Exploring Genetic and Environmental Influences on Miscarriage Rates: A Twin Study

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Miscarriage is the most common type of pregnancy loss, occurring in up to 15% of clinically recognized pregnancies. Our understanding of the etiology is still limited but is believed to be multifactorial, including endocrine and anatomical abnormalities, immunologic, genetic and lifestyle factors. The aim of this study was to explore whether genetic variability in miscarriage is under any genetic influence. 3234 MZ and DZ female twins completed postal self-completion questionnaires on pregnancies. Rates were adjusted for total number of pregnancies. The relative contribution of genetic and environmental factors to variation in miscarriage was assessed using twin intrapair correlations and quantified using a variance components model fitting approach. We found 22.7% of our twins reporting having suffered at least one miscarriage. Current age, age at first pregnancy and higher number of pregnancies all had a significant influence on reported miscarriage. The concordance of miscarriage was similar in identical and non-identical twins, 26% and 27%, respectively. Shared environment and predominantly random error and unique environment rather than genetic factors best explained the total variation of miscarriage. To our knowledge, this is the first large twin study exploring heritability of miscarriage which unlike the vast majority of common variable traits, shows no significant genetic influence. In the absence of clear environmental factors, these results suggest the influence of random factors.

Keywords: miscarriage, heritability, twins, genetic

Miscarriage is the most common type of pregnancy loss referring to any fetal loss from conception until the time of fetal viability at 23 weeks gestation. Miscarriage is commonly said to occur in 12–15% of clinically recognized pregnancies, with the rate of recurrent miscarriage being 3–5% (Garcia-Enguidanos et al., 2002; Savitz et al., 2002). However, true miscarriage rates may be higher than this. Prevalence of miscarriage is hard to measure as the different clinical sources rarely see the full range of cases and the reported prevalence rates of miscarriage tend to be pregnancy- rather than woman-based.

Our understanding of etiology is limited although a huge range of possible causes and risk factors have been reported. Besides endocrine and anatomical abnormalities, immunologic factors, inherited and acquired thrombophilia and several lifestyle factors (e.g., smoking, drug use, malnutrition, excessive caffeine and exposure to radiation or toxic substances), many investigators have acknowledged, that genetic factors may be an important risk factor (Garcia-Enguidanos et al., 2002). The most common and well-documented cause of miscarriage remains abnormal karyotype of the embryo (Simpson, 1980; Vidal et al., 1998). Most chromosomal abnormalities have been shown to occur with increasing age of the mother due to a faulty egg or sperm cell, or at the stage of zygote division (Hakim et al., 1995; Smith & Buyalos, 1996). Lately basal follicle-stimulating hormone (FSH) levels have been implicated in addition to maternal age (Thum et al., 2008).

The aim of the present study was to explore whether there is genetic variation (heritability) to the common causes of miscarriage apart from abnormal karyotype of the embryo.

Material and Methods

Study Design

Data from 3234 same-sex, female monozygotic (MZ) and dizygotic (DZ) twin individuals (aged between 17 to 84, with a mean age of 57) enlisted in the TwinsUK registry were used for this study, including 740 complete MZ pairs and 644 complete DZ pairs, and 466 singletons whose co-twins did not participate (14.4%; Spector & Williams, 2006). Nulliparous women who had never had a miscarriage were excluded from the analyses (n = 553, 15 % of all respondents; n = 3787).

All twins in the TwinsUK registry were recruited through national media campaigns and from other

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twin registers (Spector & Williams, 2006). The twins have undergone extensive clinical investigations and have been shown to be comparable with age-matched singletons in terms of disease and prevalence of lifestyle characteristics (Andrew et al., 2001; Burri et al., 2009; Hammond et al., 2000; Livshits et al., 2009; MacGregor et al., 2000; Valdes & Spector, 2009). The study was approved by the St Thomas' Hospital research ethics committee and all twins provided informed consent. Zygosity was established by using standardized questions about physical similarity that have over 95% accuracy when judged against genotyping results. Zygosity was further confirmed by multiplex DNA genotyping (Sarna et al., 1978; Ooki et al., 1999). Data on miscarriage and further information on reproductive and health history, lifestyle factors and family structure were collected by postal self-completion questionnaire in several waves between 2000 and 2008 (Table 1). Twins were not selected on the basis of variables being studied and were unaware of hypothesis being tested. All variables relating to maternal characteristics for which information was available and which according to the scientific literature on the subject have been found to be associated with the risk of miscarriage, as well as common demographic variables were tested as potential confounders (Table 2). Miscarriage itself was classified as a dichotomous variable on the basis of a subject's response to the question: 'Have you ever had a miscarriage?' Data on hypertension during pregnancy was also collected (dichotomous variable *Yes*/*No*; Table 1). BMI was calculated from an individual's height and weight.

