Placenta Previa: Preponderance of Male Sex at Birth

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To determine the relation between placenta previa and male sex at birth, the authors conducted two types of analysis: 1) a historical cohort analysis of singleton live births in New Jersey hospitals during 1989–1992 (N = 447,963); and 2) a meta-analysis of previously published studies on the subject. For the cohort analysis, subject mother-infant dyads were identified from linked birth certificate and maternal and infant hospital claims data. The infant's sex for mothers with an International Classification of Diseases, Ninth Revision, Clinical Modification, code of 641.0–641.1 for placenta previa (n = 2,685) was compared with infant's sex for mothers without placenta previa (n = 445,270). For the meta-analysis, seven published articles were located and summary effects were calculated using both fixed-effect and random-effects models. In the present cohort study, the male:female ratio at birth was significantly higher in women with placenta previa (1.19) than in those without placenta previa (1.05) (p < 0.001). The association of placenta previa with male sex persisted when the analysis was either stratified or adjusted for the effects of maternal age, maternal parity, maternal smoking during the index pregnancy, race/ethnicity, the infant's gestational age, and the infant's birth weight. The meta-analytic results from the fixed-effect and random-effects models showed a 14% excess of placenta previa when women were carrying a viable male fetus as compared with a viable female fetus during pregnancy. The results were the same regardless of whether the present cohort study was included in the meta-analysis. In conclusion, the evidence obtained from these analyses strongly argues for an association between placenta previa and male sex at birth. The mechanism for this association remains to be determined. Am J Epidemiol 1999;149:824–30.

Received for publication February 5, 1998, and accepted for publication August 25, 1998.

Abbreviations: CI, confidence interval; OR, odds ratio.
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The human sex ratio at birth appears to be influenced by variables such as race, parental age, and external circumstances (e.g., wartime vs. peacetime) (1). A number of other factors have been considered, including the psychological status of parents, the time of insemination within the menstrual cycle, parental disease at the time of conception, inadvertent exposure of the parents to deleterious chemicals, and hormonal treatment of the parents for subfertility or other conditions (1).

Earlier studies carried out in the United Kingdom and the United States (2–5) reported an excess of male births in pregnancies complicated by placenta previa. A follow-up study by Alberman and Butler (6), however, failed to replicate this finding. In fact, Alberman and Butler reported an excess of female rather than male births among cases of placenta previa, though the association did not achieve statistical significance. More than 20 years after the initial reports on this issue, South African (7) and Hungarian (8) investigators reported a preponderance of male sex at birth among pregnancies complicated by placenta previa.

All of the above reports lacked details, were mostly based on small numbers, and did not control for potential confounders. Furthermore, in some of the studies, the sample was unrepresentative. Although these reports provided promising clues to the causes of placenta previa, little attention has been given to them.

The purposes of this study were 1) to examine the relation between placenta previa and infant sex among women delivering live singleton infants in a larger and more representative population and 2) to combine the results of studies that have examined this issue, with and without the present study results, using meta-analytic methods in order to arrive at a more generalizable conclusion.
MATERIALS AND METHODS

The New Jersey cohort study

The data for this historical cohort analysis were obtained from an administrative database that contains linked birth certificate, infant death certificate, and maternal and newborn hospital discharge claims data for all singleton live births to New Jersey residents that took place in New Jersey hospitals during 1989–1992 (N = 447,963). The New Jersey Department of Health linked birth certificates and death certificates for each year, with only 43 death certificates remaining unmatched for 1989 and none being unmatched for 1990, 1991, and 1992. The Office of Telecommunications and Information Systems then linked these data to the mothers’ and infants’ hospital discharge data, which had been linked previously through the Medex System. The match rate for this database was 94.5 percent for 1989, 95.3 percent for 1990, 95.5 percent for 1991, and 95.8 percent for 1992.

Placenta previa was the outcome of interest. Mothers whose medical claims contained an International Classification of Diseases, Ninth Revision, Clinical Modification (9), diagnosis code of 641.0–641.1 were considered to have had placenta previa. The sex of the newborn was the independent variable of interest, and this information was obtained from the birth certificate. Other variables derived from the birth certificate data included birth weight, gestational age, mother’s age, race/ethnicity, parity, and smoking during the index pregnancy.

We compared the male:female ratio at birth among women with placenta previa to that among women without placenta previa using the chi-squared test (10). The sex ratios at birth were also compared between the two groups after the data were stratified by maternal age, parity, smoking during pregnancy, and race/ethnicity and the infant’s birth weight and gestational age. The odds ratios across the strata were pooled for calculation of a summary (adjusted) odds ratio using the Mantel-Haenszel method (10). We further assessed the relation between placenta previa and infant’s sex at birth using multiple logistic regression (11) after adjusting simultaneously for the effects of maternal age, parity, smoking during pregnancy, race/ethnicity, and the infant’s gestational age and birth weight. A possible interaction between infant’s sex and maternal age (categorical and continuous) was examined by introducing an interaction (product) term into the model.

