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Factors Associated with Neonatal Hypoglycemia in Premature Twins and Singletons

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Abstract. Twin gestation is associated with higher rate of neonatal hypoglycemia than do singletons. We examined the role of specific risk factors associated with neonatal hypoglycemia of 216 premature twins and 1284 premature singletons, consecutively born in the years 1994-1996 in the Department of Pediatrics of Padua University, Italy. Significantly higher risk of hypoglycemia (Dextrostix <40 and <20 mg%) was found in twins vs singletons (54% vs 32%, OR 2.49, CI 1.77-3.56; 19% vs 8%, OR 2.65, CI 1.59-4.19, respectively). Gestational age of 34-37 weeks increased hypoglycemia risk for the premature twins (77% vs 51%, OR 3.20 CI 1.49-6.88). Twin deliveries statistically differed from those of singletons in several perinatal characteristics. More twins were born by cesarean section (85% vs 55%, OR 4.15, CI 2.48-6.95), and the birth weight of twins was much lower related to prematures with BW <1.0 kg (12% vs 6%, OR 2.06, CI 1.11-3.82) and SGA (20% vs 10%, OR 2.41, CI 1.46-3.98). The risk of twin deliveries was increased at 30-33 weeks gestational age (25% vs 15%, OR 1.84; CI 1.17-2.90). Twins were found to have higher rates of hospitalization (50% vs 40%, OR 1.52, CI 1.04-2.23) and showed an increased risk of cardiorespiratory resuscitation (51% vs 31%, OR 2.36, CI 1.61-3.47), hypothermia (11% vs 4%, OR 3.02, CI 2.33-3.91), BPD (25% vs 19%, OR 2.55, CI 1.10-5.91), and PVL (4% vs 1%, OR 4.08, CI 1.23-13.5). Mortality was found more often (not significant) in premature twins. The risk for intrapartum and early neonatal morbidity was however, mostly reduced in hypoglycemic twins, while it was comparable between smaller or smaller weight discordant twins and larger twins. Similarly, SGA twins, and smaller or smaller weight-discordant twins did not show increased hypoglycemia risk. In conclusion, our findings suggest that the multiple gestation per se is the single most important relative risk factor of hypoglycemia in premature twins.

Key words: Hypoglycemia, Premature, Singleton, Twin

INTRODUCTION

Multiple gestation is well known to be associated with higher rates of premature births and neonatal hypoglycemia [7, 9, 12, 16, 18].

The concern regarding low circulating glucose concentrations in twins arises from the established risk for the neonate of neurological damage after repeated and prolonged episodes of hypoglycemia, and in view of the continuing controversy over whether "asymptomatic" hypoglycemia causes neurological dysfunction and brain damage in the premature [10, 12, 20].

This concern needs to be balanced by the need to avoid the unnecessary treatment and investigation of otherwise healthy newborn babies. At present no clinical criteria exist to identify the premature twin with low blood glucose at risk, and little is known about factors associated with neonatal hypoglycemia.

Our controlled study will examine the contribution of twinning, of prematurity and of birth weight to neonatal hypoglycemia associated with twin births. We will attempt to determine whether twin gestation itself or other perinatal risk factors, on which intervention can be based, are responsible for higher hypoglycemia occurrence.

MATERIALS AND METHODS

This study compares the incidence of neonatal hypoglycemia of 216 preterm twins and 1284 singletons up to 37 gestational weeks, chosen from the 9452 births that occurred in the Department of Pediatrics at the University of Padua among 1st January 1994 and 31 December 1996.

Information regarding sex, birth weight, gestational age, mode of delivery, postnatal cardiopulmonary resuscitation and morbility, including hypothermia, respiratory distress syndrome (RDS), persistent ductus arteriosus Botalli (PDA), intaventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and mortality, was collected retrospectively from the delivery room records, maternity and NICU ward charts. The observation interval covered the period from birth until the discharge from the hospital. No twin pairs have been excluded from the analysis because of lack of information.

Twins and singletons had routine care while hospitalized, and only laboratory tests clinically indicated were performed. All neonates were admitted to an observation nursery, where weight, temperature, and other vital signs were recorded. The infants admitted to NICU were placed under a servo-controlled radiant warmer to maintain skin temperature at 36.5° C. Skin care and bath were given after stabilization of core temperature.