Table 1

Overall Baseline Characteristics of the Study Group and According to Zygosity

	Overall	MZ*	DZ*	*p* value***
Age, years	56.9, *12.80* (17–84)	55.87, *13.83* (17–83)	58.07, *11.44* (19–84)	
Marital status**				
Single	3%	3%	4%	
Married	42%	44%	41%	
In relationship, living with partner	6%	5%	6%	
Divorced	35%	34%	35%	
Widowed	8%	8%	8%	
In relationship, not living with partner	6%	6%	6%	
BMI	25.08, *4.28* (15–45)	24.99, *4.48* (16–45)	25.16, *4.08* (15–41)	
Number of pregnancies	2.73, *1.27* (1–12)	2.71, *1.19* (1–8)	2.75, *1.33* (1–12)	
Age at first pregnancy	24.91, *4.96* (14–42)	24.97, *5.33* (14–42)	24.86, *4.60* (15–40)	
Age at menarche	12.94, *1.48* (9–17)	12.92, *1.44* (9–17)	12.95, *1.51* (9–17)	
Age at first intercourse	19.68, *3.58* (11–44)	19.59, *3.62* (11–35)	19.76, *3.55* (12–44)	
Miscarriage	22.7%	23.1%	22.2%	
Age at miscarriage	28.03, *5.63* (16–46)	27.80, *5.53* (16–46)	28.29, *5.73* (16–43)	
Hypertension	13.43%	14.49%	12.53%	

Note: $n = 3234$, nulliparous women not included.
Results are displayed with mean, standard deviation and range unless stated otherwise.
* MZ: monozygotic (identical) twin pairs; DZ (nonidentical) twin pairs.
** Results shown as frequencies.
*** Note: * *p* values corrected for the relatedness of twins.

Statistical Analysis

To determine the relationship between miscarriage (dichotomous variable) and the different ordinal and continuous independent variables, univariate and multivariate logistic regression was used. All tests were two-tailed. Unpaired 2-tailed Student's t-test was used to test for differences between MZ and DZ twins for the continuous variables. Two-sample tests of proportions were performed to look for differences in miscarriage, marital status and hypertension (ordinal variables) between DZ and MZ twin pair groups. Non-independence of twin pairs was accounted for by using the cluster function for familial relatedness which is a form of conditional regression.

Current age and number of pregnancies were found to be a modest but significant influence on reported miscarriage ($p < 0.001$) and were therefore included as confounders in the subsequent variance component analysis (Table 2). For all analyses, a *p* value less than .05 (95% confidence interval not including '1') were considered statistically significant, unless stated otherwise. Data handling and preliminary heritability analyses were undertaken using STATA (Intercooled Stata for Windows 95, Version 5.0, 1997, StataCorp, College Station, TX) while all further genetic modeling was carried out with Mx software (Neale et al., 2006).

Twin Data and Genetic Modeling

The twin model is the classic epidemiological design universally used by human behavioral genetics to study the sources of population variation in a phenotype and thereby delineating genetic from environmental factors. The twin design assumes that monozygotic twins share 100% of their genes, whereas dizygotic twins share on average 50% of their genes. By contrast, environmental influences that contribute to familial resemblance (shared environment) are assumed to affect MZ and DZ twins equally meaning that any greater similarity between MZ as compared to DZ twin pairs is attributed to genetic factors (Kyvik, 2000). Standard methods of quantitative genetic analysis were used to model latent genetic and environmental factors influencing sibling covariance for MZ and DZ twins. For a dichotomous trait, such as miscarriage, evidence for a

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Table 2

Univariate Logistic Regression Analysis of Potential Confounders for Reported Miscarriage in the Study Population