Meta-analysis and review of previous studies

The authors searched the medical literature using MEDLINE® for the period January 1966–January 1998, in order to identify studies that had examined the relation between placenta previa and infant sex. The following terms were used in locating the articles: “placenta previa,” “antepartum hemorrhage,” “bleeding during pregnancy,” “sex ratio,” “male birth,” and “infant’s sex.” In addition to articles identified by the computer search, references cited in both the primary articles and the secondary articles were also identified.

Three of the seven studies identified had been published prior to 1966. No special effort was made to exhaustively review the literature published prior to 1966. Only papers written in English were scrutinized. A total of seven articles were identified and reviewed.

Previous studies that examined the relation between placenta previa and infant sex are described in table 1. Most of the studies reviewed here were lacking in details, either because the studies were reported in letters to editors (4, 6) or because their primary objectives were different from the focus of this report (2, 5).

Estimated odds ratios and 95 percent confidence intervals were calculated from the raw data provided in the articles. Two-sided confidence intervals were used for analysis (11). To estimate the magnitude of the association between presumed placenta previa and male sex, we pooled the odds ratios from the seven studies both with and without the estimate obtained from the present study. The summary estimates for the odds ratios were calculated according to four different methods described by Eddy et al. (12). In particular, two fixed-effect methods (Peto’s method and a Bayesian method with a noninformative prior distribution) and two random-effects methods (the method of DerSimonian and Laird and a hierarchical Bayesian method) were used. Fixed-effect models assume that there is a single parameter (here, the odds ratio) that is being estimated across all studies. In contrast, random-effects models assume that the “true” parameter values (odds ratios) in the study settings can vary depending on the particularities of the study—for example, differences in effects across different populations and the different methodologies employed by the studies. Confidence intervals derived from fixed-effect models include only the variation due to random sampling, and the observed differences in odds ratios between single studies are ignored. Confidence intervals derived from random-effects models recognize two types of variation: 1) the variation due to random sampling considered by the fixed-effect models (which can be considered within-study variation) and 2) between-study variation. Therefore, confidence intervals from random-effects models are usually realistically wider than the corresponding fixed-effect confidence intervals, and they are interpreted as the range of values that one might predict for the odds ratio in the “next” study in
TABLE 1. Previously published studies that have examined the relation between placenta previa and infant sex

<table>
<thead>
<tr>
<th>Author(s) and year (ref. no.)</th>
<th>Placenta previa cases</th>
<th>Comparison group</th>
<th>No. of infants</th>
<th>Source</th>
<th>No. of infants</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record, 1956 (2)</td>
<td>1,004</td>
<td>All births in Birmingham, England, 1942–1952</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodes, 1965 (3)</td>
<td>97</td>
<td>All other deliveries at St. Thomas’ Hospital (5 years) and Lambart Hospital (4 years and 10 months), London, England, 1960–1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hibberd, 1965 (4)</td>
<td>353</td>
<td>All cases at Mill Road Maternity Hospital, Liverpool, England, 1952–1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alberman and Butler, 1966 (6)</td>
<td>80</td>
<td>All other births identified in a national survey of midwives, England, Scotland, and Wales, March 3–9, 1956</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brenner et al., 1978 (5)</td>
<td>185</td>
<td>All other singleton deliveries at McDonald House, University Hospital, Cleveland, Ohio, January 1, 1962–December 31, 1969</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacGillivray et al., 1986 (7)</td>
<td>391</td>
<td>All other deliveries in the Peninsula Maternity and Neonatal Service Region, Cape Town, South Africa, 1979–1983</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakobovits and Zubek, 1989 (8)</td>
<td>144</td>
<td>General newborn population at Toky Ferenc Hospital, Cegled, Hungary, January 1, 1972–December 31, 1988</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the population of potential studies from which the current studies are considered to be a random sample.

RESULTS

The New Jersey cohort study

Among the 447,963 singleton live births in New Jersey hospitals during the 4-year period (1989–1992), placenta previa was coded for 2,685 births (0.6 percent). The rates of placenta previa were identical in each of the 4 years. For eight births, the sex of the infant was missing.

The male:female ratio at birth was significantly higher in women with placenta previa (1.19) than in those without placenta previa (1.05) ($p < 0.001$; see table 2). Male sex at birth was associated with a 14 percent excess of placenta previa (table 2).

