OBSTETRICS

Heritability of parturition timing: an extended twin design analysis

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OBJECTIVE: The objective of the study was to assess relative maternal and paternal genetic influences on birth timing.

STUDY DESIGN: Utilizing The Netherlands Twin Registry, we examined the correlation in birth timing of infants born to monozygotic (MZ) twins and their first-degree relatives (dizygotic twins and siblings of twins). Genetic models estimated the relative influence of genetic and common environmental factors through model fitting of additive genetic (A), common environmental (C), individual-specific environmental factors, and combinations thereof.

RESULTS: We evaluated birth timing correlation among the infants of 1390 twins and their 644 siblings. The correlation in MZ female twins ($r = 0.330$) was greater than MZ male twins ($r = -0.096$). Positive correlation were also found in sister-sister pairs ($r = 0.223$) but not in brother-brother ($r = -0.045$) or brother-sister pairs ($r = -0.038$). The most parsimonious AE model indicated a significant maternal contribution of genetic and individual-specific environmental factors to birth timing, but no paternal heritability was demonstrated. Heritability of birth timing in women was 34%; and the remaining variance (66%) was caused by individual-specific environmental factors.

CONCLUSION: Our data implicate a significant contribution of maternal but not paternal genetic influences on birth timing.

Key words: birth timing, parturition, pregnancy, twins, twin study

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As the rate of preterm birth continues to rise, the search for more reliable ways to predict pregnancies at the highest risk for this complication intensifies. Preterm birth is a complex disease. Whereas many of the etiologic mechanisms leading to preterm parturition have not been clearly elucidated, they are likely multifactorial including infectious, environmental, stress, hormonal, and genetic influences.

Evidence to support a maternal genetic contribution to the timing of parturition is accumulating. A variety of approaches to indirectly measure the maternal genetic influence on birth timing have been explored. Studies demonstrating variation in the incidence of preterm birth and in the gestational length between mothers of different ethnic groups support a maternal genetic component to birth timing.[1-7] Likewise, familial studies have provided evidence that a heritable predisposition to preterm birth exists.[8,9] Familial studies, although subject to confounding by common environmental influences, have demonstrated that mothers who were born preterm are more likely to have a preterm birth, as are sisters of women who have had a preterm birth.[10,11]

Twin studies are a classic method of assessing genetic and environmental influences on a specific phenotype by comparing outcomes in monozygotic vs dizygotic twins. Two prior twin studies have suggested a significant maternal genetic contribution to the occurrence of preterm birth by demonstrating a stronger correlation in gestational length of offspring to monozygotic (MZ) than dizygotic (DZ) female twins, with heritability estimates ranging from 17% to 36%.[12,13] A possible paternal, and thus fetal, genetic contribution to birth timing has not yet been evaluated through twin studies.

Extended twin design studies include evaluating the genetic and environmental influences on particular phenotypes occurring in not only MZ and DZ twins but also first-degree relatives (eg, siblings) of twins. This design has been utilized in analyses from The Netherlands Twin Registry (NTR) to describe the heritability and familial clustering of a variety of medical and psychiatric disorders.[14-17]

We utilized data from the NTR to determine the relative contribution of genes and environment to the variation in birth timing by examining gestational age correlation in the offspring of MZ and DZ twins and singleton siblings of twins. We hypothesized that both the

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maternal and paternal genomes would contribute significantly to the genetic heritability of birth timing.

MATERIALS AND METHODS

Subjects

Subjects from twin families who are registered with the NTR participate in longitudinal survey studies of health, lifestyle and personality.[17-20] In the 2002 wave of this study, a survey was mailed to all participants (twins, their siblings, their parents, and their spouses), which contained questions about the number of biological offspring and gestational age of the offspring. A total of 10,344 individuals from 3463 families returned the survey.

