Women who deliver preterm (<37 completed weeks’ gestation) are at high risk for recurrence. This has prompted exploration of candidate genes (both maternal and fetal) associated with preterm delivery. Epidemiologists can use recurrence patterns of preterm delivery across generations to assess the relative contributions of maternal and fetal genes. The authors used data from the Medical Birth Registry of Norway (1967–2004) to identify 191,282 mothers and 127,830 fathers who subsequently had at least one singleton offspring. The authors stratified parents according to whether or not they had been born preterm and calculated the risk of preterm delivery among their firstborn. Mothers born preterm had a relative risk for preterm delivery of 1.54 (95% confidence interval (CI): 1.42, 1.67). This association was weaker for fathers born preterm (relative risk (RR) = 1.12, 95% CI: 1.01, 1.25). Among early preterm births (<35 weeks), the effect became stronger for mothers (RR = 1.85, 95% CI: 1.52, 2.27) and weaker for fathers (RR = 1.06, 95% CI: 0.77, 1.44). These data suggest that paternal genes have little, if any, effect on preterm delivery risk. This argues against major contributions of fetal genes inherited from either parent. The increased risk of preterm delivery among mothers born preterm is consistent with heritable maternal phenotypes that confer a propensity to deliver preterm.

Abbreviations: CI, confidence interval; RR, relative risk.
delivered. Specifically, we assessed the risk of preterm delivery among first births when fathers or mothers had themselves been born prematurely.

MATERIALS AND METHODS

We used data from the Medical Birth Registry of Norway, a population-based registry of all births that have occurred in Norway since 1967. As of 2004, the registry comprised 2.1 million babies, nearly a half million of whom were second-generation (born to mothers whose own births had been recorded in the registry). We created a two-generation cohort comprising parents born between 1967 and 1988 and their firstborn offspring (stillbirths and livebirths) born through 2004. Four percent of births were excluded because the birth records lacked identifying information for the father. (Maternal information was available for virtually all records.)

We limited this two-generation study to parents who were themselves singleton births and their singleton offspring. This exclusion (3 percent of families) enabled us to avoid possible distortion of preterm rates by multiple fetuses, which are more likely to be born preterm and also have a hereditary component. We restricted offspring to first births in order to avoid the analytic complications of average family size, which varies across generations, and the potential distortions that come with higher parity.

Previous studies have identified heritable risks for preeclampsia, with genetic effects that operate through the mother as well as through the fetus (16, 17). Since preeclampsia is associated with preterm birth, we excluded all persons (parents or offspring) who had been born following a preeclamptic pregnancy. This removed an additional 7 percent of our parent-offspring pairs.

These exclusions left 191,282 mothers and their firstborn offspring and 127,830 fathers and their firstborn offspring. The larger number of mothers reflects the fact that, on average, women have their first child at younger ages than men. Thus, in any given cohort, a larger proportion of women than of men will become parents by a given age.

Parental age was a potentially confounding factor. However, parents born preterm did not differ from other parents with regard to mean age at first birth (24.1 years vs. 23.9 years for term and preterm mothers and 26.1 years vs. 26.0 years for term and preterm fathers). Adjustments for parental age were therefore unnecessary.

Socioeconomic status is known to be associated with higher rates of preterm delivery. We included maternal education in our analysis in order to explore its effects as a potentially confounding factor.