	OR (CI 95%)	*p* value*
Age, years	**1.01 (1.00–1.02)**	**0.00**
BMI	1.01 (0.96–1.05)	0.69
Number of pregnancies	**2.38 (2.10–2.70)**	**0.00**
Age at first pregnancy	**1.03 (1.01–1.05)**	**0.01**
Age at menarche	0.97 (0.88–1.07)	0.55
Age at first intercourse	0 .98(0.94–1.02)	0.44
Age at miscarriage	1.01 (0.83–1.24)	0.86
Hypertension	1.13 (0.82–1.56)	0.43

Note: $n = 3234$, nulliparous women not included.
* Non-independence of twin pairs was accounted for by using the cluster function for familial relatedness.
Significant results are shown in bold.

genetic contribution (heritability) can be obtained by comparing the casewise concordance in MZ and DZ twins. Case-wise concordance (CR) describes the probability that a twin is affected, given that the co-twin is affected. The CR is calculated from the number of concordant pairs (c) and discordant pairs (d) using the Formula CR=2c/(2c+d) (MacGregor, 2000). It is important to note that for dichotomous traits, the maximum likelihood modeling method is used. This assumes that variation in the underlying liability of the dichotomous trait is normally distributed in the population. The correlation in liability among twins is estimated from the frequencies of concordant and discordant pairs using a multifactorial liability threshold model (Falconer, 1989). The level of association within MZ and DZ twin pairs can be further measured by employing tetrachoric correlations coefficients, given the assumption that the trait is discrete in expression but has an underlying continuous distribution.

Quantitative genetic model fitting is used to assign observed phenotypic variation to additive (A) and dominant (D) genetic effects, and common (C) and unique environmental (E) effects (Neale & Cardon, 1992). Initial assessment of the components (A, D, C, and E), may suggest non-significant values in one or more component. In further analysis the significance of each factor as components of the observed variance can be determined by removing each sequentially from the full model and testing the deterioration in fit of the various submodels using hierarchic chi-squared tests. In addition, the Akiake Information Criteria is considered, with lower values indicating better fit. The most parsimonious model is then used to estimate the heritability, which is defined as the proportion of total phenotypic variation in a population that is attributable to genetic variation among individuals. Detailed descriptions of twin modeling analyses can be found in Posthuma et al. (2003).

Results

Characteristics of the overall sample ($n = 3234$) and compared by zygosity are shown in Table 1. The MZ and DZ twin groups were well matched for rates in all the relevant variables; for example, reported miscarriage per person (23% and 22% respectively), number of pregnancies (2.71 and 2.75 respectively) and age at first miscarriage (27.80 and 28.29 respectively).

The analysis of our data from the UK showed a lifetime prevalence for miscarriage of 22.7%. Because we had no information on numbers of miscarriages we were not able to obtain a rate for miscarriage per pregnancy (Table 1). Not surprisingly, current age (1.01, p <.001) was found to have an influence on reported miscarriage with older women more frequently reporting ever having a miscarriage compared with younger women. Age at first pregnancy was also significantly related to miscarriage with women having first pregnancy at an older age being more likely to have had a miscarriage (1.03, p <.001 per year). In addition to age, a higher number of pregnancies significantly increased the odds of a miscarriage (OR 2.38, p <.001) (Table 2). Multivariate analysis yield no significant influence of age (0.98, p <.1), whereas number of pregnancies and age at first pregnancy remained significant predictors of miscarriage (1.127701, p <.001; 2.47, p <.001; results not shown). The commonly reported covariates BMI and hypertension during pregnancy did not show a significant influence on miscarriage in our sample, nor did age at first intercourse (OR 0.98, p >.1) or age at menarche (OR 0.97, p >.5; Garcia-Enguidanos et al., 2002).

Casewise concordance rates for miscarriage were not significantly higher in MZ compared with DZ twins as shown in Table 3 (26% vs. 27%, respectively; p < .5). The resultant risk ratio of 1.01 for miscarriage suggests that MZ co-twins are not more likely to suffer a miscarriage if their co-twin has had a miscarriage as compared with DZ co-twins. These results already indicate that genetic influences are unlikely to

Table 3

Casewise Concordance Rates Miscarriage in MZ and DZ Female Twins

Zygosity	Total twin pairs	Discordant twin pairs	Concordant twin pairs	Casewise concordance (95% CI)	Tetrachoric correlation (95% CI)
MZ	740	258	45	0.26 (0.20–0.32) %	0.0576 (0.025–0.090)
DZ	644	205	38	0.27 (0.20–0.34) %	0.1268 (0.079–0.175)

Note: $n = 2768$, nulliparous women and singletons not included.