There were 1390 twins (326 males, 1064 females, mean age 40.8 ± 11.8 years) and 644 siblings of twins (217 males, 427 females; mean age 41.3 ± 10.9 years) who reported gestational age for a first-born child. Additional information on gestational age was available from 596 spouses of twins (408 males, 185 females, 3 unknown sex; mean age 42.1 ± 11.6 years), who reported on the same offspring. For same-sex twins, zygosity was determined based on typing of deoxyribonucleic acid polymorphisms (n = 398) or a series of items about the physical resemblance and confusion by others (n = 718). Approval of the study was obtained from the Medical Ethics Committee of the Vrije Universiteit Medical Centre.

Instruments

In the 2002 survey, for the biological offspring, questions were asked about their birth weight, gestational age, and sex. For this paper, we analyzed the gestational age of the first-born offspring as the phenotype. Best gestational age value for offspring was based on mother's and father's reports. If there were inconsistencies between parents' reports, the average value was taken if the differences were not larger than 2 weeks. If the discrepancy was larger than 2 weeks, the value was set to missing.

Genetic analyses

Genetic models simultaneously analyzed the data from siblings and from MZ and DZ twins. This extension of the classical twin design provides increased statistical power, both for estimation of genetic and of common environmental influences.[21,22] We first estimated the correlations in monozygotic twins and first-degree relatives (dizygotic twins and siblings) conditional on sex, to establish that there is familial resemblance for gestational age (GA). The comparison of MZ twin pair correlations with DZ twin and sibling pair correlations provides a first indication of whether genetic differences are of importance to explain individual differences in GA.

Next, genetic models were used to decompose the variance in GA into genetic and environmental components. We explored whether familial resemblance arises from additive genetic factors (A) or shared environmental factors (C). MZ twins share all of their genes, whereas DZ twins and nontwin siblings share on average 50% of their segregating genes. Any familial resemblance because of genetic factors will therefore be higher for MZ twins than DZ twins and nontwin siblings. Shared environmental factors (eg, experiences shared by members from a family that tend to make them similar) contribute equally to the correlations in MZ and DZ twins and siblings. Differences within MZ pairs are caused by nonshared or individual-specific environment (E), which includes measurement error and individual experiences that make members of a twin pair different. Differences within DZ and sibling pairs can be caused by both E and A.[23]

All genetic analyses were carried out using the software package MX, using maximum likelihood estimation of correlations and variance components.[24] The fit and parsimony of nested models (eg, the AE model vs the ACE model) are judged using likelihood ratio tests in which the negative log-likelihood (−2LL) of the nested model is compared with −2LL of the saturated model. Subtracting the two −2LLs from each other yields a statistic that is asymptotically distributed as χ^2 with degrees of freedom (df) equal to the difference between the number of parameters in the two models.

According to the principle of parsimony, models with fewer parameters are preferred if they do not give a significant deterioration of the fit. To maximize parsimony, individual factors (eg, A and C) are tested for significance by testing whether it is allowed to constrain them at zero. Under the full ACE model, the 95% confidence intervals around parameter estimates for A and C might include zero. However, if the trait shows significant familial resemblance, this indicates that it is not possible for both A and C to be zero and model fitting is used to establish which factor offers the best explanation for the observed familial correlations. To correct for multiple testing, we tested each model in the sequence at a significance level of $P = .01$.

RESULTS

Twins can be concordant or discordant for participation in the survey, and they can be concordant or discordant for having offspring. Table 1 gives the composition of the final sample for participants with at least 1 offspring. The table summarizes the number of complete and incomplete twin pairs, stratified according to sex, zygosity, and the number of additional (singleton) siblings with offspring. In addition, Table 1 also includes families in which there were no twins but only siblings with offspring.

The correlations for GA in MZ male and MZ female twins were −0.096 and 0.330, respectively. The correlations in first-degree relatives were −0.044 for brother-brother, 0.223 for sister-sister, and −0.038 for brother-sister pairs, suggesting that genetic factors might contribute to variation in GA in women but not men.