Definitions of preterm birth

Gestational age was based on the date of the last menstrual period. We defined preterm births as all deliveries occurring between 22 and 36 completed weeks of gestation. We also defined a category of “early preterm birth,” comprising deliveries between 22 weeks and 34 weeks. We screened the gestational ages of preterm babies for gross

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<p>| TABLE 1. Relative risk of early delivery among firstborn offspring according to early delivery of the mother or father, Norway, 1967–2004 |</p>
<table>
<thead>
<tr>
<th>No. of offspring</th>
<th>Row %</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mothers (N = 191,282)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring preterm*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother term (n = 184,292)</td>
<td>10,146</td>
<td>5.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Mother preterm (n = 6,990)</td>
<td>592</td>
<td>8.5</td>
<td>1.54 1.42, 1.67</td>
</tr>
<tr>
<td>Offspring early preterm†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother term (n = 177,944)</td>
<td>4,005</td>
<td>2.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Mother early preterm (n = 2,185)</td>
<td>91</td>
<td>4.2</td>
<td>1.85 1.52, 2.27</td>
</tr>
<tr>
<td><strong>Fathers (N = 127,830)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring preterm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father term (n = 122,324)</td>
<td>6,514</td>
<td>5.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Father preterm (n = 5,506)</td>
<td>329</td>
<td>6.0</td>
<td>1.12 1.01, 1.25</td>
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<tr>
<td>Offspring early preterm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father term (n = 118,135)</td>
<td>2,507</td>
<td>2.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Father early preterm (n = 1,740)</td>
<td>39</td>
<td>2.2</td>
<td>1.06 0.77, 1.44</td>
</tr>
</tbody>
</table>

* Preterm was defined as 22–36 weeks of gestation.
† Early preterm was defined as 22–34 weeks of gestation; babies born at 35 and 36 weeks were excluded from this analysis.

errors by removing births with birth weights more than four standard deviations above the mean for that gestational age (18). This excluded an additional 8 percent of preterm births from the analysis.

Statistical analysis

We calculated the simple relative risk of recurrence of preterm delivery from mothers to their firstborn and from fathers to their firstborn, with 95 percent confidence intervals. The proportion of couples in which both parents had been born preterm was too small for separate analysis (there were 21 couples in which both parents had been early preterm, and none had a preterm baby at first birth).

RESULTS

Of the 319,112 parents in the analysis, 3.9 percent had themselves been born preterm. The rate of preterm delivery among all firstborn offspring was 5.5 percent, with a higher risk if the parents themselves had been delivered preterm (table 1). Preterm birth risk was 8.5 percent among the births
of mothers born preterm, as compared with 5.5 percent if the mother had been born at term (relative risk \(RR = 1.54\), 95 percent confidence interval \( CI: 1.42, 1.67\)). Fathers who had been born preterm had a 6.0 percent chance of their offspring’s also being born preterm, as compared with 5.3 percent if the father had been born at term \(RR = 1.12\), 95 percent \( CI: 1.01, 1.25\).

Using a more stringent category of “early preterm birth” \(<35\) weeks), the contrast between mothers and fathers became even more marked (table 1). Recurrence risk was stronger for early preterm mothers \(RR = 1.85\), 95 percent \( CI: 1.52, 2.27\), with little evidence of risk for the early preterm fathers \(RR = 1.06\), 95 percent \( CI: 0.77, 1.44\). These results were unaffected by adjustment for mother’s education, in either generation (data not shown).

We explored the effects of extreme preterm delivery further by stratifying mothers and fathers according to the degree of their own preterm birth. Continuing with less than 35 weeks as the outcome in the second generation, the risk of early preterm delivery depended strongly on the degree of the mother’s own preterm birth (figure 1). Mothers born at the earliest gestational age (before 28 weeks) had a threefold increase in the risk of delivering early. There was a complete lack of trend among the preterm fathers.

DISCUSSION

Using a population-based analysis of familial patterns of preterm delivery, we found that the risk of recurrence of preterm delivery was transmitted through mothers, not through fathers. This suggests that fetal genotype is of relatively little importance in understanding the genetic patterns of preterm delivery. To the degree that heritable factors influence preterm delivery, they apparently work through the mother only.

Strengths and weaknesses of the data

In order to make accurate measurements of the risk of preterm birth recurrence across generations, there must be well-documented gestational-age data for parents as well as for their offspring. The Medical Birth Registry of Norway provides such data for the whole population of Norway, with exact linkage of birth records for parents and their offspring through the personal identification numbers assigned at birth. The fact that these data are population-based reduces the potential for selection or bias.

