for NND was 1.8 (95% CI 1.3-2.4). The ORc for RDS-CPAP was 1.7 (1.4-2.1), for RDS-S 2.0 (1.6-2.6), for intubation 2.2 (1.7-2.8) and for sepsis 2.2 (1.6-3.0). The ORc for a composite outcome of BPD, NEC, ROP and IVH was 2.1 (1.6-2.9). Almost all models were not affected by these covariates: small for GA, newborn gender, year of birth, preterm rupture of membranes, chorioamnionitis, antenatal corticosteroids, triplet chorionicity, use of reproductive technologies to conceive, parity and maternal age. PDA and jaundice were the only outcome for which the gestational age ORc was affected by some cofactors. *Conclusions:* Gestational age, on its own, is the most important predictor of short term neonatal outcomes in triplets, with no or minimal impact from maternal or fetal factors.

INFLUENCE OF MODE OF DELIVERY AND GESTATIONAL AGE ON NEONATAL COMPLICATIONS IN TWIN PREGNANCIES?

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Many factors can have impact on neonatal complications of twin pregnancies. There are various opinions pertaining to the question 'should every twin preganancy end with ceasarian section?' Aim: The aim of this study was to compare the impact of method of delivery and gestation age on frequency of neonatal complications in twin pregnancies. *Materials and Methods:* This retrospective study has analysed a series of cases of twin pregnancies and the impact of method of delivery and gestation age on frequency of neonatal complications. The study has been executed at the Clinics of Obstetrics and Gynecology University Clinical Centre of Kosova, in the time period 2009-2010. We have analyzed 267 pregnancies delivered by cesarean section and 131 vaginal deliveries. Cases with abruptio placenta, placenta previa, congenital anomalies, Twin-to-Twin Transfusion Syndrome (TTTS), fetal deaths and pregnancies of less than 28 gestation weeks were excluded from the study. The Odds Ratio and confidence interval 95% (95% CI) has been calculated with multiple logistic regression analysis for mode of delivery and gestation age as independent variables. *Results:* Risk scale decreased for all complications for deliveries on term, regardless of method of delivery. Pre-term cesarian section deliveries have decreased the risk scale for appearance of perinatal asphyxia (OR = 0.57), IVH (OR = 0.47), RDS (OR = 0.95), need for respiratory care (OR = 0.78) and exitus (OR = 0.9), respectively. *Conclusions:* Gestational age significantly decreases the risk for appearance of any of neonatal complications, regardless of mode of delivery.

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MULTIPLE PREGNANCY: FARO HOSPITAL'S 2010/2011 EXPERIENCE

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Introduction: In the last 30 years, a worldwide tendency facing an increase in multiple pregnancy has been evolving. Many factors can explain this ascending incidence in multiple birth. Advanced maternal age and developing assisted reproductive technologies were the main contributors for this noticeable increase. However, multiple pregnancy is associated with increased risks of maternal and fetal complications, and therefore greater risk of poor perinatal outcomes. As a result, antepartum care of multiple gestations should be directed at anticipating complications more frequently affecting multiples, as well as managing regular conditions arousing even in a single pregnancy. Management algorithms for twins and higher order multiples have been adopted to minimize adverse maternal and fetal situations and accomplish successful pregnancy development. *Objectives:* Our main purpose was to review the different pregnancy related characteristics, as well as its evolution and maternal-fetal outcomes in multiple pregnancies. Material and *Methods:* A retrospective study of all cases of multiple pregnancies, whose surveillance and delivery occurred at our Hospital, between 2010 and 2011, was carried on, with review of the clinical records. We analyzed in total 90 cases of multiples, all but one cases of twins. All cases were analyzed taking in account maternal characteristics (age, parity, race) pregnancy evolution (spontaneous vs. assisted reproductive techniques, chorionicity, obstetric complications), delivery (gestational age and type of delivery), and also newborns outcomes (weight, apgar index and complications). *Results and Discussion:* Our preliminary results show us an equal distribution in number of multiple gestations in 2010 and 2011. Even in the merge of assisted reproductive medicine, in most cases, multiples pregnancy resulted of spontaneous conception, and advanced maternal age, namely 35 years of age or more, was seen in 21% of the women. As expected, a small number of monochorionic gestations was considered, and only 11% of births occurred by vaginal delivery. Obstetric complications were mainly associated to preterm labour and preterm rupture of membranes. Besides prematurity, newborn complications related more commonly to fetal growth restriction. Further results will be discussed in time. In our center experience, a small percentage of non spontaneous multiple pregnancies, can be explain by the low income population, as well as the low rate of assisted reproductive techniques. Still, maternal and fetal complications of multiple gestations mimic the worldwide tendency in the increment of preterm births and consequently newborn prematurity.

TRIPLET PREGNANCY: SYMMETRIC DEVELOPMENT OR FETAL GROWTH RESTRICTION?

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Introduction: An epidemic increase in multiple gestations has been taking place in recent decades. Triplets and higher order multiples have increased by more than 50% since then, mainly due to assisted reproductive technologies. Even so, triplet pregnancy is quite uncommon, particulary in our center, accounting for one case every 2 to 3 years. Prenatal care and management of a triplet pregnancy is quite challenging. Additional maternal and fetal conditions need to be taken into consideration as the pregnancy evolves, as the risks of developing complications is even higher than those seen in twin gestations. Close and cautious monitoring, as well as intensive and proactive interventions are required for a good perinatal outcome. Therefore an appropriate managment program and a multidisciplinary team are required for the duration of the pregnancy. Clinical Case: A healthy 27 year old women. No relevant personal history. Primigravida with a triplet pregnancy, dichorionic triamniotic, after a course of induction of ovulation.Normal evolution in the first trimester, with normal fetal growth and development.First admitted at 24 gestational weeks for a course of tocolitics and fetal maturation with corticosteroids due to the risk of preterm labour. The fetal growth was symmetric by this time. Treatment followed in an outpatient manner, with regular appointments and ultrasounds until the 28th week of gestation, when uterine contractions were noticed and the fetal fibronectin test was positive. The patient was then admitted to prevent preterm labour and tocolitic medication and a rescue course of corticosteroids was attempted, with a successful result. By this time, a fetal discrepancy of 17% between the smallest and biggest fetus was noticed, although it was still considered as normal development for a triplet pregnancy. It was then decided to keep the patient under continuous surveillance as an inpatient until delivery, in order to lower the risk of preterm labour and to allow for closer monitoring of the fetal growth. By the 32nd week of gestation, the fetal weight discrepancy was only of 6%, but the smaller fetus presented an altered umbilical artery resistance index, without further findings. Delivery occurred at 34 gestational weeks by cesarean section, one boy and two girls, birthweights 2410g, 1955g and 1140g, respectively. In the perinatal period, the smaller baby presented with objective signals compatible with Ito's hypomelanosis. *Conclusion:* A triplet gestation can be considered not only a challenge for the parents, but also an arduous task for the obstetrician. With the increased use of assisted reproductive technologies, multiple gestations have become more frequent, but still triplet pregnancies are quite rare. In our case, the pregnancy evolved quite well and a successful outcome was accomplished. Fetal

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growth was always a matter of concern, with weight discrepancies within the normal limits for triplets. In multiple pregnancies some degree of fetal growth restriction is expected and lower birth weights are considered normal. Nonetheless, the smaller baby presented with an unusual syndrome, Ito's hypomelanosis. Could this situation be responsible for fetal growth restriction?

MEDICAL AND HEALTH CORRELATES OF DISCORDANCE IN COGNITIVE PERFORMANCE BETWEEN ELDERLY TWINS: PRELIMINARY FINDINGS FROM THE OLDER AUSTRALIAN TWINS STUDY

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Background and Aim: Cognitive decline is a characteristic feature of ageing and age-related diseases like dementia. Using a sample of monozygotic twins to control for genetic influences, we have conducted a preliminary exploration of medical and general health risk factors associated with cognitive decline in later life. *Method:* The sample comprised 125 pairs of monozygotic twins (67% female; mean age: 71 years) from the Older Australian Twin Study. The potential risk factors investigated included acute myocardial infarction, angina and other cardiac conditions (any of arrhythmia, myopathy or valve disease), hypertension, diabetes, six-metre walk performance (time, posture and gait), sit-to-stand time, visual acuity, and smelling ability. Cognitive measures addressed three cognitive domains. Processing Speed was tested using Trail Making Test A (TMTA) and Digit Symbol. Executive Functions were tested using the Controlled Oral Word Association Test, Digit Span Backwards and ratio of Trail Making Test B/TMTA (TMTB/A) scores. Episodic Memory was tested using Logical Memory (immediate and delayed recall), the Rey Auditory Verbal Learning Test (RAVLT; total learning, immediate and delayed recall) and the Benton Visual Retention Test (BVRT). For each test, we determined how the difference in performance between twin pairs correlated with the difference in the presence or extent of each potential risk factor. *Results:* There were a number of significant correlations ($p < 0.05$) between potential risk factors and particular cognitive measures. Angina was correlated with RAVLT delayed recall (r = 0.215) and visual memory (BVRT, r = -0.209), while other cardiac conditions correlated with cognitive flexibility (TMTB/A ratio, r = -0.234). There were also correlations between both hypertension and sit-to-stand time and TMTA (r = 0.256 and r = 0.217, respectively), cholesterol and Logical Memory delayed recall (r = -0.187), and smelling ability and working memory (Digit Span Backwards, r = 0.257). Of the six-metre walk measures, time correlated with Digit Symbol (r = -0.342) and gait correlated with each of RAVLT total learning (r = -0.238), immediate recall (r = -0.316), and delayed recall (r = -0.207). *Discussion:* Using a sample of elderly twins, our preliminary analyses identified significant associations between differences in the presence or extent of medical and general health factors and differences in cognitive performance. Effects were found for each of the Processing Speed, Executive Functions and Episodic Memory domains. Especially interesting were correlations between measures of physical functioning and tests of both Processing Speed and Episodic Memory. Our results suggest that particular non-genetic risk factors are associated with cognitive decline in elderly individuals. Further studies are needed to verify our findings, to explore the possible interactions between risk factors, and to determine the causal relationships between medical and general health factors and cognitive decline in later life.

THE EFFECT OF LEISURE-TIME PHYSICAL ACTIVITY ON SLEEP QUALITY

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Poor sleep quality and short sleep duration are associated with adverse health outcomes and has become a worldwide problem. However, some population based studies have shown that regular exercise improves sleep quality and increases sleep duration. To study the hypothesis that leisure-time physical activity may promote better sleep quality and longer sleep duration in adults, we examined the associations between leisure-time physical activity and sleep quality in 429 participants (219 men and 210 women; 168 MZ, 186 DZ and 75 OS) aged 28-78 years (mean 49 y ± 10) from an ongoing follow-up study including twins from the Danish Twin Registry (GEMINAKAR). This constitutes about one third of the total cohort under enrolment. The participation rate of the study is so far 82%. Body weight and height were measured in a mobile examination center (MEC), i.e. an auto-camper equipped with examination and laboratory facilities. All twins willing to participate are visited at home or another place at their convenience. Physical activity during leisure-time was examined using a validated questionnaire, whereas sleep quality and duration were assessed by the Pittsburgh Sleep Quality Index (PSQI) questionnaire. The mean sleep duration was 7.06 ± 0.89 hrs. PSQI scores above 5 indicate subjects with bad sleep quality. In the present study the overall score of the PSQI was within the normal range (50% percentile = 3). There was, however, a difference in the overall score

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between the two sexes showing better sleep quality in men ($p = 0.017$). Univariate regression analysis with sleep quality as the dependent variable and sex as independent variable showed sex to be a predictor for sleep quality (ß-coef. 0.8, 95% CI 0.3 - 1.3). The median BMI was 25.3 kg/m2, men having a higher BMI than women (25.9 kg/m2 and 24.6 kg/m2 respectively, $p < 0.01$). Various univariate analyses with sleep quality as the dependent variable and level of leisure-time physical activity, BMI, age and age groups as independent variables demonstrated that none of these variables were associated with sleep quality. A multivariable regression analysis with sleep quality as the dependent variable and sex, BMI, leisure-time physical activity and age as independent variables also showed that sex was the only variable to be a predictor for sleep quality (ß-coef. 0.8, 95% CI 0.3 - 1.3). In conclusion, our preliminary results from this study suggest that sex has a significant effect on sleep quality, whereas leisure time physical activity does not.

MONOCHORIONIC TWIN PLACENTAS: COMPLICATIONS OF THE SHARED CIRCULATION

L. Lewi

Complications of the shared circulation account for the excess mortality in monochorionic twin pregnancies. During intrauterine life, dichorionic twins have separate circulations, while about 95% of monochorionic twins have anastomoses on the placental surface, which connect the 2 circulations. The typical monochorionic placenta has several artery- to-vein (AV) anastomoses, usually in both directions. AV connections allow flow in one direction only. They dip into the placenta close to one another and exchange blood at the capillary level in the depth of the placenta. Besides several AVs, there is usually also 1 artery-to-artery (AA) anastomosis that forms a direct communication between the arteries of both twins. An AA anastomosis allows blood flow in both directions, because it functions as a flexible AV connection and thus compensates for any imbalances that occur over the unidirectional AV anastomoses. Only about 1 in 4 monochorionic placentas has a direct vein-to-vein (VV) anastomosis, which also allows flow in both directions although their function is less well understood. Because of the anastomoses, the monochorionic placenta actually consists of 3 parts, 2 for each twin individually, and a third part that is shared and supplied by AV anastomoses. The nearly ever-present blood exchange between the twins can cause severe amniotic fluid discordances as typically seen in twin-to-twin transfusion syndrome (TTTS) or in severe hemoglobin differences as in twin anaemia polycythemia sequence (TAPS). In contrast to TTTS that usually occurs in mid-gestation, TAPS is a complication of the 3rd trimester. The angioarchitecture in TAPS differs from that in TTTS, because in TAPS the anastomoses are extremely small. The presence of AA anastomoses seems protective against the development both of TAPS and TTTS. Fetoscopic laser coagulation of the anastomoses is the best treatment for TTTS. However, missed anastomoses are common and probably depending on injection techniques occur in about 4% to 33% of cases. The type, number and size of missed anastomoses determine if there will be an uneventful outcome, a double demise, recurrent TTTS or TAPS. Another consequence of the shared circulation is that the well-being of one twin critically depends on that of the other. After the diagnosis of spontaneous demise of one of a monochorionic pair, the survivor has a 15% risk of death and a 25% risk of handicap because acute hemorrhage along the anastomoses into the body and placenta of its demised co-twin. Double demise is more common in the presence of an AA anastomosis. The fact that their well-being is interrelated poses specific problems in the management of severe discordant growth and imminent demise of one of the twins or if one twin has a severe anomaly and selective reduction is considered. Isolated discordant growth is primarily caused by an unequal placental sharing. When single demise occurs in the early embryonic period, the demised twin's body can continue to grow because of reversed blood supply along AA and VV anastomosis as in the twin reversed arterial perfusion (TRAP) sequence. Finally, monoamniotic twins probably have the most tightly linked blood circulations, which together with the ever-present cord entanglement make them especially vulnerable to unpredictable and often double demise.

INFLUENCE OF FETAL SEX ON FIRST TRIMESTER MATERNAL SERUM MARKERS FREE SS- HCG AND PAPP-A USED FOR DOWN SYNDROME SCREENING IN TWIN PREGNANCIES

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Objective: In the Netherlands risk estimations for trisomy 21 are conducted by the first trimester combined test, based on maternal age, ultrasound nuchal translucency (NT) measurement and maternal serum markers free ß-hCG and PAPP-A. In singleton pregnancies it is known that marker levels of free ß-hCG and PAPP-A are influenced by fetal sex. In pregnancies with a female fetus both levels of free ß-hCG and PAPP-A are reported to be increased compared to pregnancies with a male fetus. In general serum levels in dichorionic twin pregnancies are doubled compared to singleton pregnancies. Currently no data are available on the effect of fetal sex on marker levels in twin pregnancies. *Patients and Methods:* Data of twin pregnancies were extracted from the database of our tertial fetal medicine center. Euploid, dichorionic (DC) twin pregnancies on first trimester scan were selected. Maternal free ß-hCG and PAPP-A were measured between 9 and 14 weeks of gestational using the Delfia Xpress

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(PerkinElmer, Finland) and are expressed as the weight corrected multiple of the median (MoM values) compared to singleton pregnancies. Outcome of the pregnancy was known in all cases and fetal sex was determined after birth. *Results:* A total of 100 cases were included. The mean maternal age was 34.3 ± 3.7 years. The median gestational age at sample withdrawal was 83 days (range 65 (9 + 2 weeks) - 96 (13 + 5 weeks)). Of the selected DC twin cases 50 consisted of two male fetus (♀♀) and 50 of two female fetus (♀♀). The median weight corrected free ß-hCG MoM was 2.20 in pregnancies with two male fetus (♂♂ = 50) and 1.97 in pregnancies with two female fetus (♀♀ = 50) (Mann Whitney U, p = 0.48). Marker levels of PAPP-A demonstrated a tendency towards higher levels in cases with two female fetus, namely median weight corrected PAPP-A MoM was 2.11 for male fetus (♂♂ = 50) compared to 2.55 in female fetus (♀♀ = 50) (Mann Whitney U, p = 0.06). *Discussion:* Although marker levels of free ß-hCG and PAPP-A are reported to be increased in case of a single female fetus, we do not confirm this finding in dichorionic twin pregnancies. Only for PAPP-A we found a tendency towards higher levels in ♀♀ twins compared to ♂♂ twins. Application of a correction for fetal gender in twin pregnancies does not appear to be justified at this stage.

SELECTIVE AND NON-SELECTIVE INTRAUTERINE GROWTH RESTRICTION IN TWIN PREGNANCIES: A SMALL COHORT STUDY

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Introduction: Twin pregnancies account for 1-2% of all pregnancies. Intruterine growth restriction (IUGR) occurs in approximately 9.1% of all twin pregnancies and 9.9% of monochorionic (MC) twins. The IUGR phenotype in twins can be divided in two categories: selective IUGR (sIUGR), where just one of the twins meets the criteria for IUGR, and non selective IUGR (non-sIUGR), where both fetuses are IUGR. The aim of our study was to evaluate the risk factors and perinatal outcome in twins affected by sIUGR and non-sIUGR. *Materials and Methods:* The small population we considered was composed of 56 twin pregnancies followed by our 'Twin Pregnancy Ambulatory' from June 2010 to December 2011 until delivery, which occurred in our Clinic. We analyzed retrospectively the obstetric management and neonatal outcome of MC and DC pregnancies complicated by s-IUGR and non-sIUGR. The examined population was then classified in two groups, according to the corionicity, and the IUGR-categories were evaluated in the two distinct subgroups. We took an expectant management with serial ultrasound evaluation every 3-4 weeks in BC pregnancies, every 2 weeks in presence of IUGR, and every week in MC pregnancies. Delivery was carried out in most cases through a cesarean section. *Results:* In our population 62.5% were BC pregnancies and 37.5 % MC pregnancies. A fetal growth discordance occurred in 26% of the cases considered (15/56). Among these 5 were non-sIUGR (9%) and 10 were sIUGR (18%). We observed in the group of BC pregnancies only one miscarriage and one case of single fetal demise, which happened in the second trimester. Two cases of pre-eclampsia were registered: one in the subgroup of BC twin pregnancies with s-IUGR and one in the subgroup with regular fetal growth. The prevalence of sIUGR among the BC twin pregnancies was 14.3% (5/35), and the average gestational age at which delivery was carried out, was 35 weeks. Similarly, the prevalence of non-sIUGR was 14.3% (5/35) and the average gestational age at which delivery occurred, was 37 weeks. In 65.4% of the cases no growth discrepancy between the two twins was observed. The neonatal complications which occurred in this group, depended on obstetrical pathologies like pre-eclampsia, p-PROM and preterm delivery, causing a severe prematurity. We also considered the group of MC pregnancies, observing that the prevalence of sIUGR was 23.8% (5/21). Among these five MC pregnancies with sIUGR, two were complicated by sIUGR type 1, one by type 2 and two by type 3. Neonatal outcome was quite bad considering that we had 1 intrauterine fetal death, 6 cases of intraventricular hemorrhage, 3 cases of respiratory distress syndrome, 1 case of necrotizing enterocolitis and 2 cases of retinopathy. *Conclusion:* Although our sample was quite restricted, these data confirm what is already reported in the literature. Twin pregnancies show a higher rate of sIUGR than non-sIUGR. Corionicity is a risk factor for the development of sIUGR giving a worse neonatal outcome respect to BC twins with growth discordance.

FATAL CEREBRAL INJURY IN RECIPIENT TWIN WITH TWIN ANEMIA-POLYCYTHEMIA SEQUENCE

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Twin anemia-polycythemia sequence (TAPS) results from slow inter-twin blood transfusion through minuscule placental vascular anastomoses and is characterized by large inter-twin hemoglobin differences in the absence amniotic fluid discordances. The optimal management for TAPS is not clear. We report a case of TAPS detected antenatally by Doppler ultrasound examination and managed expectantly. An emergency Cesarean section was performed at 34 + 5 weeks. The recipient twin had severe polycythemia-hyperviscosity requiring partial exchange transfusion and developed abnormal clinical neurologic symptoms (apnea and seizures). Amplitude-integrated electroencephalography showed a pathological flat-trace pattern. On magnetic resonance imaging, extensive cerebral injury was detected, including diffuse ischemia, extensive hemorrhage and

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absent perfusion. The infant died on day 3. This case report demonstrates that TAPS may lead to severe cerebral injury and fatal outcome in recipient twins. The importance of Doppler ultrasound investigations and management dilemma in TAPS are highlighted.

CEREBRAL INJURY IN TTTS TREATED WITH FETOSCOPIC LASER SURGERY: A MATCHED CASE-CONTROL STUDY

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Objective: To determine the incidence and risk factors for cerebral lesions in monochorionic twins with twin-twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery compared to dichorionic twins. *Methods:* We performed a retrospective case-control study on cerebral injury detected by cranial ultrasound in monochorionic twins with TTTS treated with laser, compared with a control group of dichorionic twins matched for gestational age at birth. All TTTS-survivors and DC twins delivered at our center between 2004 and 2011 were eligible for the study. *Results:* Incidence of severe cerebral lesions in the TTTS group and control group was 9.0% (24/267) and 6.7% (18/267), respectively ($p = 0.335$). In a multivariate analysis in the TTTS group, lower gestational age at birth was the only factor independently associated with increased risk for severe cerebral lesions (odds ratio (OR) 1.28 for each week; 95% confidence interval (CI) 1.08-1.51).The incidence of cerebral lesions decreased from 13.1% (11/84) in the TTTS group treated in the first half of the study (2004-2007) to 7.1% (13/183) in the second half (2008-2011)(OR 0.51; 95%CI 0.20 1.28). *Conclusion:* Incidence of severe cerebral lesions in TTTS treated laser is similar to a matched control group and is independently associated with prematurity. We found a trend towards improvement in short-term neurological outcome in the TTTS-group treated in more recent years.

RISK FACTORS FOR PREECLAMPSIA IN TWIN PREGNANCIES: A POPULATION-BASED MATCHED CASE-CONTROL STUDY

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Objective: The objective of our study was to examine the association between several risk factors and preeclampsia in twin gestations. Patients and *Methods:* We performed a case-control study using a population dataset of twin pregnancies delivered after 24 weeks in Slovenia between 1997 and 2009. Cases were gestations complicated by preeclampsia and controls were cases matched by gestational age, parity, and chorionicity. *Results:* We identified 181 cases of preeclampsia in twins and 542 matched controls. High pre-pregnancy body mass index (BMI) and gestational diabetes were significantly associated with preeclampsia ($p<0.001$ and $p = 0.04$, respectively). The association was not significant for preexisting hypertension, maternal age, smoking, and pregnancy following assisted reproduction. *Conclusions:* High pre-pregnancy BMI carries an especially high risk for the development of preeclampsia and its complications in twin gestation.

THE EFFECT OF FETAL LOSS ON PREGNANCY OUTCOMES: LESSONS FROM ASSISTED REPRODUCTIVE TECHNOLOGY

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Introduction: Research comparing assisted-conception versus spontaneous-conception pregnancies has shown an excess of adverse outcomes in the former group, even when stratified by plurality. Important reasons for this difference may be the residual effects of fetal loss on the subsequent growth and birthweight of the surviving fetuses, or the effect of the number of embryos transferred even when plurality at conception and at birth are equal. *Materials and Methods:* Data from the Society for Assisted Reproductive Clinic Outcomes Reporting System (SART CORS) database was used to evaluate 1) the effect of first trimester fetal losses in singleton and twin births; and 2) to evaluate the effect of the number of embryos transferred in singleton and twin births when plurality at conception and at birth were equal. The Effect of Fetal Loss in Singleton Births: The study population included 21,535 singleton deliveries of ≥22 weeks gestation categorized by the number of fetal heartbeats on early ultrasound. Adjusted odds ratios (OR) were calculated with the group with one heartbeat on early ultrasound as the reference group. Preterm birth (<37 weeks, AOR 1.73, 32-36 weeks, AOR 1.59; <32 weeks, AOR 2.56) and low birthweight (<2,500 g, AOR 2.09; 1,500-2,499 g, AOR 1.94) increased significantly and term birth and non-low birthweight decreased significantly (AOR 0.52 and 0.48, respectively). The Effect of Fetal Loss in Twin Births: The study population included 9,036 twin pregnancies of ≥22 weeks gestation categorized by the number of fetal heartbeats on early ultrasound. Adjusted odds ratios (OR) were calculated with the group with two heartbeat s on early ultrasound as the reference group. Preterm birth (<37 weeks, AOR 1.35, 32-36 weeks, AOR 1.28; <32 weeks, AOR 1.47) and low birthweight (<2,500 g, AOR 1.47; 1,500-2,499 g, AOR 1.38, and <1,500 g, AOR 1.69) increased significantly and term birth and non-low birthweight decreased significantly (AOR 0.74 and 0.68, respectively). The Effect of Number of Embryos Transferred When Plurality at Conception and at Birth Are Equal: The study population included 23,645 singleton deliveries and 14,083 twin deliveries. The risk for moderate growth restriction (birthweight for gestation z-score <-1) among singletons was increased by 15%, 23%, and 37%, respectively, with 2, 3, and ≥4 embryos transferred. Among twins, the risk was increased by 50% and 105%, respectively, with 3 or ≥4 embryos trans-

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ferred. *Conclusions:* Early embryonic loss is associated with significantly increased likelihood of lowered birthweight and birthweight-for-age. Even when plurality at conception equals plurality at birth, transferring ≥3 embryos is associated with significantly increased risk of growth restriction in both singleton and twin pregnancies. These findings were originally published in Fertility and Sterility 2009; 91:2578-85, 2586-92, and in the Journal of Reproductive Medicine 2010; 55:387-94.

THE CHANGING PATTERN OF MULTIPLE BIRTHS IN THE UNITED STATES

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Rising Incidence of Multiple Births: Prior to 1980, the incidence of twin births in the United States was stable at about two percent of all births, but it has risen dramatically during the past three decades. In 2009, 1 in every 30 babies born in the United States was a twin, compared to 1 in every 53 babies in 1980; 1 in every 651 babies was a triplet or higher order multiples, compared to 1 in every 2,702 in 1980. Increases in the twin birth rate averaged more than two percent per year from 1980 to 2004, peaking at more than 4% between 1995 and 1998. Since 2005, the pace of increase has slowed to less than 1% annually. Increases in the triplet and higher order multiple rate averaged 10 percent per year and peaked at 193.5/100,000 live births in 1998, more than 400% increase over the rate of 37.0/100,000 in 1980. Since 1998 the rate has fluctuated but generally trended downward; the rate in 2009 was 153.5/100,000, 20% lower than the 1998 peak. Older Maternal Age: The rise in multiple births has been attributed to two related factors: older age at childbearing and the growing availability and use of fertility-enhancing therapies. Twin birth rates increased for women of all ages between 1980 and 2009, with the largest increases among women aged 30 and over. For women aged 30-34, the rates increased 76%, for women aged 35-39, nearly 100%, and for women aged 40 and over, the rates increased by more than 200%. In 2009, 7% of all births to women aged 40 and over were born in a twin delivery compared to 5% of births to women aged 35-39, and 2% of births to women under age 25. Use of Fertility-Enhancing Therapies: Older maternal age accounts for about one-third of the total rise in the twin birth rate over the past three decades. Two-thirds of the rise is due to the increased use of fertility-enhancing therapies, including both assisted reproductive technologies (ART) and non-ART treatments (ovulation stimulation medications without ART). About 12% of women in the United States have had infertility therapies, and their availability and use has increased over the past decade. Since 1996, the number of ART cycles has more than doubled, and the number of deliveries and live births has more than tripled. In 2009, about 32% of all live births from ART were multiples; 29% were twins and about 2% were triplet and higher-order multiples. Implications: The rise in multiple births has important health implications, including greater morbidity and mortality risks and higher health care costs. Continued research is necessary to improve the outcomes of multiple births.