The estimates from the full ACE model, plus the 95% confidence intervals, are given in Table 2. In women, there appears to be a contribution of both genetic and common environmental factors; however, for both point estimates (19% [r = 0.19] and 12% [r = 0.12], respectively), the confidence intervals include zero, suggesting that in a reduced model, they will not both achieve statistical significance. Table 3 summarizes the results from the model-

fitting procedures: the full ACE model (with sex differences in parameter estimates) can be simplified to an AE model in both sexes. Next, it is also allowed to constrain the genetic contribution in males at zero. This same constraint is not allowed in women, indicating significant heritability. However, in women, the alternative hypothesis that familial resemblance is explained by common environment also fits the data. The χ^2 for this model, however, is larger than for the AE model. Under the AE model, the heritability of birth timing in women is 34%, with 66% of the variance accounted for by unique environmental factors (but zero heritability in men).

TABLE 1
Number of families with a specific family constitution

	Additional siblings				
	0	1	2	3	4
MZM, 1 twin	72	13	2	2	0
MZM, 2 twins	23	5	3	3	0
DZM, 1 twin	50	10	1	2	0
DZM, 2 twins	8	0	1	0	0
MZF, 1 twin	219	40	6	3	1
MZF, 2 twins	111	30	13	0	0
DZF, 1 twin	138	12	8	1	0
DZF, 2 twins	50	19	2	0	0
DOS, 1 twin	149	25	9	0	0
DOS, 2 twins	26	9	7	0	0
Siblings only		240	32	0	0
Total families in analysis		1345			

Numbers in the table refer to the number of families with a particular family composition (eg, there were 13 families in which 1 MZ male twin with 1 additional sibling participated in the survey who reported having offspring).
MZM/MZF, monozygotic male/female; DZM/DZF/DOS, dizygotic male/female/opposite sex.

Kistka. Heritability of parturition timing: an extended twin design analysis. Am J Obstet Gynecol 2008.

COMMENT

Historically, studies aimed to identify etiologies of preterm birth have focused on environmental, hormonal, and infectious factors.[25,26] More recently a growing body of evidence supports that the maternal genome contributes significantly to the timing of birth.[9,27-31] As with other complex diseases, the underlying mechanisms that lead to preterm birth likely involve a variety of gene-gene and gene-environment interactions.[8] The design used in this study is unique in its capability to examine the relative contribution of both genetic and environmental factors to birth timing.

Through an extended twin design analysis, our findings suggest that maternal genetic influences might contribute as much as 34% to the variation in parturition timing. Paternal genetic influences, on the other hand, did not demonstrate a significant influence on the timing of birth. The lack of a paternal contribution to birth timing in this study differs from 2 prior studies that examined other indirect markers of paternal genetics influences on preterm birth. A study by Li[32] demonstrated that changing paternity between pregnancies influenced the incidence of early preterm birth. Similarly, Palomar et al[33] also suggested that the paternal genome influences birth timing by reporting an increased risk of preterm birth in white mothers if the paternal race was black, even after adjustment for other important sociodemographic risk factors.

It is possible that the smaller sample size in our study (n = 2034), compared with the much larger cohorts studied by Li (n = 140,147) and Palomar (n = 527,845), in addition to the relatively modest effect size detected in these studies (odds ratios 1.13 and 1.28, respectively), contribute to this discrepancy. Additionally, our study explored the correlation and heritability of overall birth timing, not just specific associations with preterm birth as reported in the studies by Li and Palomar. Moreover, we looked at gestational age of first-born offspring; whereas the Li study (by definition) compared first- and later-born children. It is possible that modest influences from the paternal genome demonstrate an effect in abnormalities in birth timing (ie, preterm birth) but not under normal circumstances.