The odds ratios for male sex associated with placenta previa remained statistically significant after we accounted separately for the effects of maternal age, parity, maternal smoking during the index pregnancy, race/ethnicity, infant gestational age, and infant birth weight (table 3). The association between male sex and placenta previa persisted even after these variables were simultaneously included in a model with infant’s


<table>
<thead>
<tr>
<th>Women without placenta previa</th>
<th>Women with placenta previa</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Infants</td>
<td>Male:female ratio</td>
</tr>
<tr>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>227,816</td>
<td>217,454</td>
</tr>
</tbody>
</table>

* Odds ratio for male sex associated with placenta previa = 1.14 (95% confidence interval 1.05–1.23).
† $\chi^2 = 11.024, p < 0.001$, as compared with the sex ratio in women without placenta previa.
In both the fixed-effect and random-effects models, the studies, including and excluding the present study, ratios for male sex in cases of placenta previa for all of deliveries was compared with that for non-placenta appeared when the male:female ratio for placenta previa was compared with the sex associated with placenta previa was compared with the sex ratio of deliveries asso-

ciacted with placenta previa was compared with the sex data from the reports of Record (2), Hibbard (4), and MacGillivray et al. (7) achieved borderline statistical significance, while data from the studies by Brenner et al. (5) and Jakobovits and Zubek (8) were statistically significant. Data from the study reported by Rhodes (3) were statistically significant. Data from the reports complicated by placenta previa. Data from the reports

Meta-analysis

The odds ratios for male sex in each of the seven studies found to report on the association between placenta previa and sex ratio at birth are displayed in table 4. With the exception of the small study reported by Alberman and Butler (6), the direction of the association between placenta previa and male sex was the same: There were more male births in pregnancies complicated by placenta previa. Data from the reports of Record (2), Hibbard (4), and MacGillivray et al. (7) achieved borderline statistical significance, while data from the studies by Brenner et al. (5) and Jakobovits and Zubek (8) were statistically significant. Data from the study reported by Rhodes (3) were statistically significant when the male:female ratio of deliveries associated with placenta previa was compared with the sex ratio for the entire United Kingdom during the study period. However, the statistical significance disappeared when the male:female ratio for placenta previa deliveries was compared with that for non-placenta previa deliveries within the study population.

Table 5 shows the meta-analytic summary odds ratios for male sex in cases of placenta previa for all of the studies, including and excluding the present study. In both the fixed-effect and random-effects models, there was approximately a 14 percent excess of placenta previa among pregnancies with a male fetus as compared with a female fetus. This was the case
TABLE 4. Odds ratios from meta-analysis of previous studies that have examined the association between placenta previa and infant sex at birth

<table>
<thead>
<tr>
<th>Author(s) (ref. no.), location, and year</th>
<th>No. of mothers with placenta previa</th>
<th>Odds ratio for male sex</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record (2), Birmingham, England, 1966</td>
<td>1,004</td>
<td>1.07</td>
<td>0.95-1.21</td>
</tr>
<tr>
<td>Rhodes (3), London, England, 1965</td>
<td>97</td>
<td>1.10</td>
<td>0.74-1.65</td>
</tr>
<tr>
<td>Hibbard (4), Liverpool, England, 1966</td>
<td>353</td>
<td>1.21</td>
<td>0.98-1.50</td>
</tr>
<tr>
<td>Alberman and Butler (6), England, Wales, and Scotland, 1966</td>
<td>80</td>
<td>0.65</td>
<td>0.42-1.02</td>
</tr>
<tr>
<td>Brenner et al. (5), Ohio, United States, 1978</td>
<td>185</td>
<td>1.34</td>
<td>1.00-1.80</td>
</tr>
<tr>
<td>MacGillivray et al. (7), Cape Town, South Africa, 1988</td>
<td>391</td>
<td>1.21</td>
<td>0.99-1.48</td>
</tr>
<tr>
<td>Jakobovits and Zubek (8), Cegled, Hungary, 1989</td>
<td>144</td>
<td>1.57</td>
<td>1.12-2.20</td>
</tr>
</tbody>
</table>

DISCUSSION

Both the present cohort study and the summary risk estimates from seven previous studies obtained from the fixed-effect models provide evidence supporting an increased male:female ratio at birth among women with placenta previa as compared with those without placenta previa. However, the summary risk estimates obtained from the random-effects models showed similar directionality but had confidence intervals that included the null value of unity (though the lower limit was typically very close to unity). This discrepancy between the results of the fixed-effect and random-effects models was due to the heterogeneity of the study results that were pooled. For example, the odds ratio reported by Alberman and Butler (6) was below unity. This observed heterogeneity between at