The overall rate of preterm delivery was higher in the offspring than in the parents. This reflects several influences. Firstly, the offspring were entirely firstborn (among whom preterm birth is more common), while the parents were a natural mix of parities. Secondly, there has been a slight increase in the rates of preterm delivery in Norway over time. Thirdly, the parental cohort included only survivors, while the offspring cohort included stillbirths and infant deaths. None of these factors would logically contribute to the observed associations.

Nonpaternity (in which the true biologic father is someone other than the father recorded in the registry) would differentially reduce an association through the paternal line as compared with the maternal line. The extent of nonpaternity in Norway has not been established, but recent population-based genetic studies have suggested that the nonpaternity rate is less than 5 percent (Min Shi, National Institute of Environmental Health Sciences, unpublished data, 2007). This low level of misclassification would have had only a trivial influence on the estimate of paternal recurrence.

In 1999, the Medical Birth Registry of Norway began to collect gestational dates based on ultrasonography as well as on the date of the last menstrual period. We explored the possible effects of errors in last menstrual period by substituting ultrasound-based gestational age for last
menstrual period for the recent time period in which data were available. There was no change in the results. We also explored the sensitivity of the results to our gestational-age definition of birth, redefining birth as reaching 28 weeks rather than 22 weeks. Once again, the results were unchanged.

It is customary to adjust for possible confounding factors in observational studies. We used restriction to control for the possible confounding effects of parity and unequal family size (by limiting our sample to first births). Similarly, we dealt with possible confounding from preeclampsia by excluding cases from preeclamptic pregnancies. We explored the importance of these restrictions by repeating the analyses after including all parities and all preeclamptic pregnancies; the conclusions were unchanged. Other possible confounding factors, such as mother’s age at first birth, did not differ between the groups.

The causes of preterm delivery are heterogeneous. Some authors have suggested that such heterogeneity can be explored by dividing preterm births into more homogeneous subtypes (e.g., spontaneous preterm birth vs. induced preterm birth) (19, 20). The proportion of pregnancies for which the timing of delivery was accelerated by clinical intervention (either induction of labor or cesarean section before the natural onset of labor) rose in Norway from 12 percent in the first 5-year period (1967–1971) to 20 percent in the most recent period (2000–2004). When we excluded all such pregnancies from our analysis, the preterm recurrence risks for mothers were slightly strengthened.

Previous literature

Investigators in previous studies have reported on preterm recurrence risk for preterm mothers, but none of these studies has included data for preterm fathers (21–23). A few studies have reported on other birth characteristics of the father and their associations with preterm birth in the offspring (24–26). In a Danish study, Basso et al. (24) examined changes in the risk of recurrent preterm birth among pregnancies arising after a father had changed his partner. They interpreted a decreased risk after a change in female partner as evidence of a lack of genetic contribution from the father (23)—a conclusion which is consistent with our findings.

Interpretation of the data

The course of a pregnancy depends on the intimate interaction of two genetically distinct individuals—the mother and her fetus. For at least one unfavorable outcome of pregnancy (preeclampsia), it has been shown that both the mother and the fetus carry heritable characteristics that contribute to the risk (6, 17). Researchers have assumed that the same is true for preterm birth and have studied genotypes of both the offspring and the mother in relation to preterm birth risk (5–9). This strategy has been supported by recent research guidelines proposing that both the maternal and fetal genotypes are involved in preterm birth risk (27).

We find no support for a substantial role of fetal genotype in preterm birth risk. Fetal genes that increase the risk of preterm delivery would, in principle, be transmitted through both the mother and the father and should therefore produce generational recurrence patterns through both parents. The absence in our data of recurrence risk through the father severely reduces the likelihood of there being major genetic effects operating through the fetus—from either maternal or paternal genes.