A study involving Australian twin pairs to evaluate possible genetic influences on preterm birth found 17% heritability for preterm delivery in the first pregnancy.[13] This is lower than the 34% maternal heritability in birth timing we detected. The study by Treloar et al,[13]

TABLE 2
Maximum-likelihood estimates and 95% confidence intervals for proportion of variance explained by genetic factors (heritability), by common environment and unique environment, in males and females

	Estimate (*r*)	95% confidence interval
Heritability males	0.002	0.00 to 0.17
Common E males	0.003	0.00 to 0.12
Unique E males	0.99	0.82 to 1.00
Heritability females	0.19	0.00 to 0.46
Common E females	0.12	0.00 to 0.34
Unique E females	0.69	0.54 to 0.84

Kistka. Heritability of parturition timing: an extended twin design analysis. Am J Obstet Gynecol 2008.

TABLE 3
Model-fitting analyses of genetic and environmental contributions to maternal and paternal influences on birth timing

	Model tested against	−2LL	Parameters, n	Δ χ^2	Δ df	*P* value
ACE males, ACE females		8930.737	8			
AE males, ACE females	1	8930.838	7	0.101	1	.751
AE model	2	8931.342	6	0.504	1	.478
AE model females, E males	2	8931.684	5	0.846	2	.655
E model females, E males	2	8952.323	4	21.485	3	< .001
CE model females, E males	2	8932.052	5	1.214	2	.545

Goodness-of-fit tests: –2 log-likelihood; number of estimated parameters; differences in –2 log-likelihood distributed as χ^2; differences in degrees of freedom; *P* value associated with χ^2 test statistic.

Kistka. Heritability of parturition timing: An extended twin design analysis. Am J Obstet Gynecol 2008.

though, was limited by a lack of specific gestational age data, resulting in an inability to correlate birth timing among twins. Preterm birth in their study was defined as a maternal report of birth occurring "over 2 weeks early."

This nonspecific definition could increase the likelihood of recall bias and inaccurate reporting. Despite the inherent variability in recall of gestational age data queried through our study, the unique design of our analysis provided us the ability to correlate birth timing data between pregnancies to twins and siblings.

Another twin study of similar design from the Swedish Twin and Birth Registers reported heritability estimates of 36% for preterm birth and gestational length.[12] Similar analyses from twin registries involving individuals from other regions of the world have not been performed but would be a useful contribution to our understanding of the relative contribution of genetic and environmental factors to parturition control within women of various ethnicities.[34-39]

The extended twin design used in this study also has the advantage of increased statistical power to discriminate between additive genetic effects and common environmental and nonadditive effects. We found that, despite a significant role of the maternal genome in determining the timing of birth, nonshared environmental factors contributed the highest proportion of influence on birth timing, 66% in the reduced AE model.

We conclude that maternal genetic influences contribute significantly to the timing of birth. This is supported by the close correlation in birth timing in the offspring of sisters, with higher correlation between monozygotic twins (r = 0.330) than dizygotic and nontwin sisters (r = 0.223). These correlations point to the possibility that there may be a small contribution of environmental factors that are shared among sisters who grow up in the same family because the DZ-sibling correlation is larger than half the MZ correlation. In the full ACE model, the contribution of common environmental factors was estimated at 12% (Table 2). Formal testing of A and C contributions showed that they could not both be omitted from the model and that the most parsimonious model is the AE model. Furthermore, we find that unique environmental factors explain more than 99% of the variance in birth timing to the offspring of male twins and male siblings and minimal paternal genetic contribution to the overall timing of parturition.

The most conclusive evidence of genetic influences on birth timing involves the identification of specific gene polymorphisms. A number of genetic alterations in maternal and/or fetal proinflammatory cytokines and mediators of collagen degradation have been linked to risk of preterm birth.[40-46] Our results indicate a significant contribution of the maternal genome to variation in birth timing but little, if any, paternal influence. Therefore, the efficiency of identifying important gene polymorphisms that influence birth timing may be improved by focusing initial genome-wide analyses on the maternal rather than fetal or infant genome. ■

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