In all subjects serial heal blood samples were obtained. An immediate bedside estimation of blood glucose concentration was made by Dextrostix [3]. Blood samples were obtained at 30-60 minutes intervals while the blood glucose concentration was above 2.2 mmol/l. Venous blood was obtained from those subjects in whom an intravenous catheter had been sited, while capillary blood was used in the other subjects. If an infant had symptoms and glucose values <20 mg/dl, treatment was started immediately with an intravenous infusion of 200 mg/kg dextrose (2 ml/kg 10% dextrose water) given over 1-2 minutes and followed by a continuos infusion of 8 mg/kg/min. Parental feeding preference determined the assignment of the subjects to bottle-fed or breast-fed groups. Feed-

ings were scheduled at postnatal ages of 2 hours, 5 to 6 hours and subsequently according to the nursery routine. Starting with the first feeding at 2 hours of age, bottle-feed infants received 5% dextrose water ad libitum and breast-fed infants were nursed.

All infants underwent gestation age assessment using a clinical estimate, based on physical characteristics and neurologic signs [10, 11]. This estimate was compared with the calculated gestation age. The initial examination included a clinical evaluation of the state of intrauterine growth, under- or overnutrition [10, 11]. In twins, weight discordance, defined as a inter-twin birth weight difference expressed as a percentage with the larger twin as 100%, was considered. We set the cut-off value for discordance at 20% [1, 18, 19].

The rates of mortality, morbidity and the distribution of qualitative variables were compared between twins and singletons. Significance of differences between two proportions P_1 and P_2 have been tested with the variable $P_1-P_2/\sigma_{1,2}$ assumed to be normally distributed. Sigma ($\sigma_{1,2}$) is the SD of P_1-P_2 as is estimated adopting a binomial distribution for the single variables 1 and 2. $P \leq 0.05$ were considered to indicate significance. Relative risk (Odds Ratio, OR) of hypoglycemia is computed assuming a 99% confidence interval (CI) to test for high significance. OR is considered significant when the corresponding CI does not include the unity.

RESULTS

In the years 1994 to 1996 there were 1500 live-born preterm infants (16%) up to 37 gestational weeks. Of these 216 (14%) were twins, including two triplets.

Twin deliveries statistically differed from those of singletons in several important characteristics (Table 1).

More twins were born by cesarean section than singletons (85 % vs 55%, OR 4.15, CI 2.48-6.95), the birth weight of twins was much lower: (Bw < 1.0 Kg 12% vs 6%, OR 2.06, CI 1.11-3.82; SGA 20% vs 10%, OR 2.41, CI 1.46-3.98), while the risk of twin deliveries was increased at 30-33 weeks (25% vs 15%, OR 1.84, CI 1.17-2.90), and reduced at 34-37 (64% vs 77%, OR 0.54, CI 0.36-0.81) than did those of singletons. Twenty (19%) out of 216 twins, including two from triplet, had BW discordance of more than 20%.

Twins were found to have higher rates of hospitalization in the NICU (50% vs 40%, OR 1.52, CI 1.04-2.23). This yielded a higher morbidity and a statistically increased risk of perinatal asphyxia (cardiorespiratory resuscitation at birth 51% vs 31%, OR 2.36 CI 1.61-3.47), of core temperature < 35°C at the admission (11% vs 4%, OR 3.02, CI 2.33-3.91), of bronchopulmonary dysplasia (BPD 7% vs 3%, OR 2.55, CI 1.10-5.91), and of PVL (4% vs 1%, OR 4.08, CI 1.23-13.5).