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Table 4

Model Fitting Results for Univariate Analysis of Miscarriage, Adjusted for 'Current Age' and 'Number of Pregnancies' (n = 3234, Nulliparous Women not Included)

Model	A (95% CI)	C/D (95% CI)	E (95% CI)	χ^2 *(df)*	*p* value	*AIC*
Miscarriage n = 2768						
ACE	0.000 (0.000–0.199)	0.078 (0.078–0.172)	0.921 (0.921–0.997)	(2763)		–3304.679
ADE	0.089 (0.082–0.205)	0.000 (0.000–0.000)	0.910 (0.794–1.000)	(2763)		–3304.275
AE	0.089 (0.062–0.092)	—	0.910 (0.794–1.000)	0.404 (2764)	0.525	–2564.370
CE	—	0.085 (0.002–0.209)	0.914 (0.790–0.992)	0.465 (2764)	0.495	–2565.292
E				**2.625 (2765)**	**0.269**	**–2564.279**

Note: Best-fit models are highlighted in bold.

A = Additive genetic effects; D = Dominant genetic effects; C = Common environmental effects; E = Unique environmental effects and random error; The variance component E is conflated with the random error in the ordinary least squares regression and therefore the confidence intervals for E cannot be explicitly estimated using DF methods. However, the point estimate for E can be estimated by subtracting the other estimated variance components from 1. AIC, Akaike Information Criterion. AIC describes the model with best goodness of fit combined with Parsimony. The submodel with the lowest AIC is the best fitting; df, change in degrees of freedom between submodel and full model; χ^2, chi-square goodness-of-fit statistic; p, probability that Dx^2.

contribute to the variance in our phenotype of interest. Both tetrachoric correlations were non-significant, indicating that the influence of C would not be significant and pointing to shared environmental influences (rMZ = 0.058, rDZ = 0.1268; Table 3). Hence, a model including only unique environment (E) would likely fit the data. The results of genetic modeling analyses on the miscarriage data support that shared or familial environments of the twins have none or minimal influence. Based on the interpretation of the main outcome parameters, univariate variance component analyses with 95% confidence intervals revealed that our best fitting parsimonious model was an E model with the total variation being accounted for by unique environmental factors and random error (E). Even when eliminating the various components (A, C, D) from the model no significant loss of fit could be observed for the submodels, with still around 91% of the total variation being best explained by E. Adjusting the best fitting model for the potential confounders such as 'current age' and 'number of pregnancies' did not significantly alter the outcome and supported the initial findings stating that the variation in our phenotype is almost entirely accounted for by unique environment, with a negligibly small genetic contribution (Table 4).

We explored the power of our current sample to detect genetic effects in MX (method described in detail in: Neale & Cardon, 1992; Rijsdijk et al., 2005). The results show that the current sample was sufficient to detect a genetic influence of up to 30% with 80% power- assuming a c^2 of 20% and a lower heritability if c^2 was closer to zero. The following formula was used:

$$N^* = \Delta x^{\overset{\lambda}{2}*} N_{sample}$$

where 7.85 is the non-centrality parameter (NCP) for 80% power and the critical c^2 value for 1 df (which is 3.84 at the .05 level). $\Delta\chi^2$ is the difference between expected and observed proportions.

Discussion

We found a prevalence rate for 'ever suffered a miscarriage' of 22.7% in our twin sample. We were not able to assess the cumulative frequency of miscarriage — which according to current literature is about 10–15% — as no detailed information on number of miscarriages was available. However, the National Women's Health Study, a large population-based reproductive cohort study (n = 12,695) conducted in the United Kingdom used the same woman-based approach to assess prevalence and reported a comparable rate of miscarriage (27.6%) (Maconochie et al., 2004; Simmonsa et al., 2006).

The previously reported risk factor, number of pregnancies, seemed to be related to miscarriage in our study population, as was age at first pregnancy, which both significantly increased the risk for miscarriage (Garcia-Enguidanos et al., 2002; Savitz et al., 2002). Increasing gestational age has been proven to be an important etiological factor therefore it is not surprising that reported age at first pregnancy acts as a potential risk factor for miscarriage in our study sample since both factors are related and therefore non-independent (Garcia-Enguidanos et al., 2002; Thum et al., 2008).