DEVELOPMENTAL GENETIC MODELING OF ADOLESCENT SMOKING

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Previous studies have suggested a changing role for the contributions of genetic and shared environmental factors to liability of smoking initiation during adolescence. The current study combines data from the twins and parents of the Virginia Twin Study of Adolescent Behavioral Development to jointly estimate the mean level of smoking initiation ('have you ever smoked a cigarette') and the causes of individual differences in smoking initiation. Structural Equation Modeling was used to fit alternative genetic models in OpenMx. Prevalence of smoking initiation increased gradually from 5% at age 11 to approximately 50% at age 17. Cross-sectional twin correlations suggested that both additive genetic and shared environmental factors influenced the liability of smoking initiation across the adolescent age range. We will model additive genetic, non-parental shared environmental and cultural transmission contributions as well as their interaction with age using longitudinal twin data. Results may have important implications for prevention/intervention efforts to decrease the consequences of smoking.

PRENATAL TWISTING OF MINIMALLY CONJOINED OMPHALOPAGUS TWINS

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Conjoined twins are a rare complication of monochorionic twin pregnancy. About 33% of conjoined twins are fused ventrally between the umbilicus and the xiphoid cartilage; that is omphalopagus twinning. Most omphalopagus twins are conjoined by a skin bridge that frequently contains hepatic tissue. We report a case of minimally conjoined omphalopagus twins who switched their relative positions during the second trimester of pregnancy. This event was associated with subsequent death of both fetuses.

THE ROLE OF ECHOCARDIOGRAPHY IN MONOCHORIONIC TWIN PREGNANCIES

N. Manning

The incidence of structural congenital heart disease (CHD) is increased in monochorionic twins; this figure

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varies between 4 and 11% in different series and includes all types of cardiac anomaly. The risk appears to increase the later the division of the embryo especially for laterality defects; reasons for this observation have yet to be defined and various theories exist. The cardiac lesions are usually discordant in spite of identical genetic material; the incidence of CHD in monozygotic dichorionic twins is unknown. Acquired structural and functional heart disease in the recipient twin is an associated complication of twin-twin transfusion syndrome (TTTS) and the complex pathophysiology will be discussed. Close monitoring of the cardiovascular status can help anticipate the need for and timing of treatment as well as monitoring its success. Assessment of cardiovascular changes, to derive a cardiovascular score, may be used in conjunction with the established Quintero staging as a more sensitive way of defining the hemodynamic disturbance of TTTS and its progression. It may also help to distinguish between TTTS and selective intrauterine growth restriction (sIUGR).

WHAT CAN A PERINATAL CARDIOLOGIST OFFER TO THE MANAGEMENT OF MONOCHORIONIC TWIN PREGNANCIES?

N. Manning

Structural congenital heart disease (CHD) is increased in monochorionic (MC) twins and an antenatal diagnosis may influence timing, method and place of delivery. Functional (and acquired) structural heart disease is a recognised complication of twin-twin transfusion syndrome (TTTS) and close monitoring is important. In many, successful treatment halts the process of disturbed hemodynamics in which the volume overloaded recipient can develop a cardiomyopathy while the volume depleted donor produces vasoactive mediators in order to preserve systemic vascular resistance. In a few, the cardiovascular pathology persists in spite of treatment; close monitoring is important as deterioration in cardiac function may be one of the factors determining optimal timing for delivery. Some of these complications, particularly right ventricular outflow obstruction, can persist and even progress postnatally; awareness of this potential is important in defining the need for neonatal cardiological assessment as well as longer term monitoring of survivors. Implications for long term health for both the donor and the recipient twin will be discussed.

THE CUBAN TWIN REGISTRY: A FOCUS ON GENETIC EPIDEMIOLOGICAL STUDIES IN COMPLEX DISEASES

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The Cuban Twin Registry is a population-based volunteer register comprising pairs of twins who agree to participate in medical and health related research aimed at investigating the roles of genetic and non-genetic risk factors, in the origin of common complex diseases in the Cuban population. It was established in 2006 and contains 55400 multiple births of all ages and regions of the country. Twins and/or their closest relatives are asked to fill in a questionnaire on physical similarity consisting of 24 items. Additional questionnaires exploring birth defects, genetic disorders, complex diseases as well as social variables have been also conducted in most of the twins. To establish a zygosity classification algorithm we used items from zygosity questionnaire, blood group tests and HLA antigens identification for a subset of 188 same sex twin pairs. Using this algorithm we correctly classify 86.2% of monozygotic pairs and 100% of dizygotic pairs, the global rate of correct classification is 92.5%. Of the total classified twin pairs, 31.3% are monozygotic. The registry has facilitated more than 140 genetic epidemiological studies in complex diseases with very high participation rates all over the country. The focus to date has been primarily in asthma, schizophrenia, major depression, hypertension, alcohol addiction and bipolar disorder. Most of the initial analyses were based on classical twin studies focusing on one trait at a time. More recently we have started to explored co-morbidity mainly in mental disorders. The heritability of affective illness was 0.62 for bipolar disorder and 0.54 for major depression. Bipolar illness, major depression and alcohol addiction were the most frequent disorders in 1st and 2nd degree relatives of twins with bipolar disorder meanwhile major depression, alcohol abuse and generalized anxiety disorder were the most frequent in relatives of twins with major depression. The Cuban twin registry is administered by the National Centre of Medical Genetics and it has become a powerful resource of data for conducting biomedical research in our country.

PROGRESS IN UNDERSTANDING THE GENETICS OF MOLINESS AND MELANOMA

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Cancer geneticists have approached the genetic contributions to melanoma both directly through large case-control GWAS studies, and indirectly through studying the genetics of moliness, which is a powerful endophenotype. Both approaches have been productive and offer complementary views of the etiology of this cancer.

HERITABILITY ESTIMATED FROM TWINS AND FROM SNP ARRAYS: HOW DO THEY COMPARE?

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In general, gene variants with large effects (such as those for diseases showing Mendelian inheritance) tend to be uncommon or rare whereas polymorphic variants (with minor allele frequency over 1%) have small effects. Genome-wide association studies have relied on common tagging polymorphisms and have mainly identified small

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effects; around 1.2 relative risk for case-control studies and 1% of variance for quantitative phenotypes. Combining data in meta-analyses allows detection of smaller effects, and in the near future typing of SNPs with frequency down to 0.1% may detect larger ones. The focus of this presentation is on exceptions to the rule; what can be learned by identifying SNPs with larger allelic effects, and are larger effect sizes found for endophenotypes than for disease? Data come from the QIMR twin and family studies, in which around 8000 adults and 3000 adolescents have genome-wide SNP typing and a wide range of measured phenotypes, including around 30 biochemical risk factors or biomarkers measured in serum or erythrocytes. From this resource, we have extracted data on the relationships between allele frequency and effect size for each phenotype, assessed the frequency distribution of effect sizes, and identified SNP-phenotype combinations where the proportion of phenotypic variance explained is over 5% in our populations. Substantial effects associated with typed or imputed SNPs have been found for bilirubin, cholinesterase, transferrin and uric acid. Other phenotypes including most lipids, liver function tests, iron markers and renal function tests showed significant hits, consistent with results from other groups, but accounting for only small proportions of the phenotypic or genetic variance. The phenotypes showing large SNP effects do have associations with disease or involvement in essential metabolic steps, but the gene variants persist at high frequencies in European (and in most cases, other) populations.

MULTIPLE PREGNANCY AND AUTOIMMUNE DISEASE

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Introduction: The coexistence between autoimmune disease (AD) and pregnancy is frequent. The course of the disease can be affected by the pregnancy and is more likely to initiate the appearance of flares. Also, these patients have more miscarriages, stillbirths, intrauterine growth restriction (IGR), preeclampsia and preterm delivery (PD). Multiple pregnancy (MP) have more complications as preeclampsia, PD and IGR. The objective of our study is to evaluate maternal and fetal outcomes in MP with AD and compare it with MP without AD. *Materials and Methods:* We conducted a descriptive and retrospective study of MP with AU managed in the High Risk Pregnancy Clinic of the Universitary Hospital La Paz (Madrid) since January 2009 to December 2011. Baseline characteristics and perinatal outcomes of women with MP with AU were analyzed and compared with MP without AD. *Results:* 10 MP with AD were found out (2 patients with Systemic Lupus Erythematosus, 2 Sjogren Syndrome, 2 Idiopatic thrombocytopenic purpura, 1 Bechet Disease, 1 sarcoidosis, 1 Miastenia Gravis, 1 Uveitis). The maternal average age (MAA) was 37.5 years. 60% of the patients had spontaneous pregnancy. 100% were dichorionic diamniotic MP. 1 patient had preeclampsia, 1 had IGR and 1 patient had a flare of the disease. PD was registered in the 90% of the patients (< 37 weeks). No significant differences in MAA and perinatal outcomes were found out when compared with MP without AD (20 patients). *Conclusions:* No significant difference in perinatal outcomes were found out in MP with AD when compared with MP without AD. More prospective studies are needed to confirm our hypothesis.

ASSESSING TEACHER KNOWLEDGE OF TWINS & MULTIPLES

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The authors explore the knowledge, preconceptions and misconceptions, of teachers in this initial study. Participants included experienced teachers, as well as, preservice teachers about to enter the profession of teaching. Results revealed that most teachers were not aware of the relevant studies on multiples and their learning / developmental issues. The participants also appeared to be unaware of the research advocating flexible placement and social-emotional sensitivity issues, especially in the early school years. Teachers were also unsure of the learning differences and parental influences on homework and achievement in school. Many respondents appeared to make judgements based on intuition rather than actual experience with twins and multiples. The researchers concluded that greater emphasis should be placed on educating teachers about these issues. Although future research is warranted, there is a need for follow-up studies in light of the increasing enrolment of multiples in our schools.

CARDIAC MORBIDITY IN TTTS: TIME TO REDEFINE PRIORITIES IN MC TWINS?

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Twin-to-twin transfusion syndrome (TTTS) affects 15% of monochorionic pregnancies and develops when uncompensated unidirectional blood flow from one twin ('donor') to the other ('recipient') causes circulatory imbalance. The cardiac effect of the underlying hypervolemia and/or endocrine dysregulation manifests in the recipient as a wide spectrum of echocardiographic findings describing the syndrome-related cardiomyopathy: 55–100% of recipients present with ecocardiographic signs of cardiac compromise, including hypertension, (bi-)ventricular hypertrophic cardiomyopathy, tricuspid regurgitation, ventricular hypokinesia, abnormal flow patterns in the DV, and most importantly right ventricular outflow track obstruction. In the donors, acquired cardiac

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pathology seems to be a much rarer event. Decreased blood volume leading to hypovolemia and reduced placental venous return results in decreased left-sided cardiac output. Coarctation of the aorta may develop and severe placental insufficiency may lead to abnormal Doppler waveforms in the DV, tricuspid regurgitation or umbilical vein pulsations. Even in treated situations with laser coagulation of the anastomoses, cardiac compromise may be caused to both the recipient and the donor. Besides, congenital heart defects occur 12 times more frequently in TTTS twins than in the general population. The MZ twinning process itself may increase the incidence of CHD, by the unequal division of the inner cell mass, disturbance of laterality and by phenotypic variability of the same genome resulting in discordant cardiovascular anatomy. Although the Quintero staging system estimates the severity of TTTS, it disregards the fundamental cardiac involvement of the disease. Therefore, the Quintero staging system for TTTS, based solely in the pathophysiological development of the syndrome, has recently been questioned as a direct and more refined measurement of cardiac function may improve evaluation of disease severity and prediction of outcome. The new cardiac profiling in monochorionic twins is presented.

WHY ARE MONOZYGOTIC TWINS DIFFERENT?

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Although popularly designated as 'identical', monozygotic (MZ) twins are rarely identical. Much has been speculated on the origin of MZ twins and several theories have been proposed. Post-fertilization events such as chromosomal mosaicism, skewed X-inactivation and imprinting mechanisms, as well as other epigenetic mechanisms are responsible for the differences between MZ twins. Innumerous discordant MZ twins have been reported including discordance for lateral asymmetry, major malformation, growth and intrauterine death of the co-twin. This discrepancy may have long-term implications on complex diseases and their predisposition, organ transplantation and interpretation of twin-based studies. We reviewed the genotypic and phenotypic differences between MZ twins and discuss their main causes.

LATE-LIFE ACTIVITY AND FUNCTIONING: A STUDY OF DANISH TWINS

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Individuals who are intellectually, socially and physically engaged function better in late-life than those who are not. Yet leading an active lifestyle does not occur at random, as it is possible that high levels of functioning result in high levels of activity as well as the converse. Twin studies can help resolve the extent to which associations between environmental factors and outcome reflect selection processes versus a causal influence. We use data from the Middle-Age Danish Twin (MADT) study to investigate the nature of the association between late-life activity and functioning. At intake, 4314 twins completed the MADT assessment (mean age of 56.9 years; range of 46-68), which covered medical, physical, intellectual and emotional functioning. Approximately 10 years later, 2387 twins completed a follow-up assessment (mean of 66.7 years; range of 56-80), which again included outcome measures in each of these domains. Additionally, at follow-up twins were assessed for their level of intellectual, physical, and social engagement. We show that the three resulting activity scales are reliable and associated with important indicators of late-life functioning. We also observe greater MZ than DZ twin similarity on each of the three scales, implicating the existence of genetic influences and raising the possibility that associations with outcome are due to selection effects. Cotwin control analysis is applied to help characterize the nature of the activity-outcome correlations. Our results are discussed in the context of the utility of natural experiments, such as twin studies, for strong inference in observational epidemiology.

GENETIC, ENVIRONMENTAL AND AGE CONTRIBUTIONS TO CAROTID INTIMA-MEDIA THICKNESS AND ARTERIAL STIFFNESS IN ITALIAN TWINS

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Atherosclerosis is a condition characterized by narrowing arteries, with endothelial dysfunction affecting the vascular function, and increasing arterial stiffness. Atherosclerosis can be considered a progressive process that starts early in age and may become clinically evident in older age, therefore it can be considered an example of an age-related disease. The purpose of this study is to estimate the genetic, environmental and age contributions to carotid thickness and arterial stiffness in a sample of Italian twins. We performed a classical twin study using 174 twin pairs (82 monozygotic and 92 dizygotic) from the Italian Twin Registry. Twins (mean age 54.5, standard deviation 12.4) underwent clinical and instrumental examinations in three hospitals in Rome, Perugia and Padua, and answered to a questionnaire regarding demographic data, medical history and personal habits. Carotid intima media thickness (IMT) on both sides, augmentation index (AIX) and pulse wave velocity (PWV) were used as markers of atherosclerosis. Common and internal IMT (CCA and ICA) were measured by ultrasound and

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average values of the IMT over the two sides in proximal and distal section were used in the analysis; Aix on brachial artery (Aixbra), aortic augmentation index (Aixao) and PWV on aorta (PWVao) were assessed non-invasively by TensioMed Arteriograph. Variance components methods were used to estimate heritability and environmental effects. In order to take age into account and to estimate its effect on total variance, we incorporated age as variance component in the model. Univariate model-fitting analysis revealed that genetic factors did not influence the variation of internal carotid IMT, common environment accounted for 14% (95% CI: 0-24) of the variance, age for 31% (CI: 22-41) and unique environment for 55% (CI: 44-68). When not accounting for age, common environmental component was 45%. The best fitting model explains variance for common carotid IMT by the effect of genetic factors (23%, 95%CI: 14-32), age (47%, CI: 37-55) and unshared environment (31%, CI: 23-41). The contribution of shared environment could also be removed from the PWVao model; heritability accounts for 38% of variance (CI: 24-50) and the remaining portion was explained by unique environmental effects (43%, CI: 0.32-0.57) and age (19%, CI: 11-28). Regarding Aixbra and Aixao, under the best model, heritability was 38% (CI: 24-50), unshared environmental effect was 43% and age contribution was 19% (CI: 11-28). This study confirms atherosclerosis as an age-related disease, and shows that, in the classical twin design, the effect of age is confounded with that of common environment, if not accounted for. Furthermore, unique environmental factors have a substantial influence on the variation of arterial stiffness and carotid thickness, and therefore primary prevention of atherosclerosis should be promoted and facilitated.

MITOCHONDRIA COPY NUMBER IN PERIPHERAL BLOOD IS A BIOMARKER OF AGING IN DANISH TWINS

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Mitochondria are maternally inherited during conception and are present in multiple copies in a variety of cell types. Both MZ and DZ pairs of twins share identical mitochondria DNA in contrast to that of nuclear DNA, where only MZ are 100% identical. Additionally mitochondria DNA replicate irrespectively of the nuclear DNA replication. Thus variability in the amount of mitochondria DNA may hold information of heritability not detected by classical twin designs. Copy numbers of mitochondria have been suggested as a biomarker of oxidative stress and furthermore to change with age. The evidence, however, is limited to small sample size studies (N<230) and there is inconsistent indications of whether copy numbers of mitochondria decline or increase with age. In addition high copy numbers of mitochondria has been correlated with better mental health in a population of Asian ancestry. Here we studied the relation of mitochondria copy number to age and health using peripheral blood from more than 700 Danish twins. A PCR assay based on the Taqman technology was adapted as a measure of the amount of mitochondria DNA compared to nuclear DNA. DNA from peripheral blood samples was analysed in triplicates to ensure robustness of the technology and results were averaged into a mitochondria copy number score. Samples of DNA were drawn from two population based Danish twin studies, in total comprising 116 twins 18 to 57 years of age and 671 twins 73 to 93 years of age. We found on average 64 copies of mitochondria DNA per nuclear DNA chromosome set in a peripheral blood sample of twins 19 to 57 years of age and a moderate decline with age by 4 copies in 10 years (corr. -0.24 $p<0.001$). Among the twins 73 to 93 years of age high mitochondria copy number adjusted for age and sex was significantly correlated with better physical strength indicated by grip strength (corr. 0.11 $p = 0.01$) and self-reported very good health (OR 1.11 $p = 0.023$). High mitochondria copy number also correlated with better mental health measured by a cognitive composite score (corr. 0.04 $p = 0.23$)) and by MMSE (corr. 0.03 $p = 0.32$), but these results did not reach significance. The intra-pair correlation of mitochondria copy number was higher in MZ twin pairs (corr. 0.26 95% CI [0.09; 0.41]) than DZ twin pairs (corr. 0.06 95% CI [-0.10; 0.22]) and mitochondria copy numbers was moderately heritable (heritability: 0.18 95% CI [0.03; 0.33]). Intra-pair analysis in DZ twin pairs showed that the co-twin with the highest mitochondria copy number had a tendency to have greater grip strength (proportion: 0.60 95% CI [0.48; 0.72]), but in MZ twin pairs no such tendency was observed (proportion: 0.40 95% CI [0.29; 0.51]). In conclusion, our results indicate mitochondria copy number is a biomarker of aging, physical and mental health in elderly populations of European decent. Twin intra-pair analysis also suggests that numbers of mitochondria copies is influenced by nuclear DNA inheritance in elderly twins.

METABOLOMIC PROFILING IS STRONGLY CORRELATED WITH NUTRITIONAL PATTERNS

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Background: Metabolomics is a promising tool for clinical, genetic and nutritional studies. A key question is to what

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extent metabolomic profiling reflects nutritional patterns. To date small interventional studies have examined the role of specific nutrients on metabolomic profiling using a limited number of metabolites. *Objective:* We assessed the relationship between metabolomic profiling and nutritional intake in a large cross-sectional community setting. *Design*: Food frequency questionnaires (FFQ) were applied to 1003 women from the TwinsUK cohort with metabolomic profiling of serum samples using the Biocrates Absolute IDQTM platform (163 metabolites). We analyzed seven nutritional parameters: coffee intake, garlic intake, and nutritional scores derived from the FFQs summarizing fruit and vegetable intake, alcohol intake, meat intake, hypo-caloric dieting and a traditional English diet. We studied the correlation between metabolite levels and nutritional traits in the larger population. We identified for each trait between 14 and 20 independent monozygotic twins pairs discordant for nutritional intake and replicated results in this set. We meta-analyzed results from both analyses. *Results:* 42 metabolite nutrient intake associations were statistically significant in the discovery samples (Bonferroni $p< 4X10-5$), 11 metabolite nutrient intake associations remained significant after validation. We observed the strongest associations for fruit and vegetables intake and a glycerophospholipid (Phosphati dylcholine diaclyl C38:6, beta = 0.0166, $p = 1.39E-09$) and a sphingolipid (sphingomyeline C26:1, beta = 0.014, p value = 6.95E-13). We also found significant associations for coffee, garlic intake and hypo-caloric dieting. *Conclusions:* We found a strong relationship between serum metabolite levels and four nutritional traits, confirming the value of metabolomic studies for nutritional research.

FIRST-TRIMESTER ULTRASOUND AND THE OUTCOME OF MONOCHORIONIC TWIN PREGNANCIES

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Objective: To assess the correlation between first-trimester ultrasound findings and outcomes in monochorionic pregnancies. *Methods:* We identified all cases of pregnancies in a two-year period, who were referred to our institution for the 11–14 week scan, which have been detected to be multiple, containing at least a monochorionic twins pair. The findings of the earlier routine scans performed in pregnancy by transvaginal ultrasound for assessment and dating were recorded when a singleton pregnancy or a multiple gestation with twins was described. According to the outcomes and complications occurred in pregnancy, two subgroups have been considered: 1) non-complicated pregnancies and 2) complicated pregnancies. Complicated pregnancies were cases with an early pregnancy complication (such as intrauterine demise of one or both fetuses in the first trimester), cases in which at 2nd trimester occurred either discordance in amniotic fluid, twin to twin transfusion (TTS) or with selective intrauterine retardation (sIUGR), cases with intrauterine demise of one fetus or both later in pregnancy and cases where an invasive procedure of fetal therapy was performed. Early scan findings were compared with outcomes. *Results:* Between January 2010 and December 2011 out of 67 monochorionic pregnancies referred, complete pregnancy outcome with early pregnancy scan information about the number of fetuses detected was obtained in 48 cases. There were 28 cases of uncomplicated pregnancies and 20 cases of complicated pregnancies. In 10 out of 20 cases in the group of complicated pregnancies (50%), the finding of early scan was of a singleton fetus and the finding of 'appearing fetus' came only subsequently while this occurred in 8 out 28 of the first group (uncomplicated pregnancies) (28%). *Conclusion:* Ultrasound findings at first trimester can detect major complications occurring later in gestation in monochorionic pregnancy. The finding of a singleton pregnancy at an early stage in the fetal development and the subsequent finding of an 'appearing fetus' in monochorionic pregnancy correlates to a sort of 'higher risk' for the pregnancy and predicts cases at higher risk for the occurrence of major complications later in pregnancy.

INVASIVE PRENATAL DIAGNOSIS IN MULTIPLES

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The most common invasive prenatal diagnosis procedures in twins and multiples are chorionic villus sampling in the first trimester of pregnancy, amniocentesis at 15 weeks of gestation and cordocentesis at 18 weeks. All samples must be performed under continuous ultrasound monitoring following exactly individuation of placentas, chorionicity and following the needle insertion. We discuss the personal experience and other centers' reports of failure and success of sampling and analysis, the fetal loss rate, the misdiagnosis and fetal abnormalities. In amniocentesis and in fetal blood sampling we can use indigo carmine as colorant in order to individuate all the sacks and fetuses. We also discuss about the probability to use transabdominal or transcervical chorionic villus sampling both or separately. Special attention is required when monochorionic pregnancies are sampled in case of monozygotic fetuses. In monochorionic monozygotic pregnancies there is the possibility to run a single sample (either by CVS or amniocentesis) or to perform two samples, one on each fetus. In these cases, the result of screening test in the first trimester can be crucial to take the action. In Assisted Reproduction Technologies pregnancies, especially, according to the method of conception (one or more embryos transferred) and the ultrasound report, the zigosity can be indirectly inferred. Usually transabdominal villus sampling by freehand technique under ultrasound monitoring is the technique of choice for single gene diseases and DNA analysis, in cases at very high genetic risk for the precocity of sampling and in case of selective feticide when women have opted for interruption of the fetus affected.

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THE GENETICS OF DIZYGOTIC TWINNING

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The tendency to conceive spontaneous dizygotic (DZ) twins is a complex trait with important contributions from both genetic and environmental factors. The frequency of twinning varies between different populations, and over time within populations, and this variation is mostly attributed to differences in DZ twinning rate because the monozygotic twinning rate is relatively constant. DZ twinning is under genetic control, with mothers of DZ twins reporting significantly more female family members with DZ twins than mothers of monozygotic twins. Animal studies identified an important role for the ovarian TGF signalling pathway in the regulation of ovarian follicle growth and ovulation number. Mutations in three genes from this pathway, bone morphogenetic factor 15 (BMP15), growth differentiation factor 9 (GDF9), and the bone morphogenetic factor receptor 1B (BMPR1B), increase twinning frequency. In women, mutations in GDF9, but not BMP15, are significantly more frequent in mothers of DZ twins. However, the mutations are rare and account for only a small part of the genetic contribution for twinning.

FETOSCOPIC LASER COAGULATION FOR SEVERE TWIN-TO-TWIN TRANSFUSION SYNDROME: FACTORS INFLUENCING PERINATAL OUTCOME, LEARNING CURVE OF THE PROCEDURE AND LESSONS FOR NEW CENTRES

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Objective: To evaluate the effects of operator experience on perinatal outcome in a single centre. Design: Prospective consecutive cohort study. Setting: Regional tertiary referral Fetal Medicine Centre in the UK. Population: Pregnant women with monochorionic twin pregnancies complicated by severe twin-to-twin transfusion syndrome (TTTS) (at ≤26 completed weeks of gestation) treated by fetoscopic laser coagulation (FLC) between October 2004 and November 2009. *Methods:* Pregnancy characteristics and outcomes were collected. Logistic regression analysis was employed to determine the effect of a priori defined variables on outcome. Main Outcome Measure: Perinatal survival (survival to 28 days or beyond) for one or more twins. *Results:* There were 164 consecutive sets of monochorionic twins. The median gestational age (GA) at FLC was 20.4 weeks (interquartile range 18-22.1 weeks), the median interval from FLC to delivery was 88.5 days (interquartile range 53-101 days) and the median GA at delivery was 33.2 weeks (interquartile range 29.7-34.9 weeks). The overall survival was 62%; perinatal survival of one or more twins was 85%. These outcomes improved after about 61 procedures were performed, and after about 3.4 years of experience. Univariate logistic regression analysis indicated that Quintero stage-IV disease decreased (OR – 0.26; 95% – CI 0.10-0.69) and prolongation of GA at delivery increased the survival of the twins (OR – 1.34; 95% – CI 1.12-1.60) (P<0.01). Increasing experience of the procedure by operator led to a significant increase in perinatal survival (P<0.01; OR – 4.59; 95% – CI 1.84-11.44). Multivariate logistic regression analysis indicated that only GA at delivery increased survival overall (OR – 1.34; 95% – CI 1.12-1.60; P = 0.01). In addition LCUSUM for these data will be presented. *Conclusions:* These data indicate that both relatively large numbers treated and experience with FLC minimises any adverse outcome in monochorionic pregnancies with severe TTTS.

UNVEILING THE HERITABILITY IN CANCER: AN UPDATED ANALYSIS FROM THE NORDIC TWIN REGISTRY OF CANCER

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Quantifying the relative contributions of genetic and environmental factors in cancer incidence informs etiology and opportunities for prevention. Given the relative rarity of cancer, studies in large twin cohorts with longterm follow-up are prerequisites to estimate the relative contribution of these factors. We present results from the Nordic Twin Registry of Cancer (*NorTwinCan*), a cohort of 400,000 twins from the national twin registries of Denmark, Finland, Norway, and Sweden followed on average for 40 years. Some important findings from NorTwinCan include more precise estimates of heritability for common cancers such as prostate, breast and colon cancer; the ability for the first time to estimate the relative contributions of genetic factors to rarer malignancies including testicular, stomach and liver cancer; and the use of novel statistical methodologies to account for competing causes of mortality and censoring which provide more valid estimates of heritability.

THE EFFECT OF ANTENATAL HEAD CIRCUMFERENCE ON DEVELOPMENTAL SKILLS IN HEALTHY INFANT TWINS

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Introduction: Low birth weight is associated with developmental delays and special education needs at school age in both singletons and twins. However, there are suggestions that developmental delays in early childhood are due to antenatal head circumference. Little is known about the effect of antenatal head size and growth on developmental skills of infant twins. This study aimed to investigate this effect on developmental skills of twins up to 24 months. *Methods:* Forty-four healthy monochorionic and 73 dichorionic twins from The Birmingham Registry for

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Twin and Heritability Studies cohort in the United Kingdom were assessed with the Ages and Stages Questionnaires (ASQ-3) at 3, 6, 9, 12, 18 and 24 months. Antenatal head circumference at 20, 28, 33 and 36 weeks were obtained from ultrasound scans. Three antenatal age windows (20-27, 28-32, 33-36 weeks) were assigned to determine the effect of head growth (mm per window) on developmental skills. We performed multilevel regression analyses, with twins relatedness as a nested level with random intercept, to study the effect of antenatal head size at each gestation and rate of growth in each age window on developmental skills at each follow-up. *Results:* A 1mm increase in head size at 20 weeks decreased monochorionic fine motor and problem solving z-scores at 6 months by up to -0.09 (95% confidence interval -0.13—0.04). Head size from 28 weeks onwards was negatively associated with developmental skills in the first year with decreases up to -0.12 (-0.20—0.04), but increased z-scores up to 0.21 (0.08-0.32) in the second year. Effect sizes of 33 and 36-week head circumference were smaller than of 28 weeks. Monochorionic head growth in 20-27 weeks was associated with up to 0.24 (0.01-0.49) increases in z-scores from 9 months onwards, while growth in 28-32 weeks were associated with up to -0.07 (-0.13—0.01) decreases in the second year. No effect of growth in 33-36 weeks was found. Effects of dichorionic head size were only found on motor and personal-social skills, with motor scores decreasing up to -0.04 (-0.06—0.02) and personal-social scores increasing up to 0.03 (0.00-0.06) in relation to 36-week head size. Dichorionic head growth in 28-32 and 33-36 weeks was related to decreased social scores up to -0.09 (-0.17—0.01) in the first year and increased scores by 0.04 (0.01-0.07) in the second year. Growth in 33-36 weeks was associated with decreased motor z-scores of up to -0.04 (-0.08—0.01). No effects were found for head size at 28 weeks and growth in 20-27 weeks. *Discussion:* This pilot study confirms a relationship between absolute head size and rate of growth and early developmental skills. Furthermore, our results suggest the possibility of critical antenatal age windows and different optimal growth windows for monochorionic and dichorionic twins. The current findings should be replicated in other studies.