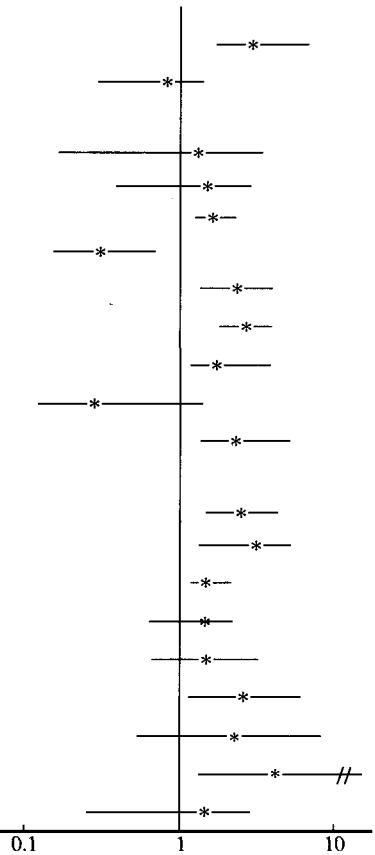
Mortality was found more often (not significant) in premature twins. Fifty singletons (4%) and twelve twins (6%) died within the observation period. In 2 cases both twins < 26 g.a. died.

Hypoglycemia risk was statistically higher in twins than in singletons (Dextrostix < 40 mg%, 52% vs 32%, OR 2.49, CI, 1.77-3.55; Dextrostix < 20 mg%, 19% vs 8%, OR 2.65, CI 1.59-4.19, respectively).

Neonatal morbidity of smaller and of smaller birth weight discordant twins, as well as the relative risks for hypoglycemic and normoglycemic twins are shown in Table 2, 3.

Table 1 - Percent distribution of selected characteristic, Odds ratios (*) and their 99% CIs in preterm twins and singletons

	Singletons 1284	Twins 216
Mode of delivery		
Cesarean	704 (55%)	184 (85%)[3]
Male	675 (53%)	107 (50%)
Gestational age (wks)		
<26	29 (2%)	6 (3%)
26-29	74 (6%)	18 (8%)
30-33	193 (15%)	53 (25%)[3]
34-37	988 (77%)	139 (64%)[3]
Resuscitation	392 (31%)	110 (51%)[3]
Temperature < 35° C	51 (4°)	24 (11%)[3]
BW < 1.0 kg	80 (6%)	26 (12%)[3]
LGA	53 (4%)	4 (2%)
SGA	123 (10%)	44 (20%)[3]
Hypoglycemia		
< 40 mg%	408 (32%)	116 (54%)[3]
< 20 mg%	101 (8%)	41 (19%)[3]
Hospitalization	504 (40%)	107 (50%)[2]
RDS	241 (19%)	53 (25%)[1]
PDA	55 (4%)	17 (8%)[1]
BPD	34 (3%)	14 (7%)[3]
IVH	24 (2%)	9 (4%)[1]
PVL	12 (1%)	8 (4%)[3]
Death	50 (4%)	12 (6 %)



BW, birth weight; LGA, large for gestational age; SGA, small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus Botalli; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

[1] $p < 0.05$; [2] $p < 0.01$; [3] $p < 0.001$

The smaller and the smaller weight discordant twins were comparable as regard the relative risk for perinatal complications. Hypoglycemic twins showed instead, a diminished risk of cardiorespiratory resuscitation (45% vs 63 %, OR 0.48, CI 0.23-0.98), hospitalization (34% vs 65%, OR 0.31, CI 0.14-0.61), RDS (14% vs 38%, OR 0.27, CI 0.11-0.65), PDA (3% vs 16%, OR 0.14, CI 0.12-0.71), BPD (3% vs 12%, OR 0.20, CI 0.10-0.61), and PVL (0 vs 7%). Also mortality risk was increased (not significant) in normoglycemic twins (10% vs 2%).

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Table 2 - Percent distribution of selected characteristic in smaller and birth weight discordant twins