One exception may be imprinted genes. Gene imprinting is a mechanism by which the parent from whom a gene originates affects the expression of that gene in the fetus. Imprinted genes are known to play a role in fetal development. It is possible that a fetal gene could affect preterm risk only if it is received from the mother, not if it is received from the father, thus producing no recurrence risk through fathers (as we observed). However, given that imprinted genes appear to be relatively rare (28), this seems to be a less likely explanation for our findings. Mitochondrial genes are another possibility for candidate fetal genes transmitted solely through the maternal line.

We found that preterm mothers (in contrast with preterm fathers) had a moderately strong risk of early preterm delivery, with the highest risk occurring among mothers who had been born very preterm. Similar associations have been seen previously, although not all studies have had enough power to demonstrate the association convincingly (21–23).

There are several biologic mechanisms that could underlie this association. There may be physical characteristics of the mother, inherited from one generation of mothers to the next, that trigger preterm delivery. For example, a mother’s body size may affect her risk of delivering preterm, as has been suggested for short women (29). Another plausible explanation of recurrence risk through the maternal line is that women and their daughters are more likely to share risk factors (such as smoking, poverty, or poor nutrition) than are women and their daughters-in-law. While shared exposures may themselves be the cause, it is also possible that the exposures interact with genetically regulated aspects of phenotype (such as susceptibility to certain kinds of infection (30)), thus making both mothers and their daughters vulnerable to certain external factors that cause preterm delivery. A further possibility is that the experience of preterm delivery produces physiologic changes in the female baby that directly or indirectly increase her own risk of delivering her babies prematurely. While this is an intriguing possibility, the biologic mechanisms by which this might occur are speculative.

We initially saw a weak risk with father’s preterm delivery that became negligible after limiting the analysis to early preterm birth. This shift deserves closer scrutiny. The fact that this weak association depended on late preterm births suggests that it is merely the lower tail of a separate association found among term births. Among births of 37 weeks’ gestation or more, the father’s own gestational age is clearly correlated with his offspring’s gestational age (31). This correlation among term births suggests that genes inherited from the father (and expressed in the fetus) contribute to natural variations in fetal growth and maturation that, in turn, play a role in triggering delivery of the mature infant. While the activity of these fetal genes may shed light on the physiologic mechanisms of normal labor, such mechanisms are apparently not very important to preterm delivery.
Our data suggest that inherited risk factors may contribute to preterm delivery, although only through the mother. The maternal recurrence risk represents the upper limit of the sum of all maternal genetic effects. If such an effect were concentrated in one gene, the relative risk might be large. However, it is much more likely that the recurrence risk is spread among many genes (and, indeed, among some non-genetic factors), so the relative risks associated with individual genes may be rather small. While these genes may not have clinical importance individually, their identification may lead to new understanding of underlying mechanisms of preterm delivery—some of which may be treatable or preventable.

Only 1.2 percent of mothers in our study were in the high-risk group born before 35 weeks of gestation. While this is a very small proportion, it is rising as better medical care improves the survival of preterm babies. Since 1967 (when the Medical Birth Registry of Norway was started), the proportion of girls born before 35 weeks’ gestation has risen from 1.7 percent to 2.7 percent of all girls surviving their first year. As this generation reaches adulthood, more women will be at risk for preterm delivery on the basis of their own early birth.

These results have implications for molecular genetic studies of preterm delivery. A rapidly growing number of investigators are reporting genetic variants associated with preterm delivery. In a 2005 review (6), nine of 18 genetic studies of preterm birth reported infant genes that were statistically associated with preterm delivery. These results notwithstanding, our data strongly suggest that fetal genes should have a lower prior expectation of affecting the risk of preterm delivery than maternal genes. Low expectations a priori are relevant, given the vulnerability of genetic epidemiologic studies to false-positive results (32). In the absence of strong and specific gene hypotheses, the mother’s genome is more likely than the child’s to yield clues to the heritable aspects of preterm delivery.

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