Miscarriage didn't seem to have a significant heritable basis in our study population. The almost equal casewise concordance rates obtained in MZ compared with DZ twins suggested no underlying genetic variation to the phenotype. The results of our quantitative genetic model analysis propose that the variance in liability to miscarriage in our female twin population is best explained by unique environment and random error. Genes did not seem to significantly affect whether or not women had suffered a miscarriage. These results of our genetic variance components analysis suggest that unlike the vast majority of variable traits studied to date, womens' propensity to common forms of miscarriage appears to have no heritable basis. Although genetic factors, e.g. chromosomal

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aberrations, abnormal karyotype, have been shown to be involved in miscarriage, our results suggest no systematic genetic influence. It is possible that genetic variability in miscarriage is maintained by a continuous and frequent input of new mutations, of which most only persist very briefly. This could explain the absent of a heritability basis found in this study.

As in all studies of this nature, there are potential limitations. Miscarriage is rather hard to measure as women can suffer a miscarriage without knowing it when, for example, embryonic death has occurred but there is not any expulsion of the embryo. Missed miscarriages and the fact, that we did not assess the total number of miscarriages per person — therefore using a sub-optimal way to assess our phenotype — might have had an influence on our analysis. Some twins might have suffered a missed miscarriage and therefore not reported it in comparison to their co-twin who might have reported a miscarriage, therefore decreasing the overall concordance rate. However unless there was a systematic under-reporting in MZ compared to DZ twins (which is unlikely) — this would not affect our estimate of heritability. We have also not been able to sub-categorise the causes of miscarriage. Some rare causes (such as Lupus anti-coagulant) could still have a genetic basis — but would have been diluted by common forms of miscarriage (Zhang et al., 1998). The assessment of other potentially relevant medical and lifestyle information that might account for some cases of miscarriage e.g. smoking, drinking, diabetes, systemic lupus erythematosus, progesterone deficiency, uterine malformations, hypothyroidism, as well as full disclosure of the subject's history and the determination of specific causes of miscarriage would be useful for future studies, though unlikely to affect our conclusions (Garcia-Enguidanos et al., 2002; Savitz et al., 2002).

The fact that we used a convenience sample of volunteers instead of a random sample of the general population may have some impact on the generalizability of the results. However the rates found for most of the variables in our study (e.g. age at first intercourse, age at first pregnancy) correspond to the rates for these phenotypes found in current literature and imply that the results obtained in this study are not biased and may be generalizable (Dunbar et al., 2008; Udry et al., 1979). The representativeness of twins is worth considering and needs to be demonstrated anew for each sample. An extensive comparative study on our twin sample however, has shown our twin population to be very similar to singletons for a wide range of common health and lifestyle factors, therefore, the conclusion derived from our study should be generalizable to the general population (Andrew et al., 2001). Our twin sample is comparable to general population for most of the variables assessed in this study e.g. lifestyle factors, number of pregnancies, BMI, age at first miscarriage and age at first pregnancy, indicating that our sample didn't seem to be biased (La Vecchia et al., 1987; Ness et al., 1993). In addition, we also accounted for the family structure of the twins in our analysis.

Although the twin method is now universally accepted by geneticists — perhaps more than any other designs — it gave rise in the past to quite polarized views on the relative merits for this study design to make speculations about genetic and environmental influences. Mostly because the design is based on the 'Equal Environments Assumption', a concept implying that the effects of the environments of the MZ and DZ twin pairs being compared are equivalent. Arguing that MZ twins experience a more similar environment than DZ would mean that MZ correlations should be higher than DZ correlations not due to a genetic effect but due to a greater environmental similarity among MZs. In this case heritability estimates would be inflated upwards which was clearly not the case in our study. Also, as can be drawn from the sample characteristics in Table 1, our MZ and DZ twins did not differ significantly in most of the traits. Moreover, a wealth of data from other sources such as twins reared apart, twins misclassified as identical, comparison with family studies and direct genotyping ignoring the twin model assumptions have shown the twin model to be a robust estimate of the genetic influence on a trait (Visscher et al., 2008).

Conclusion

We have found that unlike the vast majority of medical and behavioral traits studied to date, womens' propensity to common forms of miscarriage appears to have no appreciable genetic influence. Although most of the influence appears to be random, further research should focus on unexplored environmental influences.

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