	Discordant			
	Smaller 109	Larger 107	Smaller 20	Larger 20
Mode of delivery				
Cesarean	93 (85%)	91 (85%)	18 (90%)	18 (90%)
Male	52 (48%)	55 (51%)	6 (30%)	9 (45%)
Resuscitation	54 (50%)	56 (52%)	14 (70%)	14 (70%)
Temperature <35° C	14 (13%)	8 (8%)	3 (15%)	3 (15%)
BW <1.0 kg	14 (13%)	12 (11%)	4 (20%)	2 (10%)
LGA		4 (4%)		
SGA	30(28%)[1]	14 (13%)	12(60%)[2]	2 (10%)
Hypoglycemia				
<40 mg%	62 (57%)	54 (51%)	11 (55%)	8 (40%)
<20 mg%	21 (19%)	18 (18%)	5 (25%)	1 (5%)
Hospitalization	55 (50%)	52 (50)	13 (65%)	11 (55%)
RDS	23 (21%)	30 (28%)	2 (10%)	6 (30%)
PDA	7 (6%)	10 (9%)	1 (5%)	1 (5%)
BPD	5 (5%)	9 (8%)		
IVH	5 (5%)	4 (4%)	1 (5%)	2 (10%)
PLV	5 (5%)	3 (3%)	3 (15%)	1 (5%)
Death	8 (7%)	4 (4%)	3 (15%)	1 (5%)

BW, birth weight; LGA, large for gestational age; SGA, small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus Botalli; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

[1] $p < 0.01$; [2] $p < 0.001$

A different relative risk of hypoglycemia was found for the twins with higher gestational ages: at 34-37 weeks (77% vs 51%, OR 3.20, CI 1.49-6.88) (Table 3).

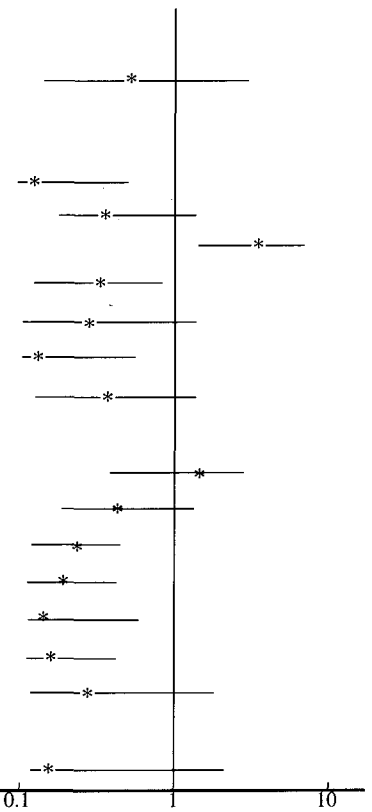
SGA twins and smaller and discordant twins did not show an increased risk of hypoglycemia, found instead in SGA singletons (48% vs 30%, OR 2.15, CI 1.35-3.41) (Table 4).

DISCUSSION

The incidence of hypoglycemia in high-risk or general newborn nurseries is difficult to evaluate because of the different criteria used to define hypoglycemia and because of dissimilar population in the various nurseries reporting [3]. It is becoming more appar-

Table 3 - Percent distribution of selected characteristic, Odds Ratios (*) and their 99% CIs in normoglycemic and hypoglycemic preterm twins

	Normoglycemic 101 (46%)	Hypoiglycemic 115 (54%)	Odds Ratio
Mode of delivery			
Cesarean	88 (87%)	93 (81%)	
Male	55 (55%)	53 (46%)	
Gestational age (wks)			
<26	5 (5%)	1 (1%)	
26-29	15 (15%)	3 (3%)[3]	
30-33	29 (29%)	24 (21%)	
34-37	51 (51%)	88 (77%)[3]	
Resuscitation	64 (63%)	52 (45%)[2]	
Temperature <35° C	16 (16%)	8 (7%)[1]	
BW <1.0 kg	20 (20%)	6 (5%)[3]	
SGA	26 (26%)	18 (16%)[1]	
LGA	2 (2%)	2 (2%)	
Smaller twin	44 (44%)	63 (55%)	
Larger twin	55 (56%)	52 (45%)	
Hospitalization	66 (65%)	39 (34%)[3]	
RDS	38 (38%)	16 (14%)[3]	
PDA	16 (16%)	3 (3%)[3]	
BPD	12 (12%)	3 (3%)[2]	
IVH	6 (6%)	3 (3%)	
PVL	7 (7%)	0 [2]	
Death	10 (10%)	2 (2%)[2]	



BW, birth weight; LGA, large for gestational age; SGA, small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus Botalli; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

[1] $p < 0.05$; [2] $p < 0.01$; [3] $p < 0.001$

ent, from other publications as well as from our results, that the risk of less or more severe hypoglycemia in multiple gestations is related to the multiplicity of the embryos per se. Thus, most differences between twins and singletons in hypoglycemia, and in perinatal clinical complications, found in this study differently disappeared once specific rates among larger and smaller or weight discordant twins were controlled for. Furthermore, hypoglycemic twins seem more protected from perinatal complications than otherwise normoglycemic twins.