MULTIPLE PREGNANCY IN HIV-INFECTED MOTHERS IN THE UK AND IRELAND 1990-2011: AN OVERVIEW

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Introduction: Comprehensive population-based surveillance data on obstetric and paediatric HIV in the UK and Ireland is collected through the National Study of HIV in Pregnancy and Childhood (NSHPC). Pregnancies in HIV-positive women, infants exposed to maternal HIV, and other HIV-infected children are notified through two parallel active reporting schemes. Historically, twins were at higher risk of mother-to-child HIV transmission. However, multiple pregnancies in HIV-positive mothers in the UK and Ireland have not previously been studied. *Methods:* Twins and triplets born 1990-2011 and reported to the NSHPC were included in this analysis. Maternal characteristics, pregnancy outcomes, perinatal and infant details were explored. *Results:* About 1.8% of reported deliveries to diagnosed HIV-positive women were multiple births. 242 women were reported with twin (239) or triplet (4) pregnancies, resulting in 483 live and 7 stillbirths (one woman had two sets of twins). Sixteen (7%) of these pregnancies delivered 1990-1999, and 227 since 2000. Median maternal age at delivery was 31 years (IQR: 27-35); 81% of women were of black African origin. 46% (110/236) had an elective caesarean, 41% (96/236) an emergency caesarean and 13% (30/236) had a vaginal delivery. Although women received antiretroviral therapy (ART) in 95% of pregnancies, 13 (5%) had no ART antenatally, including three who arrived unbooked in preterm labour, one who declined treatment, and six who delivered in the early 1990s before treatment was widely available. Eight infants died, seven neonatally and one before six months, mostly with complications of severe prematurity; HIV infection status was not reported for any of these. One surviving very preterm infant of an untreated mother was perinatally infected. No other infant born to a diagnosed woman is known to have been infected, though 24 were of indeterminate infection status at last report, some of whom subsequently left the country and/or declined further testing for their children. Another 17 infants born to nine undiagnosed women have also been reported. Ten were perinatally infected, four sets of twins, one of a twin pair, and one single twin reported without their (presumably uninfected) co-twin (ages at diagnosis: 3-20 months). Two infants died of HIV-related illnesses in their first year, and one in their second. Seven women had their babies in the 1990s, before the introduction of routine antenatal screening; of the other two, one declined antenatal testing and the other tested negative at antenatal screening and had breastfed for a prolonged period. *Discussion:* Routine recommendation of antenatal HIV screening was introduced in the UK from 2000. Prior to that diagnosis rates were poor and the majority of HIV-positive women remained undiagnosed during pregnancy. Since 2000 most infected women have been diagnosed before delivery, in time to take up interventions (about 95% since 2005); almost all infected infants reported here were born to undiagnosed women prior to 2000. Due to the limited data available it is not possible to explore factors associated with possible and confirmed discordant transmissions. An audit of recent perinatal transmissions is underway.

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AN 11 YEAR EXPERIENCE IN CARING FOR TRIPLETS

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Objective: Review the antenatal and neonatal care of triplets from a single tertiary centre. *Methods:* Historic prospective cohort study from January 1999 to December 2010 of all continuing triplet pregnancies and their liveborns delivered at the Royal Women's Hospital, Melbourne, Australia. *Results:* There were 52 sets of triplets, of which 145 babies were liveborn at a mean gestational age of 31.5 weeks (w) (SD 3.4, range 22.6-38.0). Their mean birth weight was 1595 g (SD 515). Conception was spontaneous in 28 (53.8%) sets, from IVF in 7 (13.5%) and from ovulation induction in 17 (32.7%). Chorionicity, as confirmed on histopathology, was TCTA in 30 (57.7%), DCTA in 15 (28.9%), DCDA in 1(1.9%), MCTA in 4 (7.7%) and unconfirmed in 2 (3.9%). Spontaneous conceptions were more likely to result in a monochorionic set (OR 4.0; CI 1.2-13.1). Obstetrical complications were not affected by mode of conception or chorionicity, except for TTTS. Most common obstetrical complications were: spontaneous preterm labour 19/52 (36.5%), PPROM 9/52 (17.3%), hypertensive disorders of pregnancy 8/52 (15.4%) of which 4 ultimately had pre-eclampsia (7.7%), gestational diabetes 4/52 (7.7%), and chorioamnionitis 4/52 (7.7%). Antenatal corticosteroids were given in 42 (80.8%) pregnancies, and 10 (19.2%) received two to four courses. The median interval between last antenatal corticosteroid course and birth was 0.57 w (0-6.29). TTTS occurred in 6/22 (27.3%) monochorionic pairs, at a median age of 18.4 w (15.0-24.0). Antenatal ultrasounds detected congenital anomalies in 4 (7.7%) pregnancies and 1 fetus was aneuploid (0.6%). Intrauterine growth restriction (<10th percentile) of = 1 fetus was suspected in 18 (34.6%) sets of triplets and 3 women (5.8%) were affected by the demise of = 1 fetus. Most women (57.7%) delivered by urgent or semi-urgent c-section (CS), while 28.9% had an elective CS, and 13.5% delivered vaginally. The most common reason (32.7%) for delivery was PTL or laboring PPROM. The neonatal outcomes were as follow: 97.2% of babies were admitted to neonatal intensive care unit, and 8 (3.4%) died in the neonatal period. Minor congenital anomalies were diagnosed in 10 (6.9%) newborns. CPAP was used in 54 (37%) for a median duration of 30.0 hours (IQR 312.0). For the 31(21%) intubated newborns, the median duration of mechanical ventilation was 72.0 hours (IQR 305.0). Surfactant was given to 24 (17.0%) of the 81 (57.9%) babies with RDS. BPD was diagnosed in 9 (6.43%) newborns. PDA was diagnosed in 18 (12.8%), sepsis in 13 (9.22%), IVH in 9 (6.4%) and NEC in 2 (1.4%) neonates. There was no difference in the short-term neonatal outcomes according to chorionicity or mode of conception. The "take home babies" rate for a complete set of triplets was 80.8%, while almost 1 in 5 women experienced fetal or neonatal loss. *Conclusion:* Triplet gestations still carry significant risks despite recent advances in obstetrics and neonatology. Mode of conception and chorionicity do not affect the overall maternal or neonatal short term outcomes.

ACCURACY OF PRENATAL ULTRASOUND PREDICTION OF LOW BIRTH WEIGHT IN HIGH-ORDER MULTIPLE PREGNANCIES

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Introduction: Suspicion of intrauterine growth restriction (IUGR) or Small for Gestational Age (SGA) is frequent in high-order multiple pregnancies and leads to increased surveillance and interventions in order to decrease morbidity and mortality. *Objective:* To evaluate the accuracy of prenatal ultrasound (US) in high-order multiple pregnancies to predict low birth weight. *Method:* A cohort of triplet fetuses was searched to evaluate the accuracy of prenatal ultrasound in predicting SGA babies. Using the 10th percentile (%) for gestational age (GA) from singleton growth charts, IUGR/SGA fetuses were identified using the most recent US, and then compared to neonates' birth weight. Selective terminations and stillbirths were excluded. *Results:* Regular prenatal ultrasounds were performed in 52 triplet pregnancies over a period of 11 years at the Royal Women's Hospital, Victoria, Australia. According to birth weight, 26 sets of triplets (50.0%) had no SGA babies, 15 sets (28.9%) had only one, 6 (11.5%) had two and 5 (9.6) had three SGA newborns. The sensitivity and specificity of prenatal US to predict birth weight = 10% in = 1 baby were 50.0% and 80.8% respectively. The positive predictive value was 72.2% and the negative predictive value was 61.8%. When IUGR was suspected in 1 out of 3 fetuses from a triplet set, it was confirmed postnatally in the same proportion in 5/11 (45.4%) cases. When IUGR was suspected in 2 out of 3, it was confirmed postnatally in the same proportion in 3/4 cases (75%). When IUGR was suspected for the whole set of triplets, it was confirmed postnatally in 1/3 cases (33.3%). When no IUGR was suspected in a set of triplets, 13/34 (38.2%) sets had = 1 newborn with birth weight = 10th% and 3/34 (8.8%) sets had = 1 newborns with birth weight = 3rd%. Birth weight discordance (BWD) was calculated as a percentage of the largest triplet of a set. Thirteen sets (28.9%) had a BWD of 0-9.9%; 13 (28.9%) had a BWD of 10-19.9%; 12 (26.7%) had a BWD of 20-29.9%; and 7 (15.6%) had a BWD of = 30%. BWD was significantly affected by chorionicity ($p = 0.01$), but not by parity ($p = 0.16$). To calculate the relative birth weight of the middle

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triplet, we divided the difference between the middle and the smallest by the difference between the largest and the smallest. Nine sets (20%) were low-skewed 0.75 (2 large, 1 small). Prenatal US performed better at predicting the presence or absence of SGA if triplets had low (0-9.9%) weight discordance ($p = 0.029$). *Conclusion:* Prediction of low birth weight in high order multiple pregnancies on the basis of regular tertiary level US examinations is challenging and often inaccurate.

NEUROIMAGING PHENOTYPES AND NICOTINE CONSUMPTION: CAUSE OR CONSEQUENCE?

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Data collected from the Vietnam Era Twin Study of Aging (VETSA) Magnetic Resonance Imaging (MRI) project permit the joint analysis of cortical thickness, surface area and volumetric measures of subcortical brain structures with cognitive and other phenotypes of interest. In this paper we describe the analysis of data from twins (110 monozygotic pairs, 92 dizygotic pairs) aged 51-59 years. Bivariate genetic models were fitted to data on cigarette use measured as pack-years to estimate genetic and environmental correlations between brain structure and cigarette use. In general, phenotypic correlations were small, but several significant findings emerged between lateral ventricle and frontal lobe structures. These associations were mostly attributable to genetic rather than environmental factors. The potential to distinguish between three hypotheses: cigarette use affects brain structure, vice-versa, or both phenotypes are caused by a third, common factor, is discussed.

ADVERSE EFFECTS OF AMNIOCENTESIS IN TWIN PREGNANCIES

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Objectives: To find out the rates of miscarriage in twin gestations after amniocentesis. Patients and *Methods:* Retrospective cochort study comprised of 98 twin pregnancies which underwent amniocentesis in 16th to 18th gestational week at the University Clinic of Obstetrics and Gynecology in Skopje. Pregnancy outcome was analyzed. *Results:* From 98 twin pregnancies, 21 was excluded because of detected abnormal fetal karyotype, one or both fetuses with structural anomalies, twin-to-twin transfusion syndrome and patients lost from the study. From the remaining 77 patients with twin pregnancies, 72 presented with live births of all fetuses. One case with dichorionic twins had miscarriage in the first week after the amniocentesis with significant amniotic fluid leakage and in another two cases single pregnancy loss appeared in 22nd and 23rd gestational week. The fourth case with unfavorable outcome, was again dichorionic twin with an intrauterine death of one fetus at unknown gestational week. Histologically was found to be later than 4 weeks after the intervention. Two patients had deliveries before 28th gestational week with subsequent single neonatal death. The both of the death neonates were histologically found to be severe growth restricted. The pregnancy loss for one or both fetuses within 4 weeks of amniocentesis was 1,30% (1/77). *Conclusion:* Our cohort study showed a low miscarriage rate related to amniocentesis for uncomplicated twin pregnancies.

UNRAVELLING THE DETERMINANTS OF CIRCULATING NEONATAL VITAMIN D: A TWIN STUDY

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Vitamin D is thought to be vital in normal pregnancy progression and deficiencies have been associated with adverse pregnancy outcomes including pre eclampsia. We have recently demonstrated placenta-specific methylation of CYP24A1, a gene that codes for 24-hydroxylase, the major catabolic enzyme of active vitamin D and its precursors, and have speculated that this may play a role in regulating vitamin D at the fetomaternal interface. In order to test this and to begin to unravel the relative contributions of genetic, environmental and epigenetic determinants in specifying neonatal vitamin D levels, we measured (i) circulating levels of 25-OH2D in a group of pregnant women and their twins, and (ii) placental CYP24A1 methylation. Locus-specific methylation analysis was performed using the Sequenom EpiTYPER platform. Comparative analysis of MZ and DZ twins suggests a contribution of both genetic factors and environmental/stochastic factors to the neonatal placental epigenome. However maternal circulating vitamin D is the most significant regulator to neonatal vitamin D levels, with underlying genetic and epigenetic factors playing a limited role in determining neonatal vitamin D.

EXAMINING GENE:ENVIRONMENT INTERACTIONS IN THE ESTABLISHMENT OF THE PLACENTAL EPIGENOME: GENOME-WIDE ANALYSIS OF PLACENTAS FROM 16 TWIN PREGNANCIES

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The Developmental Origin of Health and Disease (DoHAD) hypothesis predicts that many adult diseases have their origin in utero. This was first proposed to describe the observed link between low birth weight and increased risk of cardiovascular disease in later life. Given its location at the fetomaternal interface, the human placenta plays a critical role in mediating environmental effects associated with this programming phenomenon. Epigenetic modifications, such as DNA methylation, play a major role in controlling gene expression. Mounting evi-

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dence suggests an elevated level of inter-individual variation in DNA methylation profile in full term placenta relative to somatic tissues. However, mechanisms underlying this variation remain unclear. We speculate that this results from a combination of both genetic and environmental factors, which combine during pregnancy to modulate the level of methylation present at specific gene promoters. Studying twins allows researchers to begin to unravel the contributions of genetic and environmental influences on DNA methylation patterns. As part of the Peri/Postnatal Epigenetics Twins (PETS) study, we have collected multiple birth specimens from 250 twin pairs (including placenta). In the current study, DNA methylation profiling of placenta tissue from sixteen twin pairs (50% Monozygotic and 50% dizygotic) was analysed using the Illumina Infinium HumanMethylation27 platform, profiling over 27,000 genomic CpG sites. Cluster analysis revealed that sex was the biggest determinant of overall placental methylation profile. Whereas twin placentas generally show a higher correlation of DNA methylation profile than non-related individuals, there are exceptions, with some twins showing markedly different profiles of DNA methylation. Monozygotic twins showed a higher correlation than dizygotic twins, highlighting the contribution of genetic factors to the establishment of the placental epigenome. However, evidence for an environmental and/or stochastic contribution to methylation profile was also apparent.

TWINSHIP INFLUENCE ON MORBIDITY AND MORTALITY ACROSS THE LIFESPAN

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Background: Studies in twins may be questioned with respect to their representativeness of the general population, not least considering the potential importance of the fetal environment for future health and disease. To better understand the influence twinning may have on health, we compared the morbidity and mortality of twins and their singleton siblings with singletons from the population. *Methods:* We compared morbidity and mortality in twins and singleton siblings of twins. These singletons from twin families were then compared to singletons of the population to further reveal potential twin family influences on health. Familial relations were identified through the Swedish Multi-Generation Register. Among individuals born between 1932 and 1958, 49 156 twins and 35 277 of their singleton siblings were identified. Outcomes were incident overall cancer, cardiovascular disease (CVD) and death, identified in national registers. Standardized survival functions were estimated using Cox proportional hazards regression and the corresponding cumulative risks plotted against age. *Results:* Cumulative risks of cancer, CVD and death in twins did not differ from singletons of twin families, who in turn were found to be similar to singletons of families without twins. As could be expected from these findings, no differences in risks were found when twins were compared to singletons of the population. *Conclusions:* Despite their adverse intrauterine experience, twins do not seem to fare worse than singletons with respect to adult morbidity and mortality. The findings indicate that the unique experience of twinning does not lead to adverse long-term health outcomes.

THE PREDICTION OF OUTCOME IN TWIN PREGNANCY WITH FIRST AND EARLY SECOND TRIMESTER ULTRASOUND

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Objective: To establish if first or second trimester biometry (11+0 to 21+6 weeks) is a useful adjunct in the prediction of adverse perinatal outcome in twin pregnancy. Study Design: A consecutive cohort of 1028 unselected twin pregnancies was enrolled for the Evaluation of Sonographic Predictors of Restricted growth in Twins (ESPRiT) study, a multicenter prospective study conducted at eight academic perinatal centers in Ireland. Complete outcome data was recorded for 1001 twin pairs that completed the study {200 monochorionic (MC) and 801 dichorionic (DC)}. Biometric data obtained between 11 and 22 weeks were evaluated as predictors of a composite of adverse perinatal outcome (mortality, hypoxic ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress, or sepsis), preterm delivery (PTD) and birthweight discordance greater than 18% (18% BW). Outcomes were adjusted for chorionicity and gestational age using Cox Proportional Hazards regression. *Results:* Differences in crown-rump length (CRL) of 10% or 20% were not predictive of adverse perinatal outcome in either DC or MC twins. Between 14 and 22 weeks, a difference in abdominal circumference (AC) of more than 10% was the most useful predictor of adverse perinatal outcome, preterm delivery (PTD) and 18% or more BW discordance in both DC and MC twins. The strongest correlation was observed for intertwin differences in biometry obtained between 18 and 22 weeks. *Conclusion:* While first trimester biometry was not useful for predicting adverse outcome, biometry in the early second trimester can successfully identify twin

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pregnancies at increased risk of poor perinatal outcome. Intertwin AC difference of greater than 10% between 14 and 22 weeks gestation was the best individual predictor of perinatal risk in both monochorionic and dichorionic twins. Sonographic biometry in the early second trimester should therefore be utilized to establish perinatal risk, thus allowing prenatal care to be tailored accordingly.

FAMILIAL FACTORS INFLUENCE A PREMORBID RISK OF DEPRESSIVE SYMPTOMS FOR THE DECLINE OF SOCIAL ROLE

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Introduction: Social role function is fundamental in order for elderly people to maintain their autonomy and independence. Social role includes social interactions and activities such as visiting friends, being called on for advice and so on. In previous studies, disability in social role predicted mortality and the onset of disability in activities of daily living and instrumental activities of daily living. In addition, previous studies reported that higher depressive symptoms were associated with higher risk for disability in social role. However, it is deficient that understanding the mechanisms underlying this association. Therefore, the present study aims to examine the existence of familial (genetic and/or early environmental) factors which influence both social role and depressive symptoms. *Methods:* We conducted a prospective nested case-control study in a population-based sample. The present study was based on the Osaka University Aged Twin Registry. We sent self-rated questionnaires to all living, contactable, and consenting twins in 2008 and 2010, respectively. We measured depressive symptoms by Japanese version of the 15-item version of the Geriatric Depression Scale (GDS). Social role was measured by the Intellectual Activity of subscale on the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC). We calculated odds ratios (ORs) with case-control analyses (adjusting age and current chronic diseases) and with co-twin control analyses (adjusting current chronic diseases). We performed all analyses stratified by sex. *Results:* In case control analyses, higher depressive symptoms were significantly associated with higher risk for the decline of social role only among men (Odds ratio, 1.18; p-value, 0.02). In co-twin control analyses, the association was not significant and odds ratio approached 1.0 (Odds ratio, 1.06; p-value, 0.85). *Discussion:* The present study indicates that higher depressive symptoms are a significant risk factor for the decline of social role only among men. In addition, the present study suggests that this effect is buffered by familial factors which influence both social role and depressive symptoms. These findings suggest plausible mechanisms for disability in social role.

MONOZYGOTIC TWIN PAIRS DISCORDANT FOR OBESITY: A STUDY ON EPIGENETICS

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Obesity is a major global health problem. The WHO has estimated that 2.3 billion adults will be overweight and 700 million obese by 2015. Although twin studies have shown high heritability of obesity (up to 50-80%), the associated sequence variants from genome-wide association studies are estimated to account only at most 10% of the genetic variation in body mass index (BMI). The constantly increasing incidence of obesity worldwide suggests environmental factors over genetics as a leading cause of the obesity epidemic. The missing link between environmental factors, inheritance and obesity could be epigenetics. Population-based case-control epigenetic studies are limited by the underlying heterogeneous genetic backgrounds across the population. By contrast, a within-pair comparison of monozygotic (MZ) twins discordant for disease is an ideal design for studying the contribution of epigenetic factors in disease development. MZ twin's "identical" genomic background eliminates the noise of epigenetic differences due to genetic variation. Differences in the epigenome of discordant MZ pairs may explain the incomplete penetrance and variation in age at onset and severity of diseases in such pairs. We hypothesise that even though variation in DNA sequence and individual lifestyle are important factors in determining the BMI of an individual, DNA methylation changes considerably contribute to the variation in BMI and body composition among different individuals. We investigated the contribution of DNA methylation changes in acquired obesity independent of genetic influences by studying MZ twin pairs discordant for BMI. We performed whole genome-scale methylation analysis of BMI discordant and concordant MZ twin pairs using The Infinium HumanMethylation450 BeadChip (Illumina). Obesity discordant MZ twin pairs showed significant DNA methylation discordances at CpG sites mostly residing in genomic locations with potential regulatory properties. The observed methylation changes occurred in genes from key pathways previously shown to be associated with obesity. Further examinations on the relationships between DNA methylation, metabolomics and microbiome on these twins will provide novel information on the complex dependency network in acquired obesity.

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ESTIMATION OF THE CONTRIBUTION OF ASSISTED AND NON-ASSISTED REPRODUCTIVE TECHNOLOGY FERTILITY TREATMENTS TO MULTIPLE BIRTHS DURING THE LAST THIRTY YEARS IN JAPAN: 1977-2008

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Introduction: The purpose of the present study was to estimate the effect of fertility treatment; both assisted reproductive technology (ART) and non-ART ovulation stimulation, on the number and rate of multiple live births during the last thirty years in Japan. *Methods:* Japanese vital statistics according to maternal age class and plurality of live births published by the Ministry of Health, Labor and Welfare from 1974 to 2009 and Japanese ART statistics published by Japan Society of Obstetrics and Gynecology from 1989 to 2008 were gathered and reanalyzed. Total iatrogenic multiple births were estimated by vital statistics assuming that spontaneous multiple-birth rates according to maternal age class would be constant. The number and rates of ART between 1977 and 1988 were estimated using approximation formulae. The number of non-ART iatrogenic multiple births were estimated by subtracting ART multiples from total iatrogenic multiples. *Results:* The birth rates of iatrogenic multiples increased dramatically between 1977 and 2005, and decreased. The estimated maximum percentage of multiple births that were iatrogenic was 50.0% in 2005. Non-ART multiple births increased during past thirty years overall, whereas ART multiples tended to increase from 1983 to 2005 and then decreased rapidly. The number or percentage of ART multiples were almost constantly lower than that of non-ART multiples. *Conclusion:* The rapid increase of numbers and rates of multiples born to women over thirty years in Japan is mainly attributed to iatrogenic rather than spontaneous multiple births. The effect of non-ART fertility treatment is large recently.

PSYCHOLOGICAL ASPECTS OF THE PARENT-CHILD RELATIONSHIP IN TWINS

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The last 30 years have seen an increasing interest in the study of parent-infant interactions, from the very first months of life, but this interest has mainly focused on singletons. Parent-infant synchrony, the parent capability to closely match the infant affective behavior, appropriately reacting to the micro-shifts in the infant state and signals, is among the key elements of these interactions. Through synchronous interactions, parents usher infants into the social world, acknowledge their individuality, teach them the rules of social dialogue, and co-regulate infant arousal and attention. Parent infant synchrony in the first months of life has been shown to predict infant attachment security, self-regulation capacities, and cognitive skills, underlining the role of early interactions in shaping infant cognitive and social-emotional development. This synchrony and the formation of the attachment bond relies on an initial period of almost total parental involvement, and complete attention to the infant unique signals and rhythms. In case of twins, triplets or higher order multiples, this specificity is at a high risk of being disturbed and development may be compromised as a result of a parental overload and inability to provide uninterrupted attention to more than one infant simultaneously or to synchronize with the unique interactive patterns of each child. In the ecology of limited parental resources created by the birth of multiples, each infant might receive lower levels of synchronous parenting, placing multiples at a higher risk for less-than-optimal growth and development. These relational difficulties can be further increased by the fact that the birth of multiples can be very taxing, beginning with a difficult pregnancy and labor, a longer postpartum recovery period, and a substantial financial burden. Synchrony has also been shown to decrease in conditions of risk, such as maternal depression, prematurity, and insecure parental attachment representations, which have been found to have a higher incidence in case of a multiple birth. The few studies in literature that have studied parent-infant interactions in multiple births report lower parent infant synchrony in multiples, less infant distress during maternal separation, less approach at reunion, and higher internalizing problems. Mothers report lower adjustment and differentiation among siblings and the difficulty of providing sensitive parenting to more than one infant at the same time has been shown to be related to a higher risk for cognitive delays in the first 2 years of life, with an especially high risk in discordant infants, and for infant behavioral problems. Because of the importance of parent-infant interaction on the cognitive, social and emotional development of children, in the future, researchers should focus greater attention on the study of these interactions in cases of multiple births. The evidence already available in literature show that an early intervention by caregivers, aimed at supporting parents in assuring a sensitive and attentive environment for all siblings might prove beneficial for the future of these families.

SPONTANEOUS ARREST OF FLOW IN TRAP SEQUENCE: A CASE REPORT

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Twin reverse arterial perfusion (TRAP) sequence is a rare complication that occurs exclusively in monochorionic multiple gestations. It consists in a normal twin, who acts as 'pump' perfusing an acardiac twin through multiple artery-to-artery anastomoses present in the placenta. This sequence results in the 'pump' twin demise in up to 51% of the cases due mainly to heart failure and prematurity. There is controversy in its management, which varies from

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conservative management to intrafetal vessel ablation or fetoscopic laser cord occlusion. We report the case of a patient with a monochorionic twin gestation and a TRAP sequence with a spontaneous arrest of flow of the acardiac twin in the 16th week, and a favorable posterior evolution of the 'pump' fetus with vaginal delivery in 40th week. We attached prenatal ultrasonography.

HEIGHT AT CONSCRIPTION: TWINS CAUGHT-UP WITH SINGLETONS OVER THE DANISH BIRTH COHORTS 1930-90

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Several studies have compared the early-life growth of twins and singletons born in the second half of the previous century. The general picture is that twins are shorter at birth but catch-up with singletons during childhood and adolescence. Here we present a study comparing height of male twins who reports twin status from birth cohorts 1930–75 (n = 17,740) at military conscription (modus age 19) with the overall mean height at conscription. The results demonstrate that male twins from birth cohorts 1930-34 were on average 1.7cm shorter at conscript compared with the overall mean height but the differences are subject to a steady decrease until it vanishes in birth cohorts 1970-75. A linkage between the Danish Twin Registry and the conscription database, which is administered by the National Board of Health from 2006 onwards, demonstrated that no difference was present for birth cohorts 1987-90. Most likely the Danish society goes through environmental changes during the previous century that enables twins to achieve the adult height governed by their genetic potential.

TWINSHIP AND MARRIAGE: A CHALLENGE TO THE CLOSE TWIN RELATIONSHIP?

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Twins have a constant companion from the very beginning and if the relationship with the co-twin has been a close one, there might be difficulties in finding a marriage partner. Based on 35 life stories of older twins, this study focuses on personal experiences of establishing the marital relationship in relation to the co-twin relationship. The participants are a subsample of two Swedish longitudinal twin studies, SATSA and the Gender study and they were MZ/DZ, female/ male twins aged 70-91 years. All except one was or had been married. The life stories were analyzed with content analysis. The results showed that (n = 16) of the participants experienced that their marriages were negatively affected by the twin relationship and (n = 19) did not experience any negative influence at all. The most common reasons for the negative influence on marriages was that the spouses of the twins did not get along with one another or the co-twin and the second common reason was that the spouse felt threatened by the close twin relationship. The consequences of the negative influences were that the twins in a pair distanced themselves from one another. Spouses of the twins who described no influence on their marriage were accepting of the twin relationship and got along well with one another and the co-twin. Those twins who were married to two siblings or friends had the most regular contact frequency. The study showed that when twins get married, it involves not only the two individuals marrying each other, but also the relationship with the co-twin as well as the spouse of the co-twin.

OBESITY AND DIABETES: THE TWIN EPIDEMICS. FINDINGS FROM STUDIES ON FINNISH TWINS

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Obesity and type 2 diabetes (T2DM) are certainly among the most challenging health problems in the 21st century. They typically coincide. Approximately 80% of patients with T2DM are obese and more than 20% of obese adults have T2DM. The road to T2DM through obesity is complex, and involves both genetic and environmental sources. In humans, the acquired and genetic components of the relationships between obesity and T2DM have been difficult to distinguish, since groups representing different phenotypes also differ for genotype. Twin studies provide an excellent opportunity to disentangle interfaces between genotype, the environment, and human physiology. Finnish twin studies have found that:

- obesity increases the risk of T2DM by 30-fold
- despite high trait heritability estimates, only a fraction of covariation in BMI and incident type 2 diabetes is of genetic origin
- physical activity reduces the influence of genetic factors to develop high BMI
- physical activity protects from type 2 diabetes (studies in physical activity discordant MZ and DZ pairs)
- acquired obesity is associated with several prediabetic and preatherosclerotic changes already in young adulthood (studies in obesity-discordant MZ and DZ pairs)
- obesity and lack of physical activity easily lead to a vicious cycle of more weight gain and an escalation in the pathologic metabolic processes

Studies are underway on why some obese individuals remain free of insulin resistance and other metabolic complications of obesity. The 'twin epidemics' of obesity and diabetes continue to grow in our modern environment with easily accessible energy-dense foods and lack of physical activity. Twin studies continue to provide important insight into the process of weight gain over an individual's lifetime.

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TRANSCRIPTOMICS AND LIPIDOMICS OF ADIPOSE TISSUE IN OBESITY-DISCORDANT MONOZYGOTIC TWINS

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Obesity-discordant monozygotic (MZ) twins provide a powerful tool for identifying metabolic and molecular disturbances of acquired obesity, and allow disentangling genetic effects from the lifestyle, as in this design, the obese and non-obese groups are perfectly matched for genotype, age, sex, and many childhood and intrauterine factors. To this end, we have collected rare obesity-discordant MZ pairs from the FinnTwin16 and FinnTwin12 cohorts, and have so far have identified approximately 20 healthy pairs aged 22-32 years with >10 kg difference in body weight. Our examinations show that the obese co-twins had significantly decreased whole body insulin sensitivity, severe hepatic steatosis, impaired intra-arterial endothelial function and an atherosclerotic serum lipidomics profile with oxidative and inflammatory features. Adipose tissue transcriptomics analyses reveal a pronounced inflammation in the obese co-twins' fat, showing activation of both innate and adaptive immunity. We also found a remarkable decrease (50%) in mitochondrial DNA copy number and downregulation of mitochondrial gene expression pathways in obese co-twin's fat. Mitochondrial dysfunction in subcutaneous fat correlated with increases in liver fat and insulin resistance, and was a direct consequence of poor physical fitness. Adipose tissue lipididomics analyses demonstrate that as the adipocyte hypertrophy, several changes occur in the cell membrane in order to protect to adipocyte physical properties and fluidity. These protective changes have a cost, however: the kinds of lipids accumulating in the "obese" adipocytes are known to be precursors for compounds that can initiate and aggravate inflammatory cascades. We therefore propose that membrane lipid alterations in the adipocytes play a key role in the initiation of adipose tissue inflammation. Interestingly, these same lipids were associated with increased levels of liver fat. Future studies combining valuable twin resources and -omics technologies provide interesting potential for finding novel pathways in human obesity. Review: Naukkarinen, J., et al. (2011). Causes and consequences of obesity – the contribution of recent twin studies. International Journal of Obesity

TWINS: SOME LOVE THEM, SOME HATE THEM

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Twins are generally thought to elicit a universal fascination. However in only too many areas of the world, twins kindle other extreme reactions. On the one hand they are redeemed to be godly creatures or venerated, used as a link to supernatural beings, thought to be able to predict the future, enhance fertility in women and the crops and many more. Though veneration may seem as an advantage, it often leads twins to be isolated from their parents, the community and their peers. In many other ethnic groups twins are thought to be evil creatures to be disposed of, and their mothers can be punished and treated as outcasts for having hosted them in their womb. In still other regions twins are thought to have a negative influence on matters ranging from parental sexuality to copiousness of the harvest, and abandoned or raised by the old. Many other reasons lead to twin infanticide or to twin abandonment and abuse. Poverty linked with often impossible living conditions, is the main underlying factor. But superstition and other motives also play a large role. In this presentation visual (photographic) material will be shown in order to illustrate each point. Having worked periodically abroad as a doctor for many years, all this material has been collected from many areas all over the world, ranging from Africa, to South America and regions of the Pacific. Hopefully this presentation will help bringing to the fore a still hidden, huge plague as well as to highlight the depths of the gulf between the rich and the poor.

INTRAUTERINE FETAL DEATH IN MONOCHORIONIC TWIN PREGNANCY

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Introduction: During the last decade, the rate of twin pregnancies has increased and reached 3% of all pregnancies. Method: This study enrolled 36 twin pregnancies that were followed and delivered at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia over a five-year period. *Results:* The first group included 15 patients with a monochorionic twin pregnancy, and the second group consisted of 21 patients with a dichorionic twin pregnancy. The average week of gestation when the intrauterine death of one twin occurred was 29 ± 6 weeks in group 1 and 33 ± 4 weeks in group 2. The platelet count was significantly lower in patients with APGAR scores of more than 8, with an average of 185,000/ml, and in patients with a score of less than 4, the average count was 221,000/ml. The perinatal mortality rate of the surviving twin was 33% in the monochorionic group and 0.4% in the dichorionic group. *Conclusion:* The maternal and neonatal outcomes of twin pregnancies with the fetal demise of one twin are strongly dependent on the number of placenta. Female fetuses are at a greater risk for intrauterine demise than male fetuses. An increase in the maternal platelet count, can be used as a predictor for a negative neonatal outcome of the surviving twin.

MOVEMENT FOR MULTIPLES

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Our work has centred on the importance of early physical movement which is needed for children to develop: body awareness; muscle tone; balance; body control; grip and finger movements; hand-eye co-ordination. We recognise

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the crucial role played by all those involved with the care of babies and young children. Bonding and attachment opportunities provided in the first years of life underpin later well being and happiness. Parents in the project have confirmed that it is more difficult to provide the movement and play opportunities that multiples need. Treating each multiple as an individual and helping him or her to develop his own distinct personality can also be a real challenge. A Tamba bid for Welsh lottery funding enabled us to conduct the Movement for Multiples research. We designed a programme catering for multiples 0 to 3 years. It takes about 10 minutes each day and is designed to: provide multiples with an opportunity to develop gross and fine muscle co-ordination; provide parents with an opportunity to develop a close and trusting bond with each individual child; provide opportunities for the multiples to develop identity, individuality and independence; opportunities for the multiples to develop their relationship with each other. A key aspect is the development of a method using treasure baskets to occupy one child/children whilst working with another child. 11 sets of twins and one set of triplets were selected from 100 Tamba volunteers to trial and develop the programme. The programme (in DVD format) is being made available via the Tamba website and through workshops with parents. Initial Results Initial results are very positive. Parents are reporting that the treasure basket method enables them to work and relate individually with one child whilst keeping the other occupied. They are particularly able to make eye contact and to engage verbally. Parents are finding that the movements are helping their children to develop physically. They also find that they are developing the skills to play together and independently.

NORDIC TWIN REGISTERS AS BASIS FOR STUDIES OF CANCER CAUSES AND CONTROL - 400,000 TWINS, 13 MILLION PERSON-YEARS AND 40,000 PROSPECTIVE CANCERS

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The Nordic countries have a long tradition of large-scale studies based on comprehensive, population-based registries linkable on unique personal identity codes, enabling follow-up studies spanning many decades. This paper presents possibilities for joint Nordic twin register-based studies, by describing carefully specific characteristics of the Nordic twin register cohorts and cancer incidence in these cohorts. There are altogether 400,000 twins in twin register cohorts in Denmark, Finland, Norway and Sweden. As a result of joint database handling principles, the accuracy of personal identity codes and completeness of follow-up for vital status in all participating twin registers was checked and improved if necessary. Thereafter, the cancer incidence was determined using follow up through the national cancer registries. Twin registers typically showed slightly lower cancer incidence rates than the general population, presumably because of better participation rates among health-conscious subjects. So far, almost 40,000 malignant neoplasms have occurred after recruitment of a person to the twin register, and the annual increase of the cancer cases in these cohorts is about 2,200. The estimates on the population-representativeness of the twin registers will assist in interpretation of generalizability of results of future studies based on these records, and the systematic tabulations of numbers of cancer cases will serve in study power estimations

TWIN-TWIN TRANSFUSION SYNDROME: TWELVE YEARS OF EXPERIENCE

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Introduction: The twin-twin transfusion syndrome (TTTS) occurs in 15% to 20% of monochorionic, diamniotic twins. This is not an inherited or genetic condition. In the TTTS blood is transfused from a donor twin to its recipient, such that the donor becomes anemic and growth may be restricted. In contrast, the recipient becomes polycythemic and may develop circulatory overload manifest as hydrops. Aims: To report and evaluate TTTS in what concerns to incidence, complications, management and perinatal outcome in a referral hospital. Material/*Methods:* Retrospective study of the cases of TTTS over a period of 12 years (Jan02-Dez11) in a referral hospital. Maternal data, antenatal ultrasound findings, obstetric and intrapartum complications, gestacional age at delivery, mode of delivery and placental morphology were assessed. Neonatal data included birth weight, Apgar score and newborn mortality and morbidity. *Results:* Twenty (12.5%) of the 160 monochorionic, diamniotic (in a total of 560) twin pairs in this period had TTTS. The mean maternal age was 30.3±3.98 years. We reported 2 cases of twins after medically assisted procreation. The mean gestacional age at diagnosis was 23.3±3.04 weeks. Seventeen of the cases were diagnosed by severe hydramnios of the recipient and oligohydramnios of the donor. Three were diagnosed by one fetal intrauterine death. In what concerns to treatment 9 did selective fetoscopic laser photocoagulation; four had been submitted to amnioreduction and 3 had expectant treatment. The other 4, in who the diagnosis was made by fetal intrauterine death, had a close follw-up. Obstetric complication after treatment was in one case unstoppable labor after amnioreduction. The mean gestacional age at delivery was 29.2±2.95 weeks. In 19 cases was performed the c-section delivery and in 1 vaginal delivery without any complications. Mean birth weight was at the donor twin 874±411g and at the recipient twin 1277±620g. We had two neonatal deaths and neonatal morbidity was related with prematurity and in 4 cases with cerebral lesions. Placental histopathology confirmed the monochorionicity. *Conclusions:* The incidence of TTTS in our study was 12.5%, a little lower than what is described in the litera-

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ture. Prompt recognition, management and treatment is very important to avoid serious complications as fetal intrauterine death. In our study neurological morbidity was important: 20% of the cases. TTTS is an important phenomenon in view of its association with frequent and severe morbidity in the affected twins.

LIFE EVENTS PREDICT SMALL BUT EXTENDED CHANGE IN NEUROTICISM

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Introduction: High neuroticism scores predict development, presence, and persistence of many forms of psychopathology. Although being relevant, the association between stressful life events and fluctuations, or changes, in scores on a neuroticism inventory is an understudied topic. In the current six-year follow-up study three hypotheses were tested i) subjects who experience life events show an increase in neuroticism, ii) high baseline neuroticism moderates this effect, and iii) recent life events have a larger impact on neuroticism compared to distant life events. Methods. Data came from the Finnish Twin Cohort study and is based on survey data on neuroticism collected in 1975 and 1981 and life events data obtained in 1981 (n = 21,085, 50% women, mean age = 41.6 years). Changes in neuroticism were predicted from sum scores of life events and/or their interaction with baseline neuroticism. Since congruence between different methods to assess life events are relatively low, two of the most often used kinds of indices were assessed. First, Holmes and Rahe life event weights were used to calculate an index based on the extent of life change the events are assumed to produce in one's usual life (HR-index). Second, since accumulation of negative life events has been shown to predict the onset of psychopathology, a weighted sum score based on the prevalence of a life event in the current sample was calculated (NLE-index). In the current study, all hypotheses were tested for both indices separately. Timing of life events was taken into account by distinguishing recent (last six months) from distant (last five years) life events. All variables were standardized prior analysis in Stata software (version 11.1, using the cluster-option for robust standard error estimation). In this large sample a p-value < 0.01 was considered statistically significant. Results. Mean neuroticism scores slightly decreased during the six-year follow-up (mean1975 = 4.35, (SD = 2.51); mean1981 = 4.09 (SD = 2.43); p<0.001). Recent life events correlated negatively, or not at all with distant life events (r = -0.06, p<0001 HR-index; r = 0.002, p = 0.79 NLE-index). Baseline neuroticism predicted both recent and distant life event exposure (r = 0.12, r = 0.04 HR-index; r = 0.14, r = 0.08 NLE-index; all p's<0.001). Recent and distant life events in turn predicted follow-up neuroticism somewhat more strongly (r = 0.15, r = 0.05 HR-index; r = 0.19, r = 0.11 NLE-index; all p's<0.001). Neuroticism in 1981 is mainly predicted by neuroticism in 1975 (beta = 0.57 HR-index; beta = 0.56 NLE-index; both p's<0.001), but also by recent and distant life events: Recent life events have a stronger effect (beta = 0.11 HR-index; beta = 0.14 NLE-index) on neuroticism in 1981 compared to the distant life events (beta = 0.05 HR-index; beta = 0.08 NLE-index; all p's <0.001). There is no evidence that the life events had a larger impact on the neuroticism score in 1981 in subjects with higher neuroticism scores in 1975. Conclusion. Life events predict small increases in neuroticism but these changes, at least partially, decay over time. Although recent life events have more impact than distant life events, the latter's effect suggest rather persistent change in neuroticism. The findings support a model of life events driven dynamic fluctuations around a person's set-point of neuroticism.

DELAYED INTERVAL DELIVERY IN TWIN PREGNANCY: A CASE REPORT

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A 28-year-old primigravida was transferred to our department of fetomaternal medicine at 23 + 2 weeks with originally a twin dichorionic, diamniotic ICSI-pregnancy after having delivered the first fetus stillborn at 19 + 4 weeks in a peripheral center. Preterm rupture of the membranes of the first amniotic sac and regular contractions with no signs of chorioamnionitis had led to a spontaneous abortion of the leading fetus. The umbilical cord retracted instantly inside the uterus after a successful ligation with a 4-0 absorbable suture and the placenta of the first child was left in utero. Ceasing contractions within one hour after delivery of the first twin, a spontaneous reformation of the uterine cervix, and intact membranes of the remaining fetus allowed the safe prolongation of the pregnancy. A rise of the white blood cell count (from 12.000/nl to 16.000/nl) and the C-reactive protein (from 1,96 to 13 mg/dl) were rather associated with the delivery of the first twin than with a threatening chorioamnionitis. The patient responded well to the antibiotic therapy with Cefuroxime 3 × 1,5 g i.v., which had been initiated immediately after delivery for a period of 20 days before transferring the patient to our department. The ultrasound examination at admission revealed an intact singleton pregnancy with a normal amniotic fluid index. The patient was treated with relatively strict bed rest and prophylactic Enoxaparin 40 mg daily. Two doses of 12 mg of Betamethasone were given at 23 + 5 weeks intramuscularly in order to induce fetal lung maturation. A rise of the white blood cell count (from 13.000 to 16.000/nl) and the C-reactive protein (from 2,1 to 20,7 mg/dl) was noticed at 24 + 3 weeks and was treated with a 10-day antibiotic therapy with Mezlocillin 3 × 4 g and Cefuroxime 3 × 1,5 g/d i.v. No signs of chorioamnionitis were observed. A transfer back to the original peripheral

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center was initiated at 29 + 0 weeks due to the stable condition of both the mother and the fetus. Tocolysis with Magnesium (20 g in 500 ml 0.9%NaCl, application rate of 30 ml/h i.v.) as well as a second dose of 2 × 12 mg of Betamethasone was added at 30 + 0 weeks for 48 hours due to incipient uterine contractions. Primary cesarean section was performed at 30 + 6 weeks due to rising maternal infection parameters and impending chorioamnionitis. A healthy female infant was born weighing 1380 g, with Apgar scores of 9 at 1 min and 10 at 5 and 10 min, and arterial cord pH of 7,32.

VAGINAL DELIVERY IN MONOCHORIONIC TWINS: IS IT SAFE?

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Mode of delivery of twins is a controversial issue and higher concerns arise in the case of monochorionic diamniotic (MCDA) twins. Although MCDA twins present significantly increased risk of perinatal mortality and morbidity, the contribution of mode of delivery to the increase in perinatal mortality is still not clear. Moreover, perinatal mortality for monochorionic and dichorionic twins seems not to differ in deliveries after 31 weeks gestation. Nowadays, many obstetricians perform an elective c-section for uncomplicated MCDA twins at 32-36 weeks. There are still no results from randomized clinical trials concerning mode of delivery among MCDA twins, but a few reports on observational studies show no improvement in perinatal outcome among MCDA twins delivered vaginally. Among us, guidelines for twins establish the threshold for delivery in uncomplicated pregnancies at 38 gestation weeks for both MCDA and DC. Additionally, indications for c-section are the same for MCDA and DC. We assembled a retrospective cohort including consecutive MCDC twin pregnancies with 34 or more gestational weeks and without major complications such as twin-to-twin transfusion syndrome, fetal growth restriction, severe fetal growth discordance or fetal death. Perinatal outcomes of 64 MCDA twins delivered vaginally were compared with those of 226 MCDA twins delivered by cesarean section. Perinatal outcomes were more favourable among MCDA twins delivered vaginally. Delivery by cesarean section was associated with an increased frequency of 5-minute Apgar score<7, need for oro-tracheal intubation and admission to neonatal intensive care unit. There were no cases of intrapartum TTTS or neonatal death during in-hospital stay. Vaginal delivery appears to be a good option for uncomplicated monochorionic diamniotic twin pregnancies after 34 weeks gestation.

PERSONALITY TRAITS AND LIFE DISSATISFACTION AS RISK FACTORS FOR DISABILITY PENSION DUE TO LOW BACK DIAGNOSES: A 30-YEAR LONGITUDINAL COHORT STUDY OF FINNISH TWINS

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Background: Moderate to severe mental disorders may be expected to predict higher risk for permanent work incapacity due to psychiatric diagnoses. Less is known about the association of mild symptoms and subjective mental wellbeing with risk of disability pension (DP) due to somatic diagnoses. Despite the fact that low back diagnoses (LBD) are among the most common DP diagnoses, we are not aware of studies of associations of mental health and personality with DP due to LBD. There are moderate genetic influences on personality traits such as extroversion and neuroticism, life dissatisfaction and DP due to LBD. Hence, shared genetic influences may underlie the association of personality and mental health with DP due LBD. Therefore, it is warranted to study the associations between DP due to LBD, personality traits and life satisfaction with a twin design that allows for control of familial confounding (genetics and family environment). This study aimed to investigate life satisfaction and the personality traits extroversion and neuroticism as predictors for DP due to LBD accounting for familial confounding. *Methods:* Data on 24 043 twins (50% women) aged 18-65 year from a baseline survey in 1975 was followed up with national DP register data until 2004. The number of complete twin pairs in the sample were 1668 monozygotic (MZ) male, 3931 dizygotic (DZ) male, 1851 MZ female, and 3736 DZ female pairs. In addition, 1671 twins without co-twins were included. Personality traits were assessed by neuroticism and extroversion using the short version of an Eysenck Personality Inventory and used as a continuous variable (range 0-10). Life satisfaction was measured with a four item scale on levels of interest, happiness, easiness, and loneliness of life and analyzed as continuous; range 4-20. Cox proportional hazard regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Twin pairs discordant for DP due to LBD and factors of interest were used to account for familial confounding. *Results:* A total of 583 persons (42% women) were granted DP due to LBD during the follow-up. At baseline, the mean life satisfaction was 9.0 (SD 3.1), extroversion 4.2 (2.4), and neuroticism 4.5 (2.5) for those with DP due to LBD, whereas the respective means were 8.6 (2.8), 4.2 (2.5), and 4.4 (2.5) for those without

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any DP. That is, those with DP were more neurotic and more dissatisfied at baseline. A one point increase in life dissatisfaction (HR 1.06, 95% CI 1.03, 1.10) and neuroticism (HR 1.07, 95% CI 1.03, 1.10) were significantly associated with elevated risk for DP due to LBD. Extraversion did not predict future risk of DP due to LBD. These associations with life dissatisfaction and neuroticism remained when socioeconomic status, education, and marital status were accounted for. These associations were also independent from familial confounding in analyses of discordant twin pairs (119 MZ pairs and 383 DZ pairs discordant for DP due to LBD). *Conclusions:* Life dissatisfaction and neuroticism seems to be early and causal risk factors for DP due to LBD.

A TWIN STUDY OF PSYCHOTROPIC MEDICATION USE

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Introduction: In the last decades there has been a significant increase in the availability and consumption of psychotropic medication in western populations, particularly antidepressants (AD) and benzodiazepines (BZD). This fact has not been followed by a concomitant improvement in public mental health, which has stimulated interest in investigating the epidemiology of over-prescription and abuse of these drugs. Different factors have been associated with psychotropic medication use: age, sex, socio-economic status, employment, consumer relatives/friends, lack of social support, use on non-prescription drugs and, obviously, the presence of a physical or psychiatric disorder. However, the relationship between mental disorders and psychotropic medication use is less than perfect, which suggests the presence of differences in the factors affecting these variables. The heritability of different mental health disorders has been clearly established, however the influence of genetic factors on the consumption of psychotropic medication has not received much attention. Our objective was to analyze the impact of genetic influences in the consumption of psychotherapeutic drugs of adult twins. *Methods:* The data comprised 827 adult female twins from the Murcia Twin Register (Spain), (217 MZ and 220 DZ pairs). The mean age was 52.6 (SD: 7.5). Range = 43-70. Data about diagnosed mental disorders, psychotropic medication use, and drug prescription was obtained by self-report in a personal interview. Questions regarding these variables were based on the Spanish National Health Survey questionnaire. Zygosity was ascertained by questionnaire and DNA analysis. Threshold models for categorical data were fitted to quantify genetic and environmental influences on variation in breastfeeding behavior. *Results:* Nearly half of the women (41.7%) reported having suffered 'Depression, anxiety or other mental disorders' sometime in their life. A third 34.3% had taken some psychotropic medication during the last month. Most of them (31.4% of the sample) had taken 'Tranquilizers, or sleeping pills', and 15.1% 'Antidepressants or stimulant medication'. Tetrachoric correlations were consistently higher for MZ twins. Use of psychotropic medication [rMZ = .541 (CI 95%: .342, .702); rDZ = .210 (CI 95%: -.022, .426)]; consumption of tranquilizers [rMZ = .460 (CI 95%: .247, .638); rDZ = .218 (CI 95%: -.021, .440)] or antidepressants [rMZ = .429 (CI 95%: .129, .667); rDZ = .308 (CI 95%: . 015, .564)]. Model fitting suggested that an AE model offers the best fit to data in all cases: Psychotropic medication use [A: .524 (CI 95%: .339, .680); E: .476 (CI 95% .321, .661)]; consumption of tranquilizers [A: .456 (CI 95%: .263, .625); E: .543 (CI 95% .375, .737)] or antidepressants [A: .462 (CI 95%: .203, .675); E: .538 (CI 95% .325, .797)]. *Conclusion:* Preliminary results suggest that individual differences in psychotropic medication use may be moderately but significantly influenced by genetic factors. Heritability estimates for psychotropic medication use are around .50. Genetic factors involved in the consumption of psychotropic medication could present differences from those related to the related mental health disorders.

MULTIPLE PREGNANCIES AS A COMPLICATION OF IVF

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The national twin birth rates have been increasing worldwide. Ukraine is not the exception. The main reason of this is the use of assisted reproductive technologies (ART) including IVF. In Ukraine dual embryo transfer has been the standart for last few years. This is why 26,6% of the pregnancies after IVF are multiple (twins) in our Clinic. The small retrospective study for the period 2007-2010 of 46 women with twins was made in our Clinic of eproductive Medicine "Nadiya" in Kiev. 44 of the pregnancies were after IVF, 2 of them had spontaneous pregnancies. Among 44 women after IVF 8,5% of them got twins after embryo reduction of multiple pregnanies. Carrying more than one baby can put an extra complications on the pregnancy. Threatened miscarriage occurs more often and, according to some studies, so does vaginal bleeding. Talking about the miscarriages we have to mention that we had 5 cases of miscarriages among twins. Pregnancy hypertension (high blood pressure) and pre-eclampsia are also more frequent, and may mean that the babies need to be delivered early. One of the most frequent complications of multiple pregnancy is cervical incompetence. It is a medical condition in which a pregnant woman's cervix begins to efface(thin) before her pregnancy has reached term. Through our patients we had 5 cases (11%) of cervical incompetence. The solution of this problem was found. We have used cervical cerclage. The most common pregnancy problem was preterm labour. The average term of delivery among twins was 36-37 week of

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gestation.There was a caesarean section rate of 100%. The average birth weight was 2600 gramms. The above-mentioned multiple pregnancies show a higher risk of premature birth and lower birth weight.

PSYCHOSOCIAL WORKING CONDITIONS AND RISK OF DISABILITY PENSION DUE TO MENTAL DIAGNOSES: A PROSPECTIVE TWIN COHORT STUDY

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Background: Few population-based studies have addressed psychosocial working conditions, or occupational groups regarding disability pension (DP) due to mental diagnoses. Previous studies of DP in general, but also due to mental diagnoses, show increased risk for DP in jobs with high demands, low control and/or low social support, and jobs in the health care and service sectors. However, influence of familial factors, including genetics and shared environment, on such associations have not yet been investigated. The objective of this study was to investigate associations between job demands, job control, social support, the combination of these, occupational groups and DP due to mental diagnoses, accounting for influence of familial factors. *Methods:* A prospective cohort study, based on national population-based registers, was conducted including all twins born 1928-1958 in Sweden, who in January 1993 were alive, living in Sweden, not on old-age pension nor DP, and registered as working (N = 42 715). The cohort include both complete twin pairs (4154 MZ, 6072 same-sexed DZ, 6214 opposite-sexed DZ, and 841 with unknown zygosity) and 8153 twins without their co-twin. The twins were followed for incident DP due to mental diagnoses in 1993-2008. Occupation was measured according to the Nordic Standard of Occupational Classification including 320 codes. These codes were categorized into eight different occupational groups: 'technology, natural and social science & art'; 'health care and social work'; 'administration & management' (reference group); 'commercial work' ; 'agriculture forestry & fishing', 'transport'; 'production & mining'; and 'service and military work'. To measure psychosocial working conditions mean scores of job demands, control, and support were applied to the 320 codes of occupations, using a job exposure matrix. These mean scores were thereafter split into quartiles and medians. Quartiles were used to analyze job demands, job control, and support, separately, while medians were used to analyze combinations of these according to Karasek's and Johnson's job strain model: high strain (high demands, low control), low strain (low demands, high control) (reference group), active (high demands, high control), passive (low demands, low control), and iso-strain (high demands, low control, low support). Cox proportional hazards models were carried out at individual level and discordant twin pairs for DP (188 MZ, 323 DZ pairs), respectively. *Results:* High job control (HR 0.66; 95% CI 0.48-0.91), 'health care and social work' (1.41; 1.04-1.92), and 'service and military work' (2.07; 1.37-3.14) were statistically significant associated with DP, even after accounting for familial confounding in analyses of discordant pairs. Associations between passive (1.26; 1.05 - 1.50) and iso-strained jobs (1.41; 1.12 -1.77) and DP were also observed in the analyses of the whole cohort, however, these associations attenuated after accounting for familial factors. *Conclusions:* High job control and two occupational groups were independent predictors of DP due to mental diagnoses. In general, familial factors such as family socioeconomic status and genetics, had more influence on the associations between working conditions and DP than between occupational groups and DP. Future studies on risk factors for DP should consider taking potential familial confounding into account.

HERITABILITY FOR CAUSE SPECIFIC MORTALITY BASED ON TWIN STUDIES

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There has been considerable interest in studying the magnitude and type of inheritance of specific disease. This is typically derived from family or twin studies, where the basic idea is to compare the correlation for different pairs that share different amount of genes. We here consider data from the Danish twin registry and discuss how to define heritability for breast cancer. The key point is that this should be done taking censoring as well as the competing risks due to eg.
 death into account. Ohterwise the estimates will be seriouly biased. Unfortunately, this is seldom done. We describe the dependence between twins on the probability scale and show that various models can be used to achieve sensible estimates of the dependence within monozygotic and dizygotic twin pairs that may vary over time. These dependence measures can subsequently by decomposed into a genetic and environmental component using random effects models. We here present several novel models that in essence describe the association in terms of the concordance rate, i.e., the probability that both twins experience the event, in the competing risks setting. We also discuss how to deal with the left truncation present in the Nordic twin registries, due to sampling only of twin pairs where both twins are alive at the initiation of the registries.

PERSONALITY SIMILARITY IN UNRELATED LOOK-ALIKE INDIVIDUALS: RESOLVING A TWIN STUDY CHALLENGE

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A large number of twin studies have reported genetic influence on personality, yet twin research findings continue to be questioned by some members of the scientific community. A recurring misconception is that MZ co-

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twins resemble one another in personality similarity, due to their similar treatment by others. It is further argued that MZ twins' similar treatment is triggered by their identical physical resemblance. The present study brings new evidence to this question by examining the similarities in personality and self-esteem of individuals in 23 unrelated look-alike pairs (U-LAs), evenly divided between males and females. The mean age of the participants was 46.21 years (SD = 13.96). The U-LAs were identified in Canada with the assistance of photographer Francois Brunelle. Intraclass correlations for the personality scales of the French Questionnaire de Personnalite au Travail and the Rosenberg Self-Esteem Scale demonstrated negligible behavioral resemblance between U-LAs. These results are in striking contrast to those from MZ and DZ twins, both reared apart and together; for example, reported intraclass correlations for neuroticism are .25 to .61 for MZ twins, and .11 to .29 for DZ twins. The ULA findings are especially interesting with reference to DZ twins who do not look physically as alike as ULAs. Therefore, it is concluded that MZ co-twins' personality similarity mostly reflects their shared genes, and reactive gene-environment correlation best explains MZ co-twins' similar treatment by others.

COMPARISON OF PERINATAL OUTCOMES BETWEEN SPONTANEOUS AND IATROGENIC MULTIPLE PREGNANCIES

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Background: The increase number of iatrogenic multiple pregnancies was associated with increased incidence of prematurity, low birth weight and neonatal morbidity. This study was aimed to compare the fetal outcomes between spontaneous and iatrogenic multiple pregnancies in the local setting in Malaysia. *Methods:* This was retrospective case control study was done to compare the fetal outcomes between spontaneous and iatrogenic multiple pregnancies which was conducted in UKM Medical Centre. The outcomes compared were perinatal mortality, duration of hospitalization, gestational age, birth weight, and neonatal morbidity. Statistical analysis was done using SPSS 14. P value of less than 0.05 was considered statistically significant. *Results:* Seventy three mothers with multiple pregnancies delivered in UKM Medical Centre which yielded 151 babies during the study period. There were 57 spontaneous multiple pregnancy (78.08%) and 16 iatrogenic multiple pregnancy (21.92%). Prevalence of dichorionicity in iatrogenic and spontaneous multiple pregnancies were 81.08 % and 47.37% respectively. Prevalence of monochorionicity in iatrogenic and spontaneous multiple pregnancies were 18.92 % and 52.63% respectively. There were significant differences between iatrogenic and spontaneous multiple pregnancy in gestation period (32.6 weeks vs. 35.4 weeks, $p = 0.000$), birth weight (1.85kg vs. 2.26kg, $p = 0.001$), length of hospitalization (13.2 days vs 5 days, $p = 0.018$) and neonatal morbidity (85% vs 32%, $p = 0.013$). The relative risks with 95%CI in the IMP group for preterm deliveries was 4.46(1.48-13.49), low birth weight babies was 2.60(1.05-6.42) and neonatal morbidities was 2.61(1.20- 5.67)). However, there was no significant difference in perinatal mortality (0.056% vs 0.055%, $p = 1$). *Conclusion:* Iatrogenic multiple pregnancies had worse fetal outcome compared to the spontaneous multiple pregnancy but there was no significant difference in perinatal mortality in both groups.

TWIN GESTATIONS: MANAGEMENT AND OUTCOME (A RUSSIAN POPULATION-BASED STUDY)

L. Sichinava, O. Panina

The patterns of multifetal pregnancy and birth in Russia has changed dramatically during the last decades attributed mainly to the introduction of assisted reproductive technologies. The overwhelming majority of multifetal births in Russia are twins. Twinning rates have increased steeply between 2000 and 2010; the rate of twin births rose from 9,132 to 15,444. A more significant increase is observed in Moscow; from 643 to 1451. The proportion of monochorionic and dichorionic twins is unchanged during two last decades. Monochorionic placentation is associated with substantially higher risks of spontaneous abortion, IUGR, vascular anomalies including twin-to-twin transfusion syndrome and intrauterine fetal demise. Regardless of chorionicity, premature delivery is the most important contributor to the high rate of adverse perinatal outcome in twin pregnancies. Preterm deliveries in multiple gestations account for more than 50%. Sonographic cervical length has been proposed as a tool to assess the risk of preterm birth. Cervical length and internal os funneling were evaluated from 14-15 weeks of gestation in 350 patients. In patients who delivered preterm, cervical length shortening began at 22-24 weeks of gestation. For twin pregnancies the presence of a shortened cervix (19 mm or less) at 22-24 weeks was significantly associated with preterm birth at less than 32 weeks. The cervical length measurements were the same for both monochorionic and dichorionic twins. Our results prove that cervical length measured by ultrasonography from 20-24 weeks is very important predictor of preterm delivery in twin pregnancies. Assessment of the cervix may ascertain which women are at greatest risk of preterm birth establishing effective means to prevent preterm delivery or at least to postpone it until sufficient fetal growth and development have occurred. Cervical assessment in twin gestation should be incorporated in routine care and prophylactic and therapeutic interventions have to be based on TVS results.

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A QUADRUPLET PREGNANCY COMPLICATED BY GESTATIONAL DIABETES MELLITUS: OBSTETRICAL MANAGEMENT AND NEONATAL OUTCOMES.

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Infertility treatments have produced an increase in multiple gestations and the virtually related preterm deliveries. Preterm delivery (PTD) places the babies at risk for short- and long-term morbidity and mortality. We present the case of a quadruplet pregnant who was referred in October 2011 to the High-Risk Pregnancy Unit, University Federico II of Naples, at 27 gestation weeks. The pregnancy was obtained after an ovarian stimulation resulting in a tetra-amniotic, tetra-chorionic gestation of two male and two female fetuses. During antenatal ultrasonography screenings, despite an expected reduced biometry compared to singleton pregnancies, the four fetuses presented middle-high biometry parameters. A 75 g OGTT at 28 weeks revealed a condition of gestational diabetes (glycemic values: 97 mg/dl at 0', 201 mg/dl at 60';; 158 mg/dl at 120'). The women was put on hypoglycemic diet and a series of ultrasound and cardiotocographic examinations were performed to assess fetal wellbeing. Umbilical Artery Pulse Index (UA PI) of fetuses showed values within normal ranges. UA PI of each fetus at 30 weeks gestation were: 1,20 (A) ; 1,09 (B); 0,86 (C) ; 1,09 (D) and Computerized Cardiotocography (cCTG) analysis showed normal parameters. The patient underwent a caesarean section at 32 weeks gestation (the mean gestational age at delivery for quadruplet pregnancies is 29.5 weeks) and the four babies were delivered without complications; the two female newborns weighted 1630 g (A) and 1430 g (C) while the two male newborns weighted 1470 g (B) and 1740 g (D). Cord-blood samples were collected from each umbilical cord but not showed values of C-peptide > 90° percentile, which is usually considered an adverse outcome for babies of a diabetic mother. At 3 months follow-up, fetus D showed mild hypoglycemia and a biometry more than 70° percentile but no adverse outcomes, while fetus B developed necrotizing enterocolitis (incidence in quadruplet pregnancy 1,7%), underwent three operations and actually he has a short bowel syndrome. Gestational diabetes mellitus (GDM) in a quadruplet pregnancy is a very rare condition and offer an unique chance to investigate the mechanisms that underlie the physiopathology of gestational diabetes in the fetus. It is interesting to reflect on how four fetuses that shared the same maternal diabetic environment developed different outcomes. How much the individual genetic predisposition of this heterozygotic brothers influences their different neonatal outcome. This points out an intriguing topic which needs future research.

RESPIRATORY DISTRESS SYNDROME IN TWINS IN NICU

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Respiratory Distress Syndrome (RDS) is a syndrome of respiratory malfunction occurring in pre-term newborns. It was analyzed the percentage of preterm with RDS from multiply newborns hospitalized in NICU with diagnosis RDS and we have noticed that 20 % of newborns were from double pregnancies, category this endangered by RDS. Average age of mother was 21 years, average weight on birth was 1420 gram, average of gestative weeks 32; in sex aspect the masculine gender was dominate one: from 14 they are 10, from them 6 were of first births, until on basis of mood of birth: 8 were born in normal way and 6 by C.S. RDS is a problem and a special theme in NICU with same characteristics, which occur as in simple births, as well as with the high incidence of morbidity

TWINNING RATES IN THE NORDIC COUNTRIES

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In the 1970's and beginning of 1980's the multiple birth rate was exceptionally low in developed countries, with a twinning rate about 1% of all births. But within the last two decades the multiple birth rate has increased to an unprecedented high level of more than 2% in some countries. The increase has been explained by the introduction and increased use of artificial reproduction technologies (ART). The methods of ART have been refined, for example leading to the implantation of fewer embryos, and in recent years the standard procedure has been to implant only one fertilized egg. Although this change has lead to a decline in the twinning rate in some countries (e.g. Norway) the twinning rate still remains at a high level in others (e.g. Denmark). Based on register data and a survey among Danish twins born since 1983 the development in Nordic twinning rates (natural and ART-related) is discussed.

TWINNING ACROSS THE DEVELOPING WORLD

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Background: Until now, little was known about the variation in incidence of twin births across developing countries, because national representative data was lacking. This study provides the first comprehensive overview of national twinning rates across the developing world on the basis of reliable survey data. *Methods:* Data on incidence of twinning was extracted from birth histories of women aged 15-49 interviewed in 150 Demographic and Health Surveys, held between 1987 and 2010 in 75 low and middle income countries. During the interview, information on all live births experienced by the women was recorded, including whether it was a singleton or multiple birth. Information was available for 2.47

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million births experienced by 1.38 million women in a period of ten years before the interview. Twinning incidence was measured as the number of twin births per thousand births. Data for China were computed on the basis of published figures from the 1990 census. Both natural and age-standardized twinning rates are presented. Results/*Conclusions:* The very low natural twinning rates of 6-9 per thousand births previously observed in some East Asian countries turn out to be the dominant pattern in the whole South and South-East Asian region. Very high twinning rates of above 18 per thousand are not restricted to Nigeria (until now seen as the world's twinning champion) but found in most Central-African countries. Twinning rates in Latin America turn out to be as low as those in Asia. Changes over time are small and not in a specific direction. Significance: We provide the most complete and comparable overview of twinning rates across the developing world currently possible.

(EPI)GENETICS OF HYPERTENSION AND OBESITY

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After many years of fruitless searches genome-wide association studies (GWASs) finally offered genetic epidemiologist the key to unlock the genetic basis of common complex diseases. These advances in complex disease genetics have taken place at neck breaking speed. However, the majority of the genetic risk for hypertension and obesity and their underlying quantitative traits remains unexplained. Gene-environment interactions have been proposed as one possible reason for this missing heritability. For example, we have shown in a number of twin studies that genetic influences underlying individual differences in blood pressure are to a large extent dependent on the situation in which the blood pressure is measured (day vs. night, rest vs. stress, young vs. old). The epigenome provides an interface between the environment and the genome and records a variety of dietary, lifestyle, behavioral, and social cues. As such, a focus on epigenetics increasingly emerges as a promising approach to study the mechanisms behind gene-environment interaction in common complex diseases such as hypertension and obesity. The current talk will briefly evaluate the fruits of GWAS for hypertension and obesity and will indicate promising ways forward that move beyond the DNA-sequence.

AN APPROACH TO SCREENING FOR CHROMOSOMAL ABNORMALITY IN TWIN PREGNANCIES

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Recommendations have recently been developed for some of the difficulties that can arise with early multiple pregnancy chromosomal abnormality screening. These will be presented for the following issues: triplets and more, when chorionicity is uncertain, when one fetus in a twin pregnancy has no heart beat, large nuchal (> 3.5mm), DC/DA, MC/DA and MC/MA twins. Women who book late for pregnancy care can still be offered second trimester quadruple testing. Non-invasive prenatal diagnosis using ffDNA is being seriously considered for singleton pregnancies but many studies are excluding multiple pregnancies. We have compared Y-signal DNA levels in dichorionic and monochorionic twins. There was significantly higher ffDNA concentration in maternal blood from twin pregnancies with two male fetuses compared with pregnancies with one male fetus. In cases with two male fetuses, there was no statistically significant difference between monochorionic and dichorionic pregnancies. This makes ffDNA non-invasive prenatal diagnosis likely to be possible in monochorionic twins. Reference: Attilakos, G., et al. (2011). Quantification of free fetal DNA in multiple pregnancies and relationship with chorionicity. Prenatal Diagnosis, 31, 967-972.

MANAGEMENT OF MONOAMNIOTIC TWIN PREGNANCIES

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Monoamniotic twinning (MAT) is a rare event and occurs in approximately 1% of all monozygotic twin gestations thus affecting about one in 10 000 pregnancies. MAT pregnancies are formed when a single egg is fertilized and the resulting inner cell mass splits after day nine. The presence of both fetuses in the same amniotic sac commonly leads to cord entanglement and this may result in cord accidents and fetal death. In addition, MAT are susceptible to the complications faced by all monochorionic twins including preterm birth, increased rate of congenital anomalies, intrauterine growth restriction, twin-to-twin transfusion syndrome and increased perinatal mortality. MAT pregnancies in the current era are associated with a perinatal mortality of 10% - 20%.Due to the rare occurrence of MAT, only relatively small case series have been published with varying survival data, including diverse mortality rates after 30–32 weeks of gestation and varying recommendation on the need to perform early delivery. The reported incidences of perinatal mortality vary widely due to differences in ascertainment, prenatal recognition, inclusion of fetal anomalies, and individual unit practice. The presence of fetal abnormalities contributes significantly to adverse outcome data, and it is important to distinguish outcomes between these subgroups. Conjoined twins are the subgroup of MAT and these pregnancies are usually accurately diagnosed in the first trimester and are usually terminated. In MAT that are discordant for a major abnormality, selective termination (cord occlusion by laser or diathermy) may be an option; however, in such cases there may still be retrograde hemorrhage from the surviving fetus into the dead placental tissue. Published regimens for antenatal surveillance of MAT vary from ultrasound and cardiotocography (CTG) testing every two weeks to prolonged admission to hospital from as early as 26 weeks' gestation with CTG testing up to three times each week. The

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need for hospitalization is controversial and is the best individualized based on the antenatal findings. However, in-patient management has been reported to improve survival rates. Many centres plan to deliver all MAT by cesarean section to avoid cord prolapse or inadvertent clamping of the cord of the second twin. However, this is not universal, and some rare centres deliver selected MAT vaginally. According to the best available evidence, about 1 in 25 MAT is complicated by fetal demise after 32 weeks and several other series have highlighted a continued risk of demise after 32 weeks. The risk of neonatal death associated with preterm birth at 32 weeks is about 1 in 100. Delivery of MAT at this age thus carries a smaller risk than remaining in utero.The first trimester diagnosis of MAT is of essential importance for parents counseling and management strategy. Antenatal steroids should be administered at the appropriate moment to all MAT. Such pregnancies require management in the tertiary level hospitals equipped with the neonatal intensive care, Based on the current knowledge, the risk of mortality of a moderate preterm birth by elective cesarean section at 32 weeks appears to be four times lower than that of remaining undelivered.

MONOAMNIOTIC TWINS: ANTENATAL MANAGEMENT AND PERINATAL OUTCOME OF 21 CONSECUTIVE PAIRS IN A SINGLE TERTIARY INSTITUTION — AN 11-YEAR EXPERIENCE

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Objective: To describe the obstetric management and perinatal outcome of antenatally diagnosed monoamniotic twin pregnancies (MATP) in a tertiary teaching hospital. *Materials and Methods:* A retrospective chart review of all MATP in our institution diagnosed antenatally in 11-year period (2002 -2012). The diagnosis of MATP was made in all cases at the time of the first ultrasound screening and confirmed after birth or termination of pregnancy (TOP). *Results:* They were 21 monoamniotic twin pregnancies during the study period. In three cases conjoined twins were diagnosed and all have undergone elective TOP in the first trimester. One case developed an early twin-to-twin transfusion syndrome (TTTS) with consecutive double fetal demise at 17 and 19 gestational weeks, respectively. There were 17 MATPs that progressed beyond 22 weeks of pregnancy suitable for the analysis. All but one resulted in live birth of both twins at median gestational age 31+6 weeks (range 27+1 – 34+2) by caesarean section (9 elective CS, 7 emergency CS and 1 crush CS). All pregnant women received a single course of antenatal corticosteroids for the fetal lung maturation. The mean birth weights of the twins were 1727g (A-twins) and 1699g (B-twins). There were 13 female twin pairs and only 4 male twin pairs. All infants were euploid without anomalies. Multiple cord entanglement was observed in all pregnancies. There were 33 liveborns of 17 pregnancies and one stillbirth in 24+5 gestational week. Mean birth weight was 1675g (A twins) and 1697g (B twins).There was substantial and expected respiratory morbidity (20 cases of RDS and 5 cases of transient tachypnea). We observed 2 cases of neonatal sepsis and 3 cases of mild intraventricular haemorrhage. There was only one case with mild birth asphyxia without long-term consequences, the rest of the twins were born in good condition. There were two cases of TTTS: one case with mild form was treated conservatively and one case with rapidly developed TTTS and premature rupture of membranes at 26 gestational weeks treated by three amnioreductions. The latter twin pair was delivered due to the subacute chorioamnionitis at gestational age 27+1 and the infants have mild neurological delay at one year of age. The only pregnancy with stillbirth of one twin in gestational age 24+5 ended up in delivery of remained twin at gestational age 28+1. All pregnant women recovered uneventfully. *Conclusions:* With an accurate early prenatal diagnosis, intensive fetal surveillance and appropriate timed delivery, perinatal survival of monoamniotic twins is improved; it was 97% in our case-series.

COGNITIVE AGEING IN WOMEN USING A COMPUTERISED BATTERY: A LONGITUDINAL QUANTITATIVE GENETIC TWIN STUDY

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Cognitive performance is known to change with age in many domains over the age of 45, and in particular, processing speed measures show near linear decline over the whole of the adult age range. However, whilst performance at a single time point is heavily genetically influenced, to date there has been little direct evidence that change in performance is genetically mediated and this has been an unexpected failure. Studies suggest that speed measures may be more genetically influenced than other measures, but the measures used to date have involved paper and pencil tests. *Objective:* We aimed to investigate the heritability of a battery of computerized tests with a large number of speed measures, using a twin cohort of older women over a period of ten years. *Methods:* This study utilizes a subset of the female TwinsUK volunteer cohort aged 43-73 at baseline testing. 324 (127 MZ, 197 DZ) were tested twice with a ten-year interval with the 7 measures of the CANTAB battery, constituting an 81% follow-up rate of the original cohort. Cross sectional analysis was performed at each time point using standard univariate structural equation modelling and the stability of these effects over time was then analysed using a bivariate Cholesky decomposition. Longitudinal analysis of the change in each cognitive measure and the first factor from factor analysis of all the change scores was conducted, again using univariate structural equation modeling. For each cognitive change measure the raw difference scores

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were adjusted for baseline. *Results:* Heritability estimates increased in all measures over the ten years, for example from 0.36 (0.15-0.53) to 0.54 (0.38-0.67) with delayed matching to sample mean correct latency, and 0.29 (0.08-0.48) to 0.42 (0.24-0.57) in five-choice reaction time. The genetic aetiology was remarkably stable over time. In longitudinal analysis significant heritability of change was found in 5 of the 7 tests, ranging from 0.21 (0.01-0.4) in Paired Associates Learning errors, to 0.41 (0.20-0.58) in Spatial Span. The first factor from exploratory factor analysis of all the change scores was strongly associated with age (p>0.001) history of diabetes at baseline (p = 0.002) and physical performance at baseline (p = 0.001) and had a heritability estimate of 0.47 (0.27-0.62). *Conclusion:* This battery, which has a number of computerised speed measures, showed significant heritability of change in cognition in a young-old volunteer cohort. Genetic factors may have more influence on change in these measures, which are highly sensitive to age. They may be better candidates for the search for genetic pathways involved in cognitive ageing.

DOES CAREGIVING CAUSE DISTRESS OR DO DISTRESSED CAREGIVERS RUN IN FAMILIES? A COMMUNITY-BASED TWIN STUDY

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More than fifty million informal caregivers in the U.S. provide $350 billion worth of unpaid services each year to relatives and friends including daily activities such as maintenance (e.g. bathing) and/or higher level activities (e.g. reading) because of physical, cognitive, or emotional impairments. Without such help, many individuals would be unable to sustain themselves. Despite the benefit to society, caregiving has been called a prototypic stressor because caregivers are exposed to both proximal (e.g. family arguments) and distal (e.g. lost work) stressors. These can take the form of daily hassles, life events, life change and chronic stress. Such experiences can, in turn, lead to perceived stress which is a global response that includes appraisals (e.g. poor control, feelings of limited resources, general strain), symptoms of psychological distress (e.g. anxiety, depression), and burden in response to specific caregiver stressors. Indeed, an extensive literature shows that caregivers report greater levels of: perceived stress, depression/anxiety and increased burden than do non-caregivers. Unfortunately, existing studies of caregiving have been primarily observational and often poorly controlled. Those studies leave open questions about whether the observed associations are truly causal or confounded by familial factors including genetics. The present study addressed the question of familial confounding using the discordant twin design. We analyzed data on caregiving, perceived stress, anxiety, depression, and mental health functioning from 614 female same sex twin pairs who were members of the community-based University of Washington Twin Registry. Of the twins in the sample, 188 reported being a caregiver to a family member or friend. Consistent with the existing literature, we found that caregivers reported greater perceived stress (B = 1.47, p = .01), higher anxiety (B = 1.43, p = .001), increased odds of being depressed (OR = 1.66, p = .05), and decreased mental health functioning (B = -2.35, p = .006). However, when we conducted within-pair analyses stratified by zygosity, we found that all of the regression coefficients were attenuated suggesting that familial factors (i.e. common environment and genetics) account for a significant proportion of the association. Familial effects appeared to be strongest for perceived stress and weakest for anxiety. These data shed important new light on the subject of caregiving and distress and suggest that much additional research is needed to determine whether the physiological toll that is attributed to caregiving is also confounded by familial factors.

SOCIAL MEDIA EXPERIENCES OF THE NETHERLANDS TWIN REGISTER

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Most research institutes have a website, with the aim of informing their participants about ongoing research studies and research results. However, information on these sites is generally very static, and not set up for active participant contact. The present day development of social media provides an opportunity for a more active interaction with study participants. Recently, the Netherlands Twin Register (NTR) became an active player in social media. This included Facebook, twitter and Hyves. The NTR has currently 247 followers on the exclusively Dutch medium Hyves, while the number of followers on twitter is 583. The social medium with the highest impact is Facebook. On 1 February 2012, 2032 NTR followers were registered but the number of individual social networks (friends), that can be reached through these persons is more than 300.000. Indeed, the number of persons who viewed the NTR Facebook page is 3812 higher than those who are connected to it. Within the last month this number has increased to 800, showing that the reach of the NTR Facebook grows rapidly. The followers are predominantly female (78%) and in the age range of 25 to 44 (60%). In addition to scientific news related to twins, either from the NTR or other sources, the NTR Facebook page contains pictures of twins, and human interest stories related to twins. Most hits and positive responses are elicited by the last two categories. The page also contains calls for twins and

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family members to participate in research. Our experience of the last year indicates that social media, especially Facebook, can help twin registers and other research institutes, connect to their participants.

DELIVERY MODE, OUTCOME AND NEWBORN COMPLICATIONS IN TWIN PREGNANCY

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Introduction: To assess whether the increased number of twin pregnancies along with the increased use of ART has lead to an increase of obstetrical and neonatal complications. *Materials and Methods:* A retrospective study was carried out over a two year-long periods (2001 and 2011) The parameters taken into account were: 1) Delivery Mode 2) ART 3) Birth Weight 4) Presence of respiratory distress syndrome 5) Perinatal asphyxia 6) Intracerebral Hemorrhage. Summary of *Results:* Despite the fact that the number of deliveries was virtually the same in the period studied (3463 in 2001 and 3491 in 2011) the number of twin pregnancies almost doubled (28 twin pregnancies versus 51 twin pregnancies). In 2001, out of 28 pregnancies only 7 patients delivered through cesarian section; in 2011 40 patients out of 51 delivered through cesarian section. In 2001 we had only one pregnancy as a result of IFV and two after ovarian stimulation, in 2011 one third were the result of different ART (8 IVF procedures, 2 IUI, 5 ovarian stimulations) The lowest birth weight decreased to 570 g (sibling 650 g) compared with 1020 g (sibling 1340g) in 2001. Mild Birth Asphyxia was the most frequent diagnosis, incidence of sever asphyxia was 1.9% in 2001 and 3.9% in 2011 due to the drop in birth weight and gestational age as well. Another consequence of the sharp drop in both gestational age and birth weight was an increase of respiratory distress syndrome from 17.8% in 2001 to 30.3% in 2011 and in intraventricular hemorrhage from 8.9% in 2001 to 14.7% in 2011. *Conclusions:* The number of twin pregnancies is highly increased after 10 years. Gestational age dropped to 26 weeks of gestation, and fetuses with very low birth weight are now a day to day issue. Nevertheless, the percentage of newborns that required admission to intensive care unit, the low rate of RDS, of perinatal asphyxia, Intraventricular hemorrhage and overall the survival of twins without long term consequences make us to believe, that women were given proper medical care throughout the pregnancy and delivery while new-borns, were provided with careful nursing until discharge and afterwards. Maybe the only draw-back of this period, is the dramtic surge in cesarian section regardless of the complications and morbidity for both mother and fetus, that this procedures implies.

GENETIC AND ENVIRONMENTAL FACTORS OF IMPORTANCE FOR CONTINGENT SELF-ESTEEM AMONG WOMEN AND MEN

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Background: Several studies have indicated that level of self-esteem is a heterogeneous characteristic and that not only quantitative but also qualitative aspects should be examined. One important qualitative aspect of self-esteem concerns its contingency which refers to the sources and construct of self-esteem. Self-esteem is said to be contingent if it is dependent on meeting particular conditions and standards within or across various arenas or domains, such as social approval or successful performance. Individuals with high contingent self-esteem are particularly sensitive to failures as they continuously try to demonstrate and validate their personal qualities and worth. Some studies of genetic influences on global and domain-specific self-esteem have suggested that additive genetic effects explains a substantial portion of the phenotypic variance in level of self-esteem. The aim of this study was to investigate the relative importance of genetic and environmental factors for contingent self-esteem, as measured by a scale for Performance-Based Self-Esteem (PBSE). Method The source population consisted of twins from the Swedish Twin Registry born 1959-1986 who participated in the Study of Twin Adults: Genes and Environment (STAGE) web-based questionnaire in 2005. The study sample included in total 21,703 individuals with complete information on PBSE and zygosity. Of these 5085 were same sexed (3022 MZ and 2063 DZ) and 1998 were opposite sexed (OS) twin pairs. The PBSE-scale includes items on cognitions related to general contingent self-esteem such as contingency and imperative beliefs and ego-oriented motives without references to any specific domains. The scale consists of the following four items: 'I think that I sometimes try to prove my worth by being competent', 'My self-esteem is far too dependent on my daily achievements'; 'At times, I have to be better than others to be good enough myself'; and 'Occasionally I feel obsessed with accomplishing something of value', with a response format from 1 (fully disagree) to 5 (fully agree). The arithmetic mean of the responses to these items formed the PBSE score for each individual. Within-pair similarity for PBSE was assessed by calculating intraclass correlations and genetic and environmental influences on PBSE were estimated by applying structural equation modeling. We tested whether there were any sex differences, quantitative and qualitative, in the whole data sample, that is, inclusive OS twins. Results All the MZ intraclass correlations were higher than the DZ intraclass correlations, suggesting that genetic influences are important for PBSE. We estimated the relative contributions of additive genetic (A)

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influences, non-additive genetic (i.e., dominance or epistasis) (D) or shared environmental (C) influences, and non-shared environmental (E) influences on PBSE. Results from the model fitting showed heritability estimates of 34% for PBSE in men and 38% in women, and results indicated qualitative sex differences. Non-shared environmental influences accounted for the remaining variance. Conclusion Genetic factors seem to be of importance for contingent self-esteem and the mechanisms involved might differ between women and men. However, contingent self-esteem is also largely influenced by environmental factors as has also been reported for global and domain-specific self-esteem.

A PROSPECTIVE COHORT STUDY OF STABILITY AND CHANGE IN HEALTH BEHAVIOURS AS RISK FACTORS FOR DISABILITY PENSION DUE TO MUSCULOSKELETAL DIAGNOSIS AMONG SWEDISH TWINS

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Background: Stability or changes of health behaviors have not been studied in association with incidence of disability pension (DP). A twin study with a sufficient number of twin pairs discordant for DP would be an effective tool to investigate whether health behaviour, stable or altered, could modify the risk for DP since both health behaviors and DP are known to have moderate heritability. The aims were to investigate if stability or changes in health behaviours predict DP due to musculoskeletal diagnosis (MSD), to evaluate if an association exists also for DP in general, and to account for familial confounding (genetic and shared environment). *Methods:* The study sample included 16,713 like-sexed twin individuals born in Sweden between 1935-1958 (6195 complete twin pairs of whom 2659 were MZ and 3536 were DZ pairs) who had participated in two surveys 25 years apart, who were alive, and not old-age pensioned at the time of the latest survey. Cox proportional hazards analysis was used to assess the associations (hazard ratios [HR] with 95% confidence intervals [CI]) between stability and change in health behaviours (physical activity, tobacco and alcohol use, body mass index [BMI]), and number of pain locations collected at two time points 25 years apart and the incidence of DP until 2008. Twin pairs discordant for DP, including 223 MZ pairs and 354 DZ pairs for DP in general, and 183 MZ pairs and 267 DZ pairs for DP due to MSD, were used to account for familial confounding. *Results:* During a mean follow-up time of 6 years, 1843 (11%) individuals were granted DP whereof 747 due to MSD. More women (64%) than men were granted DP in general and due to MSD (27%) of all diagnoses. Increase in BMI (HR 1.21, 95% CI 1.03, 1.41) and stable use of tobacco products (HR 1.48, 95% CI 1.17, 1.85) were predictors for DP due to MSD and DP in general (HR 1.10, 95% CI 0.99, 1.21, HR 1.41, 95% CI 1.22, 1.62, respectively). The stability in the frequency of physical activity and increased frequency of physical activity were protective factors for DP due to MSD only when accounting for familial confounding. The number of pain locations (stability, increase, or decrease) was the strongest predictor for future DP due to MSD (HR 3.69, CI 2.99, 4.56) and DP in general (HR 2.15, CI 1.92, 2.42). In discordant pair analysis, the HRs for pain were lower, indicating potential familial confounding. *Conclusions:* Health behaviour in adulthood, such as long-term use of tobacco products, BMI increase, physical activity, and both stability and change in the number of pain locations has an effect on the incidence of DP. In particular, the effect of physical activity is related to adulthood choices or habits, not being affected by the childhood environment. Therefore, to keep a stable weight and to continue to be physically active throughout the lifespan, when possible, is of importance.

THE OCCURRENCE ANTI-CITRULLINATED PROTEIN AUTOANTIBODIES IN RHEUMATOID ARTHRITIS DISCORDANT TWIN PAIRS

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Introduction: Rheumatoid arthritis (RA) is a complex autoimmune disease. It is clinically diverse and there is evidence to suggest that RA consists of two distinct disease subsets with different underlying pathogenesis. Several studies have found various degrees of interaction between the hitherto strongest genetic risk factor identified, the shared epitope, and smoking for the development of anti-citrullinated protein autoantibodies (ACPA) positive RA and not ACPA negative RA. So far, no twin studies have addressed the genetic background for ACPA seropositivity. Objective To determine if there is evidence of a genetic component in the occurrence of ACPA. Methods ACPA was measured cross-sectionally in 27 monozygotic (MZ) and 51 dizygotic same sexed (DZss) RA discordant twin pairs The co-twin control study includes both MZ and DZ RA discordant twin pairs. This design corresponds to a matched case-control study where the RA affected twin in each pair is the case while the unaffected co-twin serves as control. The presence of an autoantibody is the exposure and RA the outcome. Only pairs discordant for exposure contribute to the conditional logistic regression analysis performed separately for the MZ and the DZ pairs. This design enabled us to stratify for the effect of age and sex in DZ pairs and in MZ pairs for genes as well. Thus, if RA and autoantibody production have a shared

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background, the odds ratio (OR) for the autoantibody in MZ twins would significantly exceed that of DZ twins since genetic variability is absent in MZ pairs. Conversely, if shared genetic factors are involved a significantly higher OR in DZ twins compared with MZ twins would be expected. In ACPA positive RA discordant twin pairs a logistic regression analysis was performed on the non-RA co-twins to adjust for the possible confounding effect of the shared epitope, sex, discordance time, age at onset, and age. A higher OR in monozygotic co-twins compared to dizygotic co-twins is suggestive evidence for the effect of genes. Results The probandwise concordance rates of ACPA was significantly different between MZ twins 61.9% (44.5-79.3) and DZss twin 32.9 (18.8-46.9). In twin pairs discordant for both RA and ACPA the odds ratio of ACPA was 5 (0.5 - 236.5) in MZ twin pairs and 17 (4.4 - 146.1) in DZss twin pairs. In the healthy co-twins there was an OR of 18.9 (95%CI: 3.5 to 101.7) for the risk of ACPA in MZ compared with DZ twins, adjusted for the covariates shared epitope, sex, age at onset, discordance time and age. Conclusion The higher concordance rate in MZ twins indicates genetic effects on the occurrence of ACPA. The RA discordant MZ pairs, in which only the healthy co-twin was positive for ACPA emphasizes that environmental factors may trigger the expression of these antibodies independently of RA in persons genetically susceptible to RA. The logistic regression analysis in the non-RA co-twins conditioned on the corresponding index twin being RA autoantibody positive revealed an MZ/DZ odds ratio of 18, indicating a genetic effect on the occurrence of ACPA independent of the shared epitope.

EVALUATION OF CHANGE IN THE COURSE OF TWIN DELIVERIES OVER THE YEARS

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Aim: The aim of the study was to evaluate the change in the course of twin deliveries over the years, with particular regard to: history of infertility, duration of pregnancy, the way of delivery, indications for caesarean section (CS) and infants condition. Material and *Methods:* The material of the study consisted of three groups of patients who delivered twins in the 1st Department of Obstetrics & Gynecology, Medical University of Warsaw: 92 women in years 1987-1991 (G1), 62 in years 1997-2001 (G2) and 126 in years 2007-2010 (G3). *Results:* An increase in twin deliveries in relation to the total number of births over years was noted (1.03% vs 1.09% vs 1.77%;$p<0.05$ for G3). The average age of patients was similar in G1, G2, G3 (p = ns). The rates of twins after infertility treatment were 7.6 vs 16 vs 43.3% ($p<0.05$ for G3). The average duration of pregnancy was: 35.9 vs 35 vs 34.8 weeks (p = ns). Premature deliveries contributed to 38.4% vs 63.9% vs 64.3% of all cases. Manual manoeuvers on 2nd twins were applied in 25% vs 6.5% vs 0.79% of deliveries ($p<0.05$). CS was performed in 47.8% vs 58% vs 90.5% of all cases ($p<0.05$ for G3). In G1 CS was most often performed when the presentation of the 1st fetus was non-cephalic (53.3%). In G2 and G3 the non-cephalic presentation of the 1st or 2nd fetus was equally important as an indication for CS (30.5%, 30.5% and 19.3%, 21.9%). In G3 infertility treatment was an important indication for CS (0% vs 5.6% vs 23.7%;$p<0.05$). The 2nd twins were delivered in significantly better condition in G2 and G3 than in G1 (Apgar 8-10 points: 79.7% vs 93.3% vs 92.6%;$p<0.05$). *Conclusions:* Twin pregnancy rate almost doubled over the years, mostly owing to increasingly popular infertility treatment. CS is increasingly being chosen to deliver twins. The non-cephalic position of the 2nd fetus has become an important indication for CS. Change in the way of twin deliveries can be beneficial for the 2nd twin condition.

PRELIMINARY ANALYSIS OF GENETIC AND ENVIRONMENTAL FACTORS INVOLVED IN SLEEP BRUXISM IN TWINS

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Objective: Sleep bruxism is an oral parafunctional activity that is characterized by the grinding of the teeth and/or the clenching of the jaw and classified as one of the most common sleep disorders. Sleep bruxism could cause tooth wear, fracture, breakage of dental prosthesis, and disorders of the orofacial function. It has been reported that the etiology of the problematic sleep bruxism can be quite varied. Although the pathophysiology of sleep bruxism has been quite intensively reported, a critical etiology of sleep bruxism has not been identified yet. Recently, it was suggested that an influence of gene polymorphism is potentially linked to the pathogenesis of sleep bruxism. Several studies have tried to clarify the contributions of genetic factors and environmental factors of sleep bruxism. However, these studies were inconclusive because the presence of sleep bruxism was determined only by the self-reported questionnaire and/or the presence of a tooth wear. The objectives of this study were to assess the sleep bruxism events in the twins using electromyography and obtain the preliminary data to reveal the importance of genetic factors and environmental factors involved in sleep bruxism in twins. Method: The subjects consisted of 40 twins who are registered in the Twin Research Center, Osaka University Graduate School of Medicine and whose parents belong to the Twin Mothers Club, Japan. Of those, 24 twins are monozygotic (12 pairs) and 16 twins are dizygotic (8 pairs). In order to obtain the definitive diagnosis of sleep bruxism, the electromyographic activity of temporalis muscles was evaluated using a portable automatic sleep bruxism analyzer (Grindcare 3.0, Medotech A/S). Although the gold standard for diagnosing sleep bruxism is the use of a polysomnography, the present study minimizes the uncertainty of measurement by using this device that can analyze the muscle activities using a signal recognition algorithm and exclude most events that are unrelated to sleep bruxism. This

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device was sent to each subject along with the operating manual to record the activity of sleep bruxism at their home for three consecutive nights. At the same time, subjects were asked to self-administer the questionnaires such as Symptom Checklist-90-Revised (SCL-90-R, Pearson) and Tokyo University Egogram II (TEG II, Kanekoshobo) along with several questionnaires. SCL-90-R instrument helps evaluate a broad range of psychological problems and symptoms of psychopathology. TEG II consists of five egostates (critical parent, nurturing parent, adult, free child, adapted child). Pearson's product-moment correlation coefficient both in monozygotic twins (MZ) and dizygotic twins (DZ) for each variable was calculated using IBM SPSS Statistics 19. This study was approved by the Osaka University Institutional Review Board (#H22-E40), and all participants provided full and informed consent. This study was supported by KAKENHI #22390363. *Results:* A high heritability (>0.50) was observed in obsessive compulsive, interpersonal sensitivity, anxiety, psychoticism, adult, and free child, while the heritability of sleep bruxism events per an hour was 0.286. *Conclusion:* From the results of this preliminary study, it was concluded that the environmental factors might be more important than the genetic factors for the sleep bruxism in twins.

TWIN STUDY ON COMPREHENSIVE CARDIOVASCULAR PARAMETERS

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Objective: To assess the heritability of arterial stiffness, central blood pressure, carotid intima media thickness and carotid flow velocities. *Methods:* 223 monozygotic and 144 dizygotic Hungarian, Italian and American twin pairs (mean age 53±14 years) underwent arterial stiffness (brachial and aortic augmentation index /Aix/, aortic pulse wave velocity /PWVao/) and central systolic blood pressure (SBPao) (TensioMed Arteriograph), carotid intima media thickness (IMT, ultrasound, Carotid Analyzer) and carotid Doppler ultrasound (peak systolic /PSV/ and end diastolic velocities /EDV/ in proximal common carotid artery /CCA/ and internal carotid artery /ICA/ bilaterally). Results refer to different subject numbers. A questionnaire was performed in order to depict habit and environmental factors. *Results:* Age-, sex- and country-adjusted heritabilities were the following: 46.8% for brachial AIx (95% confidence interval /CI/, 1.1 to 73.8%), 48.7% for aortic AIx (95% CI, 1.7 to 74.0%), 50.1% for aortic PWV (95% CI, 26.0 to 66.8%), 45.5% for central SBPao (95% CI, 10.5 to 60.0%). The heritability of the investigated IMTs ranged between 0% and 38%. Heritability for the right proximal CCA EDV was 60% (95% CI, 49 to 69%), right proximal ICA PSV was 46% (95% CI, 32 to 57%) and EDV was 25% (95% CI, 11 to 38%), left proximal ICA PSV was 25% (95% CI, 0 to 67%) and EDV was 15% (95% CI, 0 to 57%), left proximal CCA EDV was 14% (95% CI, 0 to 58%). Unshared environmental effects accounted for the largest part of variance. *Conclusions:* Most of the investigated cardiovascular parameters (arterial stiffness, central blood pressure, carotid intima media thickness and carotid flow velocities) are moderately heritable.

RESPIRATORY AND VASCULAR HARMONY — OR NOT?

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Background: An association between reduced pulmonary function and an increased risk of atherosclerotic vascular events has been reported but the underlying mechanisms are still unknown. So far no twin studies have examined the cross-sectional association between subclinical atherosclerosis and pulmonary function. *Objective:* To estimate association of lung function and arterial stiffness and to assess heritability and environmental effects on these parameters. *Methods:* 147 monozygotic and 40 dizygotic healthy adult Hungarian and American twin pairs were included in this classical twin study. MIR Minispir spirometer and TensioMed Arteriograph (TensioMed Ltd., Budapest) were used for the assessment of lung function and arterial stiffness, respectively.

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MPlus Version 6 software was used for the statistical analysis. Cholesky decomposition model was run to investigate the genetic covariance. *Results:* Age and gender-corrected heritability of observed forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), predictive FVC and FEV1 were 62.9% (95% confidence interval /CI/, 12.6 to 80.2%), 79.3% (95% CI, 51.4 to 88.5%), 57.0% (95% CI, 4.7 to 91.9%) and 56.2% (95% CI, 7 to 91.9%). Heritability of aortic and brachial augmentation index (Aix), aortic pulse wave velocity (PWV) indicated 48.7% (95% CI, 1.7 to 74%), 46.8% (95% CI, 11 to 73.8%), and 50.1% (95% CI, 26.0 to 66.8%). No genetic covariance only phenotypic correlation was found between FVC, FEV1, and AIx, PWV. *Conclusions:* The lung function parameters of observed and predictive FVC and FEV1 are strongly heritable and they are phenotypically but not genetically associated with arterial stiffness. The observed relationship can aid understanding of the background of vascular changes in different airway diseases and vice versa.

FETAL BEHAVIOUR AND HEART RATE PATTERNS IN TWINS

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Fetal movements and fetal heart rate (FHR) are established markers of fetal well-being and of maturation of the fetal central nervous system. The purpose of this article is to review and discuss the available knowledge on fetal movements and heart rate patterns in twin pregnancies. A computerized literature search of PUBMED (1970–2011) and a manual search of bibliographies of pertinent articles were conducted. Similarly to singletons, twins reveal a progressive decline in fetal activity over pregnancy, but seem to have lower fetal activity than singletons. Chorionicity is associated with synchrony in FHR patterns, onset and frequency of inter-twin contacts and intra-pair differences in fetal movements and FHR over the course of pregnancy. Fetal activity seems largely independent of chorionicity, sex combination, and presentation. Higher intra-pair synchrony is observed on FHR patterns than on fetal movements. Preliminary evidence suggests the emergence of relatively stable individual differences in fetal movements and FHR patterns. Fetal movements and FHR have been considerably less often investigated in twins than in singletons. Comparisons between studies are limited by large methodological differences and absence of uniform concepts and definitions. Future studies with high methodological quality are needed to provide a more comprehensive knowledge of normal fetal behavior in twin pregnancy.

THE ANATOMIC MIRROR: VISUALIZING HOW TWINS REFLECT THE HUMAN CONDITION

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The literature lacks a carefully designed study to assess the impact of environmental influence on anatomic expression. Since 1989, the faces of more than 226 pairs of Monozygotic (MZ) Twins were anatomically mapped using highly standardized photographic techniques. Scanning of the original transparencies and digital image analysis allowed quantification of findings. Extreme concordance of skin surface features was identified in the cohort, but mirroring of findings was recognized in a subset of subjects, confounding the analysis. Image-overlay and digital subtraction techniques were devised to cross-check the findings and definitively establish the presence or absence of anatomic mirroring, which agreed with skin findings in each pair studied. Once inherent lateralization (presence or absence of mirroring) was established and confirmed, then all recognizable skin features on both sides of the faces of both members of each twin pair were tabulated. The Mirror Phenomenon was present in 64% of male pairs and 23% of female pairs in a subset of 32 pairs with confirmed zygosity. If one allowed for slight variations in the degree of expression and for differential rates of embryologic tissue migration within a dermatome, extreme concordance of skin features was found to a level not previously documented. All clinically identifiable skin surface features in a pair of non-mirrored MZ twins and a pair of mirrored MZ twins were tabulated. Lateralized concordance was identified in 59 of 66 distinct anatomic findings, giving a p-value of 1.19×10^{-11}. The chance that such alignment and mirrored alignment could happen concurrently is virtually nil, negating the idea that the environment plays any significant role in the development of skin characteristics. Also, several pairs showed spatial concordance or mirroring of pre-cancerous skin lesions, and one pair of non-mirrored twins, both developed basal cell epitheliomas in the same location on the left ears one year apart from each other, suggesting that the three-dimensional location of vulnerable cells had been established at the time of conception. In addition, skin findings match the lateralization of asymmetries of facial and body shape in each case studied to date, and correlate strongly ($p = 0.016$) with handedness, suggesting that brain dominance is lateralized in concert with the surface structures of epithelial and mesothelial origin. Of note, these findings were true in twin pairs at all ages and with extremely different environmental exposures, suggesting that the entire body is genetically predetermined for its lifelong anatomic expression. Interestingly, those skin findings previously thought to be in-part due to environmental exposure (e.g. actinic keratoses, lentigos, and basal cell epitheliomas) were

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present on opposite sides of the face within the same dermatome in each mirror twin pair studied, suggesting that the three-dimensional location was pre-encoded, and that the passage of time alone was responsible for their appearance. It is extremely unlikely that environmental factors play any significant role in the development of common anatomic facial features. Environment cannot unilaterally affect development on one side of one twin and only the same (or mirror opposite) side of the other twin in a consistent manner for each skin structure over a lifetime. The longstanding controversy of 'Nature vs. Nurture' – at least with regard to human anatomy — may be less relevant now that previously unrecognized anatomic mirroring can be digitally diagnosed and analyzed. Future work should extend this concept to evaluate paired organs for the presence of the Mirror Phenomenon and the possibility of genetically- and spatially-predetermined disease entities.

PROSPECTIVE RISK OF STILLBIRTH NEAR TERM IN MONO- AND DICHORIONIC TWINS

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Monochorionic (MC) pregnancies are routinely delivered electively at various late preterm gestations with the intention of avoiding stillbirth. The aim of this study is to evaluate the prospective risk of late stillbirth in a large regional cohort and undertake a systematic review of the literature on routinely managed twin pregnancies of known chorionicity. We undertook a retrospective study of all twin births of known chorionicity from a large regional cohort of 9 hospitals (STORK collaborative) taken over a 10 year period matched to a mandatory national register of stillbirth (CMACE). The data of the current study was included in a systematic review of selected studies of stillbirth in routinely managed twin pregnancies of known chorionicity. A total of 3005 twin pregnancies delivered after 26 weeks' gestation in the STORK collaborative, and this was combined with data from 8 studies selected from the systematic review of the literature. The total risk of stillbirth after 26 weeks in MC twins (21.7 per 1000 fetuses) was significantly higher (OR 3.26, 95% CI 2.36 to 4.5) than in DC twins (6.7 per 1000 fetuses). The prospective risk of stillbirth in MC twins did not change significantly between 26+ weeks (3.6 per 1000 fetuses) and 36+ weeks (5.2 per 1000 fetuses, OR 1.85, 95% 0.3-13.2). The equivalent figures for DC twins were 0.8 per 1000 fetuses and 1.7 per 1000 fetuses, respectively (OR 3.4, 95% 0.9-13.2). The risk of stillbirth in MC twins does not appear to increase significantly near term. This data does not support a policy of elective birth before 36 weeks' gestation in MC pregnancies.

WHICH TWIN IS WHICH? SYSTEMATIC LABELLING OF TWIN PREGNANCIES ON ULTRASOUND

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Correct labelling of twin fetuses is needed for consistency in assigning and interpreting longitudinal scan and prenatal screening/diagnostic results. We undertook a retrospective first-trimester study of all twin pregnancies assessed by ultrasonography at our centre between 2000 and 2010. The fetus contained in the gestational sac closer to the maternal cervix was designated as Twin 1 and the relative orientation of the fetuses to each other was then defined as either lateral (left/right) or vertical (top/bottom). In discordant-sex twins, their sex and presenting order on the final scan prior to delivery were documented and compared with the sex and birth order at delivery. A total of 416 twin pregnancies were seen during the study period. At the 11-14-week scan 90.9% of twins were in lateral orientation while the remainder were oriented vertically. None of the vertically oriented twin pairs but 32 (8.5%) of the laterally oriented twin pairs changed their presenting order between the first and the last ultrasound scan prior to delivery. There were 108 discordant-sex twins scanned in the third trimester, of which the birth order changed in 20.3% that were delivered by Caesarean section and in 5.9% of those delivered vaginally. The study demonstrates that antenatal labelling of twins according to laterality or vertical orientation is reliable. The technique ensures continuity of biometric assessment from serial scans at each visit, and as such should be adopted as the preferred method of twin labelling. Furthermore, the use of orientation for antenatal labelling of twins rather than assignment of a number based on proximity to the cervix, precludes any misconception regarding which twin will be born first and ensures that parents and paediatricians are aware of the significant likelihood of a peripartum switch.

TWIN CHILDREN'S EXPERIENCES OF STARTING SCHOOL

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Children are important informants about their experiences and it is only in speaking with children that we can establish how they view and experience the world around them. The transition to school is an important milestone in young children's lives and has important implications for children's developmental outcomes. This study looks at the experience of starting school from the perspective twins who are unique in that they transition with a sibling, and singletons classmates. We report on qualitative data from 162 children (75 twins and 87 singletons) attending their first year of school in Brisbane, Australia. Semi-structured interview were conducted with children asked to describe and draw pictures about their feelings when starting school and about their friendships. These interviews were used to examine (1) how

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children feel when starting school, (2) what is important to them about these experiences and (3) if there were qualitative differences between twin and singleton children in the description of their experiences. The data was analysed for emergent themes and provide a rich insight into the experiences of starting school from the perspective of the children. The results highlight the importance of inter-personal relationships in children early school experiences. For both twin and singleton children having existing relationships with both peers and teachers and establishing new ones, was important to children's feelings about starting school. Few differences between twin and single-born children were found.

TO SEPERATE OR NOT TO SEPERATE? PARENTAL DECISION MAKING REGARDING THE SEPARATION OF TWINS IN THE EARLY YEARS OF SCHOOLING

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Entry to school is typically the first point at which the question about whether to separate twin children or place them together in the same class arises. The decision centres on the inter-twin relationship and the intended outcome is to optimize social-behavioural adjustment and scholastic attainment of each twin child. In recent times concerns about possible adverse effects of early separation and advocacy for individual rights have resulted in a movement away from organizational level policies about the separation of twin children as they enter school. Instead, individualized approaches that focus on the twin children's characteristics and family perspectives have been proposed. Drawing on an Australian sample, this study examines the decisions made by parents (N = 156) regarding the placement of their twin children in the early years of school and importantly the rationale for parental's decisions in a context where they are free to make choice. The results indicate that most parents opted for placement together in the early years of schooling. Our data suggests many parents believe the twin relationship provided emotional support and familiarity in the new environment of the school and the choice of keeping twins with their co-twin on transition to schooling was viewed as the least disruptive option. The choice to separate twins at school entry was associated with parent identification of risk in the twin relationship, while being kept together was associated with parent identification of absence of such risk. The findings are discussed in light of the current evidence against separation, and suggest that parent choices regarding the separation of twin children in the early years are informative to educational policy and practice.

INTER-TWIN RELATIONSHIP AND PSYCHOPATHOLOGY

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The inter-twin relationship involves the negotiation of individual and couple identities. How successfully these are balanced is hypothesised to affect psychological functioning yet there has been limited empirical testing of this hypothesis We present two studies examining the association of inter-twin relationship and psychopathology. Study 1. This study assessed (1) the prevalence of twin-relationship types defined by the typology of Preedy (2001) (2) the stability of relationship type across the transition from preschool to school and (3) the association of relationship with emotional and behavioural difficulties and (4) whether extremes of inter-twin relationship (dependent or extreme individualising) precede or result from psychopathology. A longitudinal study across preschool and the first school year was undertaken in a community sample of 224 twin pairs. The majority of inter-relationships were balanced and unproblematic. There were no cases of extreme individualising and closely-coupled relationships were of low prevalence and declined across time. The small group exhibiting close-coupling had clinical levels of hyperactivity-inattention and conduct problems. It is likely that dependent twin relationships are a result of psychopatholgy rather than a cause because the associations found were with cognitive dysfunction not siocial dysfunction. Study 2. This study examined the hypothesis that highly dependent relationships are a marker for underlying psychopathology. From a cohort of preschool twin pairs, four pairs were identified as having highly dependent relationships using observations of interaction in preschool settings. These children (n = 8) were followed up 3 years later in middle childhood and compared with a control group of twin children sampled from the same cohort who were not highly dependent (n = 38). Cognitive and language tests of all children were undertaken by researchers blind to relationship status. Parents provided data on obstetric history and completed the SDQ and Connors 3. Children reported on their friendships. Results indicated a specific raised risk of hyperactivity-impulsivity but not inattention. Number of friendships however were not different. Together the papers suggest that highly dependent relationships could be an early marker of psychopathology and warrant further investigation as a potential early indicator for intervention.

TWINS' RELATIONSHIP IN RETROSPECT: DOES ZYGOSITY MATTER?

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Twins constitute a special relationship. Closeness in twins is described in numerous reports where MZ twins are reported to be closer within the pair than DZ twins. This is in accordance with the working hypothesis in evolutionary psychology that persons with high genetic similarity also are more easily attracted to each other. From this you may expect that MZ twins would perceive their relationship as closer than DZ twins. The aim of the present study is to explore the nature of the twin relationship in both zygosity groups. As a contribution to a deeper understanding of thiese complex relationships, we will examine whether selfreport of perceived closeness to twin is con-

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gruent with ratings of interview data by an independent observer, in both zygosity groups. Method: 53 pairs of samesexed twins were followed from birth to adulthood. 82 of these twins were studied at the age of 30 years, 28 monozygotic (MZ) pairs and 13 dizygotic (DZ) pairs. About equal numbers of the twins were men and women. Nancy Segal's questionnare about intrapair closeness when growing up, was given to each twin separately. As part of an AAI interview, a section of questions related to the twins' experience of attachment to the co-twin, were added.These questions were: Tell me about your relation to your twin when you grew up, and describe some supporting memories. These interview data were later rated about closeness to twin. High interrater reliability was established by two independent raters. Results showed high agreement between the two measures in the DZ group. In the MZ group the selfreport of closeness differed from the interview ratings. The MZ twins reported clearly less withinpair closeness than showed by the interview ratings. This finding gives us an opportunity to further explore the complicated nature of twins' relationships.

GENETIC AND ENVIRONMENTAL FACTORS IN ASSOCIATIONS BETWEEN CONSECUTIVE PERIODS OF INFANT GROWTH AND ADULT CARDIOMETABOLIC RISK PROFILE IN TWINS

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Background: Accelerated growth in infancy is associated with an adverse adult cardiometabolic risk profile. However, it is unclear which periods during infancy are most important for which specific risk factor. Furthermore, it is not known what the importance of genetic and environmental factors to these associations is. Objective To examine the association between different periods of growth in infancy (0-1, 1-6, 6-12 and 12-24 months) and adult cardiometabolic risk factors (anthropometry, blood pressure, insulin sensitivity, lipids, leptin and fibrinogen) and to study the importance of genetic and environmental factors in these associations. Design: Cardiometabolic risk factors were assessed in 424 twin pairs (aged 18-34 years) from the East Flanders Prospective Twin Survey. Infant growth was defined as change in weight z-score. Results Associations between growth and total-to-HDL cholesterol ratio were found from 0-1 month (-0.26 per z-score, $P = 0.007$) and from 1-6 months (-0.28 per z-score, $P = 0.002$). Fibrinogen was associated with growth from 1-6 months (0.05 ln mg/dl per z-score, $P = 0.04$) and an association between growth and systolic blood pressure was only identified from 12-24 months (2.82 mmHg per z-score, $P = 0.03$). Regressing intra-pair differences in growth against intra-pair differences in the risk factors, revealed significant associations in monozygotic twins, but not in dizygotic twins in associations with lipids (e.g. total-to-HDL cholesterol ratio: -0.94 per z-score, $P = 0.004$ in monozygotic twins and 0.00 per z-score, $P = 1.00$ in dizygotic twins from 1-6 months), blood pressure (e.g. systolic blood pressure: 5.95 mmHg per z-score, $P = 0.01$ in monozygotic twins and -1.64 mmHg per z-score, $P = 0.82$ in dizygotic twins) and insulin sensitivity. This indicated a role for environmental factors in these associations. Genetic factors were important with regard to the association between growth from 0-1 month and fibrinogen (16.18 mg/dl per z-score, $P = 0.32$ in monozygotic twins and 232.79 mg/dl per z-score, $P = 0.005$ for dizygotic twins). *Conclusions:* Associations between infant growth and adult cardiometabolic risk factors in adulthood vary for different periods within infancy, therefore growth research should focus more within infancy. With regard to associations in which environmental factors are important, for example between growth from 12-24 months and adult blood pressure, the infants will possibly benefit more from growth interventions or parental counseling than in more genetically determined associations, such as the association between growth from 0-1 month and adult fibrinogen levels.

A PROSPECTIVE STUDY OF SOCIAL ACTIVITY AS A PREDICTOR OF AGED DEPRESSIVE SYMPTOMS IN JAPANESE TWINS

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Objective: The aim of this study was to investigate the longitudinal relationship between social activity and depressive symptoms. *Methods:* Our subjects were registrants of Osaka University Twin Registry (N = 380), aged 60 years and older, who responded to both the same self-administered questionnaire in 2008 and 2010. Depressive symptoms were measured by the 15-item version of the Geriatric Depression Scale (GDS). GDS score were dichotomized with cutoff point at five and who has more than five points classified as having depressive symptoms. Social activity of respondents was measured using four

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variables: the opportunity of speaking with persons except for family member living together, the frequency of going out in the last month, the degree of participating activity and the feeling of having purposeful life. Logistic regression was performed in combination with prospective analyses for all subjects with the adjustment for the effect of age, sex, the number of present diseases and the number of painful parts in the body and co-twin control analysis was performed with the adjustment for the number of diseases and the number of painful parts. *Results:* A total of 380 respondents were replied the questionnaire in 2008 and 2010 respectively, including 33 monozygotic twin pairs. The mean age was 74.33±7.5 and 67.1% of the respondents were male. Of them, 31.1% had depressive symptoms. Odds ratio were varied in co-twin control analysis in the following four variables: the opportunity of speaking with persons except for family member living together, the degree of participating activity and the feeling of having purposeful life. *Conclusion:* This study suggests that higher social activity decrease the risk of aged depressive symptoms and that familial factors play some roles in the associations between depressive symptoms and social activity.

GENETIC FACTORS OF LIFE SATISFACTION AMONG ELDERLY TWINS WITH HYPERTENSION IN JAPAN

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Introduction: Life satisfaction is one of the ways to assess psychological well-being among elderly people. In previous studies, it has been suggested that lifestyle diseases are related to not only physical but also psychological well-being. However, it is unclear whether there are familial (genetic and/or early environmental) influences on the association between psychological well-being and lifestyle diseases in the elderly. Therefore, this study aimed to examine the familial association between psychological well-being and lifestyle related diseases, with a particular focus on hypertension. *Method:* We conducted a cross sectional study in a Japanese sample of twins registered with The Osaka University Aged Twin Registry. We sent a self-reported questionnaire to eligible twins aged 39 - 100 living in 2005 by mail. We measured with a Japanese version of the self-reported 20-item Life Satisfaction Index-A (LSI-A) asking presence or absence of hypertension, age, sex, history of present illness (other than hypertension), and lifestyle factors such as sleeping hours, smoking behavior, and stress. We conducted three steps of analyses, i.e. intraclass correlation analysis of LSI-A, longistic regression analysis with non-twin case-control subjects analysis, and logistic regression analysis with co-twin case-control pairs. Odds ratios were calculated to estimate the associations between hypertension and LSI-A adjusting for age, sex, history of present illness, and lifestyles. Statistical analyses were performed with SPSS 16.0 software. *Results:* In the intraclass correlations, we found different correlations between monozygotic twins; (18 pairs, r = 0.33, $p<0.01$) and dizygotic twins; (9 pairs, r = 0.11, n.s.), suggesting genetic influences. In the non-twin case-control analysis, we found a significant association (OR = 0.90, $p<0.00$) between hypertension and LSI-A. In addition, in the co-twin control analysis, the odds ratio did not change (OR = 0.84, n.s.). *Conclusions:* We found that life satisfaction is influenced by some genetic factors, whereas we could not find common familial factors in the association between LSI-A and hypertension.

CHIMERIC TWINS: WHY MONOCHORIONICITY DOES NOT GUARANTEE MONOZYGOSITY

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Introduction: Monochorionic placentation has been considered pathognomonic of monozygosity for generations of obstetricians. In recent years there have been a number of reports of monochorionic dizygotic (MCDZ) twins, almost exclusively following treatment with assisted reproductive technologies (ART), often involving microinjection techniques. Case Report: A 36 year old woman spontaneously conceived. Monochorionic diamniotic (MCDA) twins were diagnosed on her 12 week ultrasound. A 19 week ultrasound confirmed the diagnosis. At 22 weeks gestation she developed Quintero stage I twin-twin transfusion syndrome (TTTS). The condition persisted but did not progress and no intervention was required during her pregnancy. She was carefully monitored and was eventually delivered by cesarean section at 36 weeks gestation. Both twins were male. They weighed 2490 and 2310 grams respectively. Pediatric examination was normal and long term outcome has been unremarkable. Histological examination of the placenta confirmed MCDA placentation with no other pathological features. Despite the clear evidence of monochorionicity the twins' parents were unable to reconcile the presumed diagnosis of monozygosity with their sons' significantly discordant facial features at 14 months of age. Zygosity testing was arranged at a local DNA laboratory and suggested dizygosity. The first author was then contacted for clarification of the confusing situation. Chimeric twins were suspected and appropriate investigations were arranged. A 12 marker microsatellite test was performed. In buccal cell DNA only three loci were shared by the twins. In leucocyte DNA 12 out of 12 loci were shared by the twins. This confirms that the pair were dizygotic in a non-shared tissue and apparently monozygotic in blood as a result of extensive blood sharing in association with placental vascular anastomoses. In addition, at 6 out of 6 informative loci the genotype in leucocytes of twin 2 belonged to twin 1, indicating a net

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flow of blood from the latter to the former. *Discussion:* In recent years the obstetric mantra that monochorionicity guarantees monozygosity has been disproven, albeit with exceptional rarity. Almost all cases of MCDZ twins have involved treatment with ART, often with microinjection techniques and, in two cases, by spontaneous fertilisation following ovarian stimulation. There are only three previous reports of spontaneous MCDZ twins and in only one of these reports is there clear histological and genetic evidence confirming the diagnosis. We report the second case in which there is absolute proof of spontaneous MCDZ twinning. Blood chimerism is a feature of MCDZ twins. Despite having cells of cross reacting blood types the two genetically different blood lines in DZ chimeric twins do not seem to recognise each other as foreign. Therefore, these twins are likely to be a good immunological match for each other despite their dizygosity. *Conclusion:* This is the second case reported of histologically and genetically proven spontaneously conceived MCDZ twins. For these boys the importance is their potentially excellent immunological tolerance for each other. For obstetricians the importance is the recognition that, in exceptional circumstances, monochorionic twins can be dizygotic and this should be considered when twins are phenotypically distinct.

MULTIPLE PREGNANCIES: THE REDUCED IMPACT OF IN VITRO FERTILIZATION IN AUSTRALIA

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Introduction: Treatment with assisted reproductive technologies (ART), in particular in vitro fertilisation, is widely attributed as being the major driving force behind the increased numbers of multiple births worldwide. This study investigated the impact of ART on the overall burden of multiple deliveries in Australia, the United Kingdom and the United States, and examined the impact of the introduction of policies of single embryo transfer (SET) to reduce the overall rate of multiple births. *Materials and Methods:* Birth data was analysed from the National Perinatal Data Collection Service in Australia and Australian and New Zealand Assisted Reproduction Database. Comparative data was obtained from the Office of National Statistics for England and Wales and from the National Vital Statistics System, National Center for Health Statistics for the United States. *Results:* The twin delivery rate in Australia peaked at 16.5 per 1000 deliveries in 2002 and had fallen to 15.5 per 1000 deliveries by 2008. The high order multiple delivery rate peaked at 43.1 per 100,000 deliveries in 1997 and had fallen to 20.9 per 100,000 deliveries by 2008. There was a steady fall in the twin delivery rate for ART from 203.7 per 1000 deliveries in 2002 to 96.4 per 1000 deliveries in 2008 ($p<0.01$ for linear trend). In contrast, the rate of non-ART twin deliveries was constant over this time. In 2008, 16.9% of all twin deliveries in Australia were attributed to ART compared to 24.4% in 2002. During this time the proportion of SET rose from 30.0% to 76.0% in women under 35 years of age, from 28.7% to 67.5% in women aged 35-39, and from 29.8% to 54.1% in women aged 40 years and over. *Discussion:* In recent years SET has been strongly encouraged to reduce the burden of multiple births. Internationally, policies in relation to SET vary in regard to the degree of government regulation. The Human Fertilisation and Embryology Authority (HFEA) which regulates IVF in the United Kingdom now strongly promotes SET. The proportion of SET cycles rose from 4.8% in 2008 to 13.8% in 2010. In parallel, the proportion of multiple births following ART fell from 24.7% in 2008 to 21.5% in 2009. In the United States there is no state regulation of the number of embryos transferred. The proportion of SET amongst fresh non-donor cycles increased from 6% in 1999 to 12% in 2008. The multiple live birth rate following fresh non-donor cycles decreased from 37% to 32% during the same period. The Fertility Society of Australia (FSA) continually modifies, a voluntary Code of Practice (COP). The guidelines with regard to multiple births have been regularly reviewed so as to reduce the incidence of multiple births following ART which now accounts for approximately 17% of all twin births from 4% of all conceptions in Australia. Over 72% of the decline in twin deliveries from 2002 until 2008 was a consequence of a policy of SET following the introduction of guidelines by the FSA COP. This study demonstrates that improved outcomes can be achieved with a policy of self-regulation.

POSTTRAUMATIC STRESS DISORDER, MAJOR DEPRESSION AND INCIDENCE OF CORONARY HEART DISEASE

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Background: Posttraumatic stress disorder (PTSD) is a psychiatric condition characterized by a persistent maladaptive reaction resulting from exposure to severe psychological stress. It has long been hypothesized that PTSD increases the risk of coronary heart disease (CHD) but empirical evidence is limited. Additionally, few studies have accounted for the confounding effect of major depression, which often concur with PTSD and is an established CHD risk factor. We sought to determine the relative contributions of PTSD and major depression to CHD risk in a prospective study of twins. Methods. Monozygotic and dizygotic middle-aged male twins included in the study were members of the Vietnam Era Twin Registry. Lifetime diagnoses of PTSD and major depression were assessed at baseline in 1992 with the Diagnostic Interview Schedule. Among twin pairs free of CHD at baseline, we selected three groups: 1) pairs dis-

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cordant for PTSD, 2) pairs discordant for major depression, 3) pairs without a history of PTSD or major depression. These underwent a follow-up clinic visit and [N13]PET myocardial perfusion imaging between 2002-2010 (median follow-up 15 yr). Outcomes included CHD (previous myocardial infarction, unstable angina, and coronary revascularization) and stress total severity score (STSS) quantifying myocardial perfusion abnormalities. GEE and mixed models were used to account for pair cluster and to separate between- and within-pair effects. Results. A total of 540 twins (270 pairs) were included, with mean age at baseline of 41 yr (range 34-48). Of these, 110 pairs were discordant for a lifetime diagnosis of PTSD and 109 for major depression. The incidence of CHD was higher in twins with PTSD only (23%) or both PTSD and major depression (21%), intermediate for those with major depression only (13%) and lowest for those with neither (8%). When PTSD and major depression were included in the same model adjusting for sociodemographic and behavioral factors, the relative risk for PTSD was 1.9 ($p = 0.01$), and for major depression it was 1.3 ($p = 0.24$). Within twin pair results were similar with RRs of 1.8 ($p = 0.03$) for PTSD and 1.2 ($p = 0.52$) for major depression. PTSD, but not major depression, was also associated with higher STSS, denoting more perfusion defects. The mean STSS was almost doubled in twins with PTSD (68.9) than in their brothers without PTSD (38.8), $p = 0.01$. The difference persisted after adjusting for sociodemographic and behavioral factors and major depression. Conclusions. Among Vietnam era veterans, PTSD is a significant risk factor for CHD and a stronger predictor of CHD than major depression. Comorbidity of PTSD and major depression does not increase the risk associated with PTSD alone.

THE COMBINATION OF SEXES IN TWIN PAIRS AND THE WELL-BEING OF THE FAMILY

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The study focused on multiple birth families, which were clients in Child Welfare Services in City of Helsinki. The data consists of 244 individual twins or triplets, of which 208 children were under 18 years old. They were picked up from the client register. The client register consists of families that became clients after that somebody reported his or her worry about the well-being of children. Those reasons can be for example behavioral problems, drinking problems, parenting problems, child abuse etc. It was found out, that the combination of sexes in twin pair (same-sex pair or opposite-sex pair) has something to do with the well-being of the family. Tiredness of the parents was the most common reason for inquest after somebody s report. Parents were most tired in the families with 1-6 year old multiples. Tiredness was more common in opposite-sex twin pair families compared to male-male twin pair families or female-female twin pair families. In opposite-sex twin families the tiredness was the most common reason for inquest in all age-groups. The study suggests that it is more demanding to bring up opposite-sex twin pair as same-sex twin pair. That is because opposite-sex twin pair parents can t use collective upbringing methods as easily as same-sex twin parents. The study is one part of Project 'Good beginning to parenting multiples' and it is organized by Finnish Multiple Births Association. The study was funded by non-profit organizations: Finland's Slot Machine Association (RAY) and Alli Paasikivi Foundation.

EXPLORING GENE BY AGE INTERACTIONS IN EXTENDED PEDIGREE MODELS

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The impact of genes and the environment on behavioral phenotypes change as people age (Kendler, Gardner and Lichtenstein, 2008). Accordingly, the relative contributions to the genetic and environmental variance of a phenotype would also be expected to change as people age insinuating a gene by age interaction. While gene by age interactions have been identified in a number of studies using the Classic Twin Design, the use of extended pedigrees has been underemployed. Extended pedigree models are particularly effective tools for illuminating more specific pathways of genetic and environmental transmission across generations, however, the inclusion of additional relatives - specifically parents - increases the probability of attributing a significant amount of variance to non-additive genetic variance which is more likely the result of gene by age interactions. Specifically, because the correlations between parents and children are generally lower than what would be expected given biometric theories of genetic transmission the typical explanation of these discrepancies is often attributed to non-additive genetic variance, such as dominance or epistasis. If gene by age interactions are present in the data but ignored in the analysis, the pattern of covariance between relatives would mimic this type of non-additive covariance. Moreover, this problem is independent of the linear effect of age on the phenotype. Accordingly, in this paper we explore various model phenotypes that vary in genetic and environmental modes of transmission to gain traction on the general importance of gene by age interactions within a large pedigree study. In some cases, the gene by age interactions would not be expected to be significant while in others they would be. The limiting conditions of this method are also discussed.

A BEHAVIORAL GENETIC STUDY OF HUMOR STYLES IN AN AUSTRALIAN TWIN SAMPLE

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The present study investigated the extent to which individual differences in humor styles are attributable to genetic and/or environmental factors. Participants were

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934 same-sex pairs of adult twins from the Australian Twin Registry (546 MZ pairs, 388 DZ pairs) who completed the Humor Styles Questionnaire (HSQ). The HSQ measures four distinct styles of humor positive (affiliative, self-enhancing), and two negative (aggressive, self-defeating). Affiliative humor refers to the tendency to tell jokes and to engage in witty banter in order to facilitate relationships. Self-enhancing humor involves the use of humor as a means of coping with stress. Aggressive humor entails the use of critical or disparaging jokes in an effort to manipulate others. Lastly, self-defeating humor is characterized by the use of jokes made at one own expense in an effort to build bonds with others. Results revealed that additive genetic and non-shared environmental factors accounted for the variance in all four humor styles, thus replicating results we previously obtained in a sample of twins from the UK but not from a United States sample. These results contribute to a cross-cultural understanding of humor, and elaborate on previous results showing that the etiology of humor styles differs across cultural groups.

ALEXITHYMIA AND TRAIT EMOTIONAL INTELLIGENCE: A BEHAVIORAL GENETIC INVESTIGATION

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In the present study, we investigated alexithymia in relation to trait emotional intelligence using univariate and bivariate behavioral genetic (BG) methodology. A total of 2000 twin pairs from the United Kingdom took part in the study. Participants completed the Toronto Alexithymia Scale (TAS-20), measuring participants self-reported deficiency in processing, understanding, and describing emotions. They had also previously filled out the Trait Emotional Intelligence Questionnaire (TEIQue), which assesses individual differences in participant self-perceived emotion-related abilities. At the univariate level, results revealed that individual differences in alexithymia and in trait emotional intelligence were primarily attributable to genetic and non-shared environmental factors. As expected, alexithymia and emotional intelligence were negatively correlated at the phenotypic level, and bivariate BG analyses revealed that these correlations were primarily attributable to common genetic factors and secondarily to common non-shared environmental factors. These results replicate those that we obtained previously in a much smaller North American sample.

MONOAMNIOTIC TWINS DISCORDANT FOR BODY STALK ANOMALY

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Introduction: Body stalk anomaly is a rare development malformation with a prevalence of 1 in 7500 pregnancies in the first trimester. Numerous hypotheses have been proposed to explain the pathogenesis of this condition. The presence of this anomaly in monozygotic twins is extremely unusual. As far as our concern, only five cases of monozygotic twins discordant for this malformations were reported; three in monoamniotic pregnancies. Our case represents the fourth reported monoamniotic pregnancy discordant for body stalk anomaly with diagnosis made by ultrasound and the third diagnosed in the first trimester. Case report: A 37-year-old primigravid woman with 11 weeks of gestation was referred to our center for an abnormal fetus in a monoamniotic twin pregnancy. A detailed sonographic examination revealed a monoamniotic twin pregnancy with a normal fetus (fetus A) and a severely malformed (fetus B). Fetus A had a normal morphology and nuchal translucency thickness for 11 weeks. The venous ductus was abnormal. Fetus B had a large anterior abdominal wall defect, anomaly of the spine, and no evidence of lower extremities. It seems to be attached to the placenta at the abdominal level. Nuchal translucency thickness was above the 95th percentile of the normal range. The diagnosis of body stalk anomaly was made. Parents were counseled as to the condition of one of the fetus and they chose to undergo a termination of pregnancy with prostaglandin induction. The fetal autopsy shows that fetus A had a cleft palate without other alterations. Fetus B had a eventration of thoracic and abdominal organs with no abdominal cavity and a deformed thoracic one; absence of one lower limb and the other deformed and attached to the dorsal region. A single placenta with a single membrane was identified. Two umbilical cords with two arteries and one vessel were identified; the one that connect fetus B to the placenta was twice fold shorter and attached to the internal surface of the placenta. The diagnosis of body stalk anomaly was confirmed. No karyotype examination was performed. *Conclusion:* Body stalk anomaly is a rare and lethal condition in both single and twin pregnancy. The ultrasound assessment of twin pregnancies at 11-14 weeks can identify cases with this anomaly.

DIFFERENTIAL DIAGNOSIS OF INTRATHORACIC TUMOR COMPLICATING A TWIN PREGNANCY

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Fetal intrathoracic tumors are a rare condition. When they are present lung or chest wall origin must be determing. Diagnosis, prognosis and treatment are different in each case. Ultrasonography and fetal MRI can help locate, identify and characterize the type of tumor. Chest wall mesenchymal hamartomas are extremely rare benign tumors that usualy occur during childhood, and they are an exceptional finding during the prenatal period. The clinical presentation varies from asymptomatic to severe respiratory failure requiring intubation. Definitive diagnosis is histological, using imaging techniques to stablish prenatal suspicion and provide the best treatment after delivery. We present a case report of a twin pregnancy with one fetuses diagnosed of an unilateral intrathoracic tumor of rapid growth. Prenatal ultrasound

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suspected cystic adenomatoid malformation. Fetal MRI reported the possibility of pulmonary blastoma or brolquialveolar carcinoma, which has a bad prognosis. Finally the pathology analysis confirmed the presence of a chest wall mesechymal hamartoma. We attached fetal MRI, prenatal ultrasonography, neonatal CT scan.

COTININE LEVELS IN SMOKERS AND NON-SMOKERS AND THEIR RISK FOR DEPRESSION AND ADHD

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Both active and passive smoking have been associated with an array of adverse effects on health. The most commonly used objective method of ascertaining nicotine exposure is measuring the biomarker cotinine in blood or urine. Cotinine is a metabolite of nicotine. The level of cotinine in the blood is proportional to the amount of exposure to tobacco smoke, so it is a valuable indicator of tobacco smoke exposure, including secondary (passive) smoke. There is a link between tobacco consumption and mood disorders. It has been suggested that some individuals smoke to manage their mood, however, there is also some evidence indicating that tobacco consumption can induce negative mood. The Netherlands Twin Register (NTR) has collected biological samples (mRNA, DNA, serum, plasma, urine) in their participants. In the present project, we measured cotinine in serum of 2143 smokers and 2141 non-smokers. We will compare the risk for depression in smokers, non-smokers exposed to cigarette smoke and non-smokers who were not exposed to cigarette smoke. We hypothesize that second-hand smoke exposure is associated with depressive symptoms and will test causality by comparing depression score in twin pairs concordant and discordant for smoking.

PLACENTAL INDEX IN TWIN PREGNANCIES CONCEIVED WITH ASSISTED REPRODUCTIVE TECHNOLOGY

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Objective: It is known that pregnancies conceived by assisted reproductive technology (ART) are at increased risk of adverse maternal and neonatal outcomes. Previous studies have suggested an increased placental index and placental weight to be associated with adverse pregnancy outcomes. Recently was clearly demonstrated an association of ART singleton pregnancies with increased placental index. Our aim was to study placental index influence on outcome and its association with ART in twin pregnancies. *Materials and Methods:* We retrospectively analyzed 868 twin pregnancies, who were delivered between 2001 and 2010 in a third level Clinic of North-East Italy. We took into consideration pregnancy outcome, placental index and ART. Data was analyzed by R(version 2.14.1), considering significant $p<0.05$. *Results:* We found in twin pregnancies conceived with ART a significant lower placental and neonatal weight than spontaneously conceived twin pregnancies. Placental index was slightly lower in ART pregnancies ($p = 0.079$). Moreover, in multivariate logistic regression models high placental index, low gestational age at delivery and Sub-Saharan origin of women were independent risk factors for low Apgar score (<6) at delivery. Furthermore, low neonatal weight MoMs and low gestational age at delivery were independent risk factors in multivariate model for neonatal intensive unit care hospitalization. Finally, the following were independent risk factors in multivariate model for delivery before 28 gestational weeks: high placental index, high neonatal weight MoMs, ART conception, neonatal male gender, and Sub-Saharan ethnic origin. *Conclusions:* We found also in twins high placental index to be associated with adverse maternal and neonatal outcome but in twin pregnancies conceived with ART placental index seems to be lower than in controls. Our results probably could be related to a different placental behaveour in twin and singleton pregnancies conceived with ART.

INTRAUTERINE GROWTH RESTRICTED TWIN FETUSES WITH DOPPLER VELOCIMETRY ALTERATIONS SHOW INCREASED ABDOMINAL AORTA INTIMA MEDIA THICKNESS INDEPENDENTLY TO GENDER AND CHORIONICITY

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Objective: The aim of this study was to assess aorta intima media thickness (aIMT) in intrauterine growth restriction (IUGR) twin fetuses with Doppler velocimetry alterations considering gender and chorionicity. *Materials and Methods:* A prospective study of 78 twin pregnancies was performed from January 2009 to July 2011. Fetuses were classified into three groups: IUGR fetuses with an estimated fetal weight (EFW) below the 10th percentile and umbilical artery pulsatility index (PI) Doppler velocimetry > 2 standard deviations (Group A), fetuses with EFW below the 10th percentile and normal Doppler velocimetry (Group B) and fetuses with an EFW appropriate for gestational age (Group C). The aortic diameter and aIMT values were determined at a median gestational age of 32 weeks. The comparison was made among groups and between each twin with its co-twin also considering gender and chorionicity. There was no differences in aIMT between dichorionic diamniotic and monochorionic diamniotic twins, and between female and male twin ones. *Results:* Seventy-eight women with 156 twins were eligible for this study. There were 110 dichorionoc diamniotic and 46 monochorionic diamniotic twins. The

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median gestational age at delivery did not differ in the three groups (median 35 weeks, $p = 0.50$). Twenty-five fetuses were classified as Group A, 36 Group B, and 95 as C. Median aIMT was 0.9 mm (range 0.8-1.1) in Group A, 0.7 mm (range 0.6-0.8) in Group B ($p<0.0001$), and 0.6 mm (range 0.5-0.7) in Group C (P: . There was a statistically significant difference between aIMT of the twin and its cotwin in Group A and B ($p<0.0001$). Gender as well chorionicity did not correlate with aIMT. Birth weight was inversely correlated with aIMT (r = -0.22, $p = 0.006$). There was a significant correlation between aIMT and Doppler alterations in the fetuses in Group A ($p = 0.05$). *Conclusions:* The present study highlights that IUGR fetuses with Doppler abnormalities showed higher values of aIMT compared to IUGR with normal umbilical artery velocimetry and AGA twins. Gender and chorionicity did not influence aIMT among the groups.

RATES OF MATERNAL AND PERINATAL MORTALITY AND SEVERE MORBIDITY IN MULTIPLE VS SINGLETON PREGNANCIES

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Multiple gestations are considered high-risk pregnancies due to their association significant maternal and perinatal complications. Although the rate of multiple pregnancies in developing countries is generally lower, the feto-maternal risks are higher due to a scarcity of human and maternal resources. Limited antenatal care, sub-standard or lack of skilled attendance during labour, delivery and in the postpartum and neonatal periods can result in adverse outcomes for both mother and neonate. We used the WHO Global Survey on Maternal and Perinatal Health (2004-2008) dataset to determine the rates of multiple pregnancies per region and country and the rate of maternal and perinatal mortality and severe morbidity in twin versus singleton pregnancies. The WHO Global Survey is a cross-sectional survey of deliveries in randomly-selected facilities across 23 developing countries in Africa, Latin America and Asia. Individual data on over 280,000 women was collected on a range of demographic, medical, obstetric, delivery and postnatal variables. Institutional-level data was also collected on the capacity and services available at each facility. Of 282,665 births captured in the WHO Global Survey, 276,189 (97.6%) were singletons, 6,476 (2.3%) were twins and 207 (0.1%) were higher-order multiple births, with the highest rates of twin births in Nigeria (4.2%), DR Congo (3.8%) and Niger (3.6%). 0.4% of births in Nigeria were higher-order multiple births. We are also conducting multivariate analysis to assess the contribution of neonatal, maternal and facility-level variables to the risk of severe adverse neonatal outcomes (stillbirth, early neonatal death and neonatal "near miss") and the risk of severe adverse maternal outcomes (maternal death, admission to ICU, blood transfusion or hysterectomy) in twin pregnancies in developing countries.

LEISURE-TIME PHYSICAL ACTIVITY, WEIGHT GAIN AND HEALTH -A PROSPECTIVE FOLLOW-UP

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The aim of this study was to find out whether leisure-time physical activity (LTPA), adjusted for genetic factors and childhood environment, protects against mortality, type 2 diabetes and other chronic diseases and against increases in weight and waist circumference. All participants were selected from the large Finnish Twin Cohort, which included over 12 069 twin pairs in 1975. To investigate the occurrence of type 2 diabetes (T2D), 20487 individuals were selected who were free of diabetes and had data on LTPA and BMI in 1975. These individuals were divided into quintiles according to their LTPA MET index. T2D risk was assessed between 1.1.1976 and 31.12.2004. For the long-term discordance analyses, 146 from 5663 healthy adult twin pairs were identified as discordant for both intensity and volume of LTPA in 1975 and 1981. Mortality analyses were carried out between 1.1.1983 and 31.12.2004. Among the 146 pairs, 95 sets of twin pairs (76 DZ, 19 MZ) were alive and participated in a follow-up telephone interview in 2005 (mean age 58.5y, range 48-78). The interview included detailed questions on the continuation of LTPA, self-measured weight and waist circumference and occurrence of chronic disease. Paired tests (McNemara's test, t-test, conditional logistic regression, Cox proportional hazard model) were used in the statistical analyses. The paired type 2 diabetes analyses among the whole 1975 cohort showed that the BMI-adjusted hazard ratio for the active (quintiles II-V) compared to sedentary (quintile I) co-twins at follow-up was 0.54 (95% CI 0.37-0.78).[1] Among the 146 LTPA discordant pairs, 24 co-twins (16 inactive and 8 active) had died by the end of 2004. The active co-twins had a reduced risk of all-cause mortality as social class-adjusted HR was 0.39 (95 % CI 0.18 - 0.85). This was not found among the small number of MZ pairs. Among the 95 interviewed pairs, the risk of type 2 diabetes or glucose intolerance (OR = 0.09, $p = 0.022$) and incident elevated blood pressure (OR = 0.46, $p = 0.039$) was lower among the active co-twins.[2] The active co-twins were more satisfied with their life at follow-up ($p = 0.047$) and had less psychiatric medication use (OR = 0.22, $p = 0.054$). In contrast, the active co-twins showed a tendency towards more sports-related injuries (OR = 1.9, $p = 0.051$). Within the subgroup of 42 pairs discordant for LTPA over 30 years, mean weight gain from 1975 through 2005 was 5.4 kg (95% CI 2.0-8.9, $p = 0.003$) less and waist circumference 8.4 cm smaller (95% CI 4.0-12.7 cm, $p<0.001$) at follow-up among the active compared to inactive co-twins. Physical activity helps in maintaining overall health by decreasing the rate of weight gain, lowering waist circumference and reducing the risk for clinical T2D.

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However, genetic factors may play a role in explaining some of the associations between mortality, disease occurrence and physical activity, as some of the findings were clearer among the dizygotic than monozygotic twin pairs discordant for LTPA. Some data previously published in [1]Waller et al. (2010) Diabetologia, [2]Waller et al. (2010) Med Sci Sport & Exercise.

REDUCING CANADA'S REPRODUCTIVE TECHNOLOGY-RELATED MULTIPLE BIRTHS: MULTIPLE BIRTHS CANADA'S (MBC) ROLE

K. Weatherall

International Council of Multiple Birth Organizations, and Multiple Births Canada

Canada has one of the highest rates of multiple births due to the use of assisted human reproduction technologies. Multiple Births Canada (MBC) (a national nonprofit organization supporting families with multiple-birth children) understands the risks and challenges that conceiving and raising multiple-birth children can bring to a family. At the same time, we understand and appreciate the desire of an infertile patient to have a child of their own. In partnership with Assisted Human Reproduction Canada (AHRC), Canadian fertility organizations, medical professionals and other patient groups, MBC has been assisting in the development and sharing of educational products to ensure that all fertility patients are educated about the risks associated with a multiple pregnancy. While the medical community works to implement policies and guidelines with regards to the number of embryos to transfer, and the government of Canada provincially and nationally addresses the funding of fertility treatments, MBC has chosen to use education as a means to reduce the incidence of multiple births. MBC's mission is to improve the quality of life for multiple-birth individuals and their families in Canada, so we cannot ignore the fact that many fertility patients are making uninformed decisions about their fertility options, and risking a multiple pregnancy. A healthy singleton baby is definitely a better outcome than some of the realities that our members have experienced. During this session Kimberley Weatherall will share with International Council of Multiple Birth Organization (ICOMBO) members how the relationship was formed, the importance of working with this community to represent the needs of multiple-birth families, and highlight some of the educational and other resources that have resulted from this partnership.

TWIN-REVERSED ARTERIAL PERFUSION SYNDROME IN MONOCHORIONIC MONOAMNIOTIC TWINS SUCCESSFULLY TREATED BY MICROINVASIVE INTERSTITIAL LASER COAGULATION

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Here we report a case of monochorionic monoamniotic (MCMA) twin pregnancy diagnosed at 11 wks with twin-reversed arterial perfusion (TRAP) syndrome. The mother was 30 y.o. primidgavida who conceived spontaneously. After the diagnosis serial weekly scans were performed. Gradually the normal twin had developed signs of hemodynamic compromise. Tricuspid regurgitation and reversed a-wave in ductus venosus were observed. The acardiac twin showed marked subcutaneous oedema. While at 11+1 wks both placental umbilical cord insertions were clearly seen and both cords were loose, shortly before the procedure marked umbilical cords entanglement was observed, resulting in decreased range of movements in both pump twin and oedematous acardiac. At 16+1 wks we performed diode laser coagulation of pelvic vessels in the acardiac twin under ultrasound guidance. The subarachnoid anaesthesia with iv sedation was administered. We used 17G needle and 0.6 mm laser fibre. The needle was introduced into the pelvic region of the acardiac twin through the abdominal wall. The laser fibre was introduced into the needle until seen protruding from the tip of the needle for approx. 5mm. The power output was set at coagulation at 15W at the beginning of the procedure and then increased to 20W. A series of laser bursts lasting 5-10 seconds were fired, until cessation of blood flow in acardiac's pelvic vessels and umbilical cord was confirmed using color Doppler. The laser coagulation of the acardiac's pelvic tissue was monitored on grey scale ultrasound as color Doppler produced vast amount of artefacts. A single dose of iv antibiotic was given after the procedure. The postoperative course was uneventful. On the next day an ultrasound scan was performed confirming viability of the normal twin. No blood flow in the acardiac twin was detected. The patient was discharged 48 hours after the procedure. The pregnancy is still ongoing. The interstitial laser coagulation of acardiac twin is less invasive than fetoscopic umbilical cord coagulation as the outer diameter of the 17G needle is much smaller. This technique also allows avoiding buying expensive embrioscopy set. Cord occlusion in the presence of short, thin or hydropic cord may be associated with substantial technical difficulties. A meticulous comparison of these methods would require a randomised study, but at 16wks of MCDA twin pregnancy with marked cord entanglement, interstitial laser coagulation seems to be the method of choice.

HEALTH AND BEHAVIOR IN TWINS DISCORDANT FOR BEING MARRIED AND HAVING CHILDREN

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Studies consistently show that married men and women are in better health than people who remain single or are divorced. Twin comparisons can inform us about the mechanisms that underlie this association. A twin comparison in Danish twins discordant for marital status by Osler et al. (2008) showed a role for selection effects related to genetic and environmental factors, as well as

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evidence for causal effects of marriage dissolution. The present study aims to replicate these findings in a sample of Dutch twins. In addition, the role of having children is examined in married individuals. Data are available on subjective health, smoking, alcohol use, and personality in 3527 same sex twins (69% monozygotic) from the Netherlands Twin Register. Using Mplus and the option Complex to correct for the inclusion of related individuals, we first investigate the association between marriage and having children with the health, behavior and personality indices. Age and sex effects and interactions are examined. Next, we determine whether twins discordant for marriage and having children differ on these variables. Our first analyses show that single men and women, in particularly when divorced, smoke more often and drink more alcohol than married men and women. Single men and women who never married score higher on neuroticism and lower on extraversion than married individuals. Having children is also related to more health behavior, in particular in women. Our discordant twin pair comparisons will show whether these differences are the results of the beneficial effects of marriage or should be contributed to selection effects.

THE ROLE OF GENES IN AUTONOMIC NERVOUS SYSTEM ACTIVITY

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There are large individual differences in the activity of the autonomic nervous system (ANS) that play a key role in the risk for cardiovascular disease. To determine the degree to which genetic factors influence variation in autonomic nervous system activity, we conducted a literature review. We identified 15 heritability studies on indices of parasympathetic activity and 8 on sympathetic activity. Twin studies demonstrate significant genetic contributions to resting levels of heart rate variability in the respiratory frequency range (RSA), the measure of choice to index parasympathetic activity. Heritability estimates for RSA range from 25% to 71%. For preejection period (PEP), reflecting sympathetic activation, heritability estimates range from 48% to 74%. The genetic variance in these traits seems to further increase under conditions of psychological stress. Identifying the genetic variants that influence parasympathetic and sympathetic activity may increase our understanding of the role of the ANS in cardiovascular disease.

SPINE CURVATURE IS HERITABLE AND ASSOCIATED WITH DISC DEGENERATION

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Background: Degenerative spondylosis (DS) is common in middle age and elderly and, if severe, may lead to respiratory compromise and abdominal content crowding. Lumbar disc degeneration (LDD) is known to be a cause of back pain: a considerable cause of work absenteeism and a major social problem in industrialised societies. LDD is heritable but its precise relationship with spine curvature is unclear. We performed an MR and plain radiograph study on well characterised twins from the TwinsUK register (www.twinsuk.ac.uk) known to be representative of the general population. *Methods:* T2 weighted MR scans and long spine standing radiographs were obtained at the same morning visit on twin pairs. Midline sagittal MR images were coded for LDD on a 4-point scale over 4 subphenotypes: disc signal intensity, disc height loss, anterior osteophytes and disc bulge and summed over the 5 lumbar discs to give a summary LDD score. On the plain films, points were applied to the 4 vertebral body corners using SpineviewTM software which then calculated the angles of curvature of the whole spine. Subjects having vertebral fracture were excluded. A classical twin study was performed to determine the relative contributions of genetic and environmental factors to spine curvature. Multivariate regression analysis was used to determine the association between spine curves, LDD and confounders (age, body mass index). *Results:* Complete phenotype data were available on 246 female twins, 110 monozygotic (MZ) and 136 dizygotic (DZ) twins. Mean age was 64.3 years (range 40 &179.3); age was associated with increasing lumbar lordosis ($p = 0.02$). The AE model (comprising additive genetic and unique environmental factors) was the most suitable model for both lumbar lordosis and thoracic kyphosis (as determined using the Akaike information criterion). Heritability estimates = 59% (42-71%) for lumbar lordosis; and 61% (46-74%) for thoracic kyphosis. After adjusting for age and BMI, lumbar lordosis was significantly associated with a number of features of LDD including disc signal intensity and osteophytes. *Conclusion:* Lumbar lordosis and thoracic kyphosis of the spine have considerable heritable component. Furthermore, lumbar lordosis is significantly associated with many of the features of LDD something which may be clinically apparent but has not, as far as we know, been formally studied in a population sample. Longitudinal work will be required to confirm the direction of effect of this association. That the spine curves themselves are heritable suggests that a search for individual gene variants influencing spine curve would be a reasonable next step. Identifying gene variants for curve would inform the biology underlying the normal degenerative process and might throw light on the pathology of other scoliotic conditions.

HEARING ABILITY WITH AGE- A TWIN STUDY

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Age-related hearing impairment (ARHI) affects 25-40% of individuals over the age of 65. Despite the high prevalence

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of this complex trait, ARHI is still poorly understood. We hypothesized that variance in hearing ability with age is largely determined by genetic and epigenetic factors. We collected audiologic and genetic data on female twins of Northern European ancestry and determined the heritability of hearing ability with age. A web-based speech-to-noise ratio (SNR) hearing test was compared with pure-tone thresholds to see if we could determine accurately hearing ability on people at home and the genetic contribution to each trait compared. Volunteers were recruited from the TwinsUK cohort. Hearing ability was determined using pure-tone audiometry and a web-based hearing test. Using structural equation modeling based on the classical twin model the heritability of ARHI, as measured by the different phenotypes, was estimated and shared variance between the web-based SNR test and pure-tone audiometry determined using bivariate modeling. Pure-tone audiometric data was collected on 1033 older females (age: 41-86). 1970 twin volunteers (males and females, age: 18-85) participated in the SNR. The SNR test showed a sensitivity and specificity of 89% and 80%, respectively, in comparison with pure-tone audiogram data. Univariate heritability estimates ranged from 0.70 (95% CI: 0.63-0.76) for (PC1-PC2) to 0.45 (95% CI: 0.18-0.63) for SNR. The genetic correlation of PC1-PC2 and SNR was -0.67 showing that the 2 traits share variances attributed to additive genetic factors. ARHI showed considerable heritability in our sample. We have shown that the SNR test provides a useful surrogate marker of ARHI. This will enable a much larger sample to be collected at a fraction of the cost, facilitating future genetic association studies. Monozygotic twins discordant for hearing ability with age could be used to understand the epigenetic basis of hearing.

GENETICS OF METABOLIC SYNDROME PERSISTENCE

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Metabolic syndrome (MetS) is a cluster of insulin resistance and its complications such as and hypertension. MetS and its components are not fixed, but do change across time. Although an association between MetS and cardiovascular disease is well-established, the factors that result in fluctuations in MetS or effects of persistence in MetS are not well known. The aim of this study is to explore genetic and environmental influences on the persistence of having MetS. *Methods:* The study subjects were participants in the Healthy Twin Study who agreed to informed consent and took clinical examinations including body measurements and blood sample tests. A total of 1,651 participants were followed for their MetS status. Average duration between two check-ups was 2.60 years. MetS was defined by the criteria of International diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP). We also categorize them into four groups according to their changes in MetS status; normal to normal (NN), normal to MetS (NM), MetS to normal (MN) and MetS to MetS (MM). Heritability of each status change in MetS, NM, MN, and MM were relatively analyzed compared to heritability of NN. To estimate heritability of status change in MetS, we fitted a variance component model to partition the total phenotypic variance of MetS changes into additive genetic (da2), shared environmental component (dc2), and unique environmental components (de2). Shared environments (dc2) were estimated in three levels; household effects, sibling effects, and generation-specific effects within household. The Sequential Oligogenic Linkage Analysis Routines program (SOLAR, ver. 4.2.7; Southwest Foundation for Biomedical Research, San Antonio, TX) was used for estimating each component *Results:* Prevalence of metabolic syndrome increased at the second visit (20.29% as IDF and 17.69% as NCEP-ATP) than that of the baseline (18.41% as IDF and 17.14% as NCEP-ATP?). We identified that there is apparently genetic influences on not only consistent status, but also change in status of having MetS as IDF and NCEP ATP definition both. And the trend as IDF definition was coherent also as NCEP ATP. First, according to the definition of IDF, genetic influence on change of normal status to metabolic syndrome (NM) comparing to that of consistent normal status (NN) was not significant at every sharing groups. Change of metabolic syndrome to normal status (MN) comparing to that of consistent normal status was 42% of heritability within family groups, generation groups and monozygotic twins groups and 37% within siblings. Heritability of MM comparing to that of NN was 49% within sibling groups and within monozygotic twins, 46% within generation groups and no heritability within family groups. Second, genetic influences on NCEP ATP-defined Mets status were as below. No heritability on the NM change was significant in any sharing groups. Genetic influence on MN change comparing to that of NN status was 48 % in siblings and 54% in all other sharing groups. Heritability on MM was 42% in family sharing groups and 62% in other groups.

ASSOCIATION BETWEEN PERSONALITY TRAITS AND OBESITY INDICES: FAMILY AND CO-TWIN ANALYSIS

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Purpose: Personality traits of an individual affect one's attitude towards life and one's life style factors determin-

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ing health status. Since emotional disruption, such as depression and mood disorders, and unhealthy life habits are established risk factors of obesity, investigating the association between personality, life style, and obesity will lead to development of efficient intervention or preventive measure for obesity, according to their personality profiles. To this end, we attempted to explore the associations between Temperament and Character Inventory (TCI)'s seven dimensions and obesity indices: body mass index (BMI), waist circumference, waist hip ratio (WHR), trunk and total body fat percent measured by Dual-energy X-ray absorptiometry (DXA) in Korean twins and their families Additionally, we aim to discriminate environmental and genetic effect of TCI on obesity using pair-wise analysis of each and combined monozygotic twins (MZ), dizygotic twins (DZ) and sibling pairs adjusted for age and sex. We expected that estimating non-genetic association between personality traits and obesity will specifically show potential target chains interconnecting personality, life style and obesity. *Methods:* A total of 3079 individuals (1217 men, 661 families) of the Healthy Twin Study in Korea were involved in this study. This population includes 531 MZ pairs, 120 DZ pairs, and 1172 sibling pairs. Association between TCI and obesity was analyzed using adjusting for age, sex, smoking history and alcohol consumption. A random effect model (REM) was applied to adjust familial correlations. For co-twin and sib-pair analyses pair-wise regression models using pairwise-difference values were used. *Results:* In conventional regression analyses (REM), among seven domains of TCI, novelty seeking had the strongest association with BMI. Decreased persistence (ß = -0.0003), self-directedness (ß = -0.00024), cooperativeness (ß = -0.00028), and self-transcendence (ß = -0.00026) had association with WHR. In pair-wise regression model, an association between persistence and WHR /trunk fat percent were further dissected; ßW in MZ data was higher than ßW in DZ-sibling data and pooled data, indicating that persistence is associated obesity, and in this association, there are more environmental effects than genetic effect. *Conclusions:* The results all confirm the previous findings that self-transcendence resulted with negative association with WHR. By comparing the ßW of different datasets, we could conclude that there is high environmental effect on the association, and that there is more environmental effect on the TCI associated obesity than genetic effect, suggesting an individual's personality profiles can be integrated into personalized intervention of obesity.

WEIGHT GROWTH OF TRIPLETS FROM INFANCY TO TWELVE YEARS OF AGE

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Introduction: Triplets have been found to be behind singletons in their physical development even in mid-childhood in spite of the rapid catch-up growth during the first year of life. However, there have been no reports of weight growth of triplets after six years of age. The purpose of this study was to analyze the characteristics of weight growth in Japanese triplets from birth until 12 years of age. *Methods:* The participants of this study were recruited from the Osaka City University Higher Order Multiple Births Registry, which consisted of 578 mothers with triplets who were born between 1978 and 2006. The data were collected through a mailed questionnaire sent to the mothers (response rate 67.0%). After excluding 36 triplets with unknown sex, we had 1,128 triplet children of 376 mothers in our data. For these births, data on triplets' weight growth, gestational age, sex, parity, maternal age at delivery, maternal height, and maternal body mass index were obtained from records in the Maternal and Child Health Handbooks and records in the school which children receive health check-ups. The weight deficit of the triplets was calculated as the percentage difference between the value of the general population and that of the triplets divided by the value of the general population. The weight deficits were calculated using mean values of the official growth standards. The statistical significance of regression coefficients of the covariates, where assessed from the fixed effects and these were adjusted for familial clustering (i.e. sets of triplets) by introducing random effect in the linear mixed model. The factors associated with weight at six, eight, 10 or 12 years of age were explored by the linear mixed effects multiple regression analysis. *Results:* The weight deficit of the triplets compared to the general population of Japan remained between 10% and 17% until 12 years of age. Moreover, at 12 years of age, the differences of weight between the general population and triplets were approximately -4.75 kg for boys and -6.00 kg for girls. Very low birth weight had the strongest contribution to body weight until eight years of age. After eight years of age, maternal body mass index was a significant factor affecting the weight of triplets until 12 years of age. *Conclusions:* Triplets have lighter weight than singletons and the weight deficit of the triplets compared to the general population of Japan remained between 10% and 17% from six to 12 years of age. Further follow-up of the triplets should reveal whether their growth catches up with singletons before adulthood.

THE NATURAL HISTORY OF THE MONOCHORIONIC TWIN PREGNANCY: ANALYSIS OF A CASE STUDY

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Objectives: To report the natural history of the monochorionic twin pregnancy in a group of patients supervised through a specific surveillance's protocol and to identify possible risk factors for fetal and perinatal mortality and morbility. *Methods:* A prospective study over a group of 178

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patients with monochorionic diamniotic twin pregnancy, supervised at our hospital between May 2001 and December 2010, was conducted. The patients underwent to the measurement of the nuchal translucency (NT) and then to ultrasound examinations every two weeks from the 16th week of pregnancy to delivery. Since 2005, regnancies with a diagnosis of severe twin to twin transfusion syndrome (TTTS) have been treated with laser-ablation of the placental anastomoses. *Results:* Pregnancy data were available in all the 178 cases. In 10.7%of cases a NT >95°percentile has been detected in at least a twin. This turned out to be related to an increased risk of adverse outcome ($p< 0,01$), due to a more frequent occurrence of spontaneous abortion, TTTS, IUGR, intra-uterine death and neonatal death. Severe congenital anomalies occurred in 1% of cases and in one case a karyotype's discordance with a 45,X0 fetus was detected. 12.9% of pregnancies were complicated by TTTS. The total mortality was of 7.9%, the neonatal mortality of 0.6%. TTTS and premature labour <32 weeks turned out to be independent risk factors for neonatal mortality and morbility. *Conclusions:* Despite an intensive prenatal monitoring, monochorionic twin pregnancies remain at high risk of mortality.

FETOSCOPIC LASER COAGULATION OF PLACENTAL VASCULAR ANASTOMOSES IN TTTS: PRELIMINARY RESULTS FROM A NEW CENTER

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Objective: The aim of our study was to evaluate preliminary results of fetoscopic laser ablation therapy for severe Twin-to-Twin Transfusion Syndrome (TTTS) treated at our center. *Materials and Methods:* A prospective cohort study of a tertiary referral fetal medicine unit between April 2008 and March 2011 was conducted. Forty-six monochorionic twin pregnancies complicated by TTTS before 26th week of gestation underwent fetoscopic laser ablation therapy for TTTS. Six pregnancies are still ongoing and outcome results were non available. In all cases endoscopy has been chosen to identify placental vascular equator and for selective photocoagulation of anastomoses, if feasible. *Results:* The overall survival rate was 52.5% (42/80) with a survival rate of = 1 twin of 65% (26/40), with a survival rate of both twins of 40% (16/40) and with a percentage of miscarriage or death of both twins of 35% (14/40). The study showed a recurrence of TTTS in 10% of cases (4/40). Two cases were complicated by intrauterine bleeding after fetoscopic laser treatment. One case was complicated by PPROM post-laser. An average of 7,5 vessels were ablated during each procedure, with a mean operative time of 42 min (range 12-80 min). *Conclusions:* Our three-year experience of fetoscopic laser ablation therapy for severe Twin-to-Twin Transfusion Syndrome showed equivalent results to those previously reported in the Literature.

CROWN-RUMP LENGTH AND ABDOMINAL CIRCUMFERENCE DISCREPANCY AS EARLY PREDICTORS OF LATE ADVERSE PREGNANCY OUTCOME IN MONOCHORIONIC DIAMNIOTIC PREGNANCIES

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Objectives: To investigate the value of intertwin discordance in crown-rump length (CRL) and abdominal circumference (AC) to predict adverse pregnancy outcome (APO) in monochorionic diamniotic twin pregnancies. *Methods:* Cohort study on 150 consecutive monochorionic diamniotic twin pregnancies followed at our Department from the first trimester to delivery between January 2001 and December 2010. Intertwin discordance in CRL, and z-score discrepancy in AC were assessed at 11+0-13+6 and 19+0-21+6 weeks, respectively. Receiver-operating characteristics (ROC) curves were used to determine their predictive ability for subsequent development of APO. Clinical and perinatal outcomes were reviewed. APO was defined as intertwin growth discrepancy >20%, intrauterine growth restriction, small for gestational age or neonatal intensive care unit admission. Pregnancies complicated by twin to twin transfusion syndrome or intrauterine death before 20 weeks were excluded. *Results:* 137 pregnancies were included in the study. Pregnancies that developed APO (n = 39) showed a median CRL discordance of 4.7% (IQR 2.6-7.3%) and a median z-score discrepancy in AC of 0.83 (IQR 0.41-1.71). Uncomplicated pregnancies (n = 98) showed a median CRL discordance of 3.0% (IQR 1.4-6.3%) and a median z-score AC discrepancy of 0.60 (IQR 0.28-0.98). Z-score discrepancy in AC at 20 weeks was significantly larger ($P < 0.01$) in pregnancies that subsequently developed APO. The prediction of subsequent development of APO, expressed as the area under ROC curve, provided by the discordance of CRL was 0.60 (95% CI 0.50-0.71), while it was 0.65 (95% CI 0.54-0.75) for AC. *Conclusions:* Although we observed a significant difference between complicated and uncomplicated pregnancies, the discrepancy in AC at the 20 weeks scan does not seem to be a useful predictor of the subsequent development of APO.

COMPLICATIONS AND OUTCOME OF INVASIVE PRENATAL DIAGNOSIS IN TWIN PREGNANCIES

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Objectives: To report our experience on the complications and outcome of twin pregnancies undergoing amniocentesis or chorionic villus sampling (CVS) for prenatal diagnosis. *Methods:* Retrospective review of all cases of twin pregnancies that underwent invasive prenatal diagnosis at our Institution in the last 10 years. Chorionicity and indication for invasive testing were retrieved from the clinical

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notes. The following outcomes were analysed: fetal loss within 4 weeks from the procedure and <24 weeks' gestation; preterm premature rupture of membranes (PPROM) within 4 weeks from the procedure and <34 weeks' gestation; spontaneous preterm delivery (PTD) <32 weeks of gestation. *Results:* A total of 267 twin pregnancies underwent invasive prenatal diagnosis during the study period, 212 dichorionic diamniotic and 55 monochorionic diamniotic. Amniocentesis was the most frequent procedure in both groups. Indications for invasive testing, type of procedure used, and pregnancy outcomes are described in Table 1 and reported with their 95% confidence intervals. *Conclusions:* We observed a fetal loss rate <24 weeks of 1.5% (95% CI, 0.3â€“4.3). As expected, monochorionic pregnancies had a higher incidence of adverse pregnancy outcome. Dichorionic twins (n = 212)Monochorionic twins (n = 55)Total(n = 267) Indications -increased NT 7% (3.8-11.8) 15% (7.4-25.7) 9% (5.9-13.4) -structural abnormality 11% (6.8-16.3) 19% (10.8-30.9) 13% (9.2-18) -maternal age 78% (71.6-84) 63% (50-74.2) 74% (68-79) -other 4% (1.5-7.7) 3% (0.4-10.4) 4% (1.7-6.7) Amniocentesis 87% (81.2-91.5) 84.8% (73.9-82.5) 87% (83-91) CVS 13.0% (8.5-18.8) 15.2% (7.5-26) 13.0% (10-19) Fetal loss within 4 weeks 0.7% (0-3.8) 0% (0-6.5) 0.5% (0-2.7) Fetal loss <24 weeks 0.7% (0-3.8) 3.4% (0.4-11.7) 1.5% (0.3-4.3) PPROM within 4 weeks 2.1% (0.4-6) 0% (0-6.5) 1.5% (0.3-4.3) PPROM <34 weeks 4.9% (2-9.8) 3.4% (0.4-11.7) 4.4% (2-8.2) Spont PTD <32 weeks 4.3% (1.6-9) 10.2% (3.8-20.8) 6.0% (3.1-0.2)

PROMOTER METHYLATION OF GLUCOCORTICOID RECEPTOR GENE IS ASSOCIATED WITH SUBCLINICAL CARDIOVASCULAR DISEASE: A MONOZYGOTIC TWIN STUDY

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Background: Epigenetic mechanisms are increasingly being recognized as a key factor in the pathogenesis of cardiovascular disease (CVD). Endothelial dysfunction assessed by brachial artery flow-mediated dilation (FMD) is a marker for early atherosclerotic CVD, a predictor of future cardiovascular events. The glucocorticoid receptor gene (NR3C1) regulates a variety of biological processes including cardiovascular, metabolic, immunologic, and homeostatic functions. Genetic polymorphisms in NR3C1 have been associated with atherosclerosis and several cardiometabolic risk factors. However, no study has yet investigated the potential role of NR3C1 promoter methylation in atherosclerosis. *Objective:* To examine the potential association between NR3C1 promoter methylation and FMD in a monozygotic (MZ) twin sample. *Method:* We studied 84 male-male monozygotic twin pairs drawn from the Vietnam Era Twin Registry. These twin pairs were recruited by the Emory Twins Heart Study, which investigates psychological, behavioral and biological risk factors for subclinical cardiovascular disease using a twin design. The twins were free of a self-reported previous diagnosis of cardiovascular disease at the time of enrollment. Brachial artery FMD was measured by ultrasound. The methylation levels of 25 CpG residues in the NR3C1 promoter region in peripheral blood leukocytes was quantified by bisulfite pyrosequencing. The association between DNA methylation variation and FMD was examined using nonparametric regression by regressing the intra-pair difference in FMD on the intra-pair difference in DNA methylation level at each CpG site, separately, adjusting for potential confounders including age, smoking, body mass index (BMI), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), blood glucose level and systolic blood pressure. Multiple testing was controlled by the false discovery rate. *Results:* Mean methylation level of the 25 CpG sites encompassing the NR3C1 promoter region was 2.1%. Methylation levels at 7 of the 25 CpG residues were significantly associated with FMD. On average, a 10% increase in mean methylation was associated with a 0.13 increase in FMD (95% CI: 0.09-0.17; $p<0.0001$) after controlling for confounding factors. *Conclusion:* Increased promoter methylation of NR3C1 is significantly associated with decreased risk for subclinical atherosclerosis assessed by FMD. Given the critical role of this gene in regulating hypothalamic-pituitary-adrenal axis (HPA) function, it is possible that aberrant promoter methylation of this gene may affect atherogenesis through its influence on the HPA system, a mechanism known to be involved in cardiovascular disease.

UNIQUE ASPECTS OF GENETIC COUNSELING IN TWINS

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Recently, we started a multidisciplinary outpatient clinic, TWIN-VUmc, focusing on medical, psychosocial and other problems, directly related to twin status. Genetic counselling for twins is a key feature of our clinic. Form our work, it is obvious that being a twin or multiple influences genetic counselling in many aspects. We here illustrate this with four cases, with complex issues faced in risk estimation and counselling. In the first case, monozygotic (MZ) female twins came to our clinic because of hereditary breast cancer in their family, due to a mutation in the BRCA-1 gene. First, there is a need to make a joint decision whether to test or not, because the test results of one twin are also informative for the co-twin. Both females wanted to test for the familial mutation, but after they were found to be carrier of the mutation they experienced difficulties making different decisions on prophylactic strategies. Secondly, male MZ twins visited our clinic with their parents because they wanted to know

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the cause and recurrence risk for the congenital heart defect they were both suffering from. Besides the common approach, concordance rates, heritability estimates and the occurrence of congenital heart defects in twins should be taken into account in the analysis. In the third example, a family contacted our clinic because of paternity questions. The male twin pregnancy, was the result of artificial insemination more than 20 years ago. By that time, in the particular clinic, it was usual practice to mix donor semen with semen of the partner before insemination. The boys and there parents now wanted to know whether the pregnancy was donor-conceived. Theoretically it was even possible that the two boys were dizygotic with different biological fathers, which made the decision whether to test for paternity or not, even more complex. The fourth case, a 48-year old female wanted to know whether there was an increased risk of breast cancer because breast cancer was identified in her (possibly MZ) twin sister. In assessing the susceptibility for breast cancer zygosity should be determined, a familial susceptibility or high-risk gene should be considered and if needed tested. Moreover, heritability estimates should be taken into account in all MZ pairs.. In conclusion, in genetic counselling in twins, a modified approach is often needed. The results of twin studies may be helpful in individual risk estimation in concordant and discordant monozygotic twins. Knowledge and insight in the genetics of twinning and results of twin studies is needed for counsellors.

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