These conflicting data regarding the increased risk of hypoglycemia in twins and the reduced incidence of perinatal complications in hypoglycemic twin pairs do not clarify

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Table 4 - Hypoglycemia risk (Odds Ratio and its 99% CI) in SGA premature singletons and twins

	AGA	SGA	Odds Ratio
Singletons 408	337 (30%)	56(48%)[1]	—*—
Twins 116	96 (60%)	18(36%)[1]	—*—
			0.1 1 10

AGA, appropriate for gestational age; SGA, small for gestational age; LGA prematures are not computed.

[1] $p < 0.001$

the open debate over whether the CNS abnormality is primary and precedes the hypoglycemia or whether the hypoglycemia may be the cause of CNS damage of prematures. Both of these views may be valid, and besides the risk associated with asymptomatic hypoglycemia can not be defined from our data.

About increased overall morbidity in twins with respect to premature singletons, for almost all recorded diagnoses, these data agree with the results of Erkkola et al. [5] and Rydhstrom [15], who found a higher mortality and morbidity in smaller twins . In fact, in these studies, the antenatal course of pregnancies with discordant twins was analyzed, whereas the present study was restricted to the neonatal outcome of live-born twins. We found an excess risk of overall morbidity in twin neonates, which in our sample reached statistical significance for cesarean section, BW <1.0 kg and SGA twins, cardiorespiratory resuscitation and hypothermia at birth, hospitalization rates, leukomalacia and long term respiratory sequelae, according to the observations of Ghai et Vidyasagar [8], who found significantly elevated birth weight specific risks in twins for birth asphyxia, RDS, other respiratory disorders, and mortality.

Our findings disagree instead, with those of other workers, who related the higher incidence of the reduced glucose blood levels in twins at birth to prematurity, and/or intrauterine malnutrition as it is in singletons [2]. This could be because we have achieved considerable control for confounding by birth weight and different gestational age categories, using the three categories (LGA, AGA, SGA) described by Lubchenco et al., sufficient to remove most of association between twin birth and perinatal morbidity, among hypoglycemic twins and among larger and smaller or birth discordant twins. Consequently, we feel that, in twin populations, increased hypoglycemia risk may be only in part related to the increased occurrence of cesarean section associated with reduced circulating stress hormones [15]. In particular, some mechanisms responsible for hypoglycemia in SGA twins could be vastly different from those in SGA infants.

The etiology of premature birth and related frequent intrauterine under nutrition in the twin pairs, and the related risk of hypoglycemia occurrence is heterogeneous, including physiological factors such as different genetic growth potential in dyzygotic twins and pathological conditions like placenta insufficiency or severe disease affecting only one of the twins. As a consequence, the etiology of hypoglycemia of affected twins remains obscure. Inter-twin analysis hypoglycemia risk in SGA twins was similar from that of larger twins, while it was found increased in SGA singletons. Two reasons may account for these contrasting results. In some of the twin-pairs weight discordance may be due to pathological factors [18]. In the remaining cases, malnutrition, due to patho-

logical changes of the placenta or the umbilical cord, results in hypotrophy of the affected twin [4, 6, 14, 17]. Thus, as previously suggested by Sonntag et al. [18], the present study provides evidence that surviving hypotrophic twin glucose homeostasis is not impaired significantly, once the inter-uterine malnutrition is ended.

In conclusion, our results tend to confirm the opinions that higher rates of neonatal hypoglycemia and perinatal complications in twins compared to premature singletons are related to twinning itself. The association of twin pregnancy with either frequent delivery by cesarean section, earlier gestational age, lower birth weight, and discordant birth weight of twins resulted less influent.

Follow-up studies of premature twins, which take into account mainly gestational age, IUGR, and perinatal asphyxia are however, needed to unravel the role of hypoglycemia with later central nervous system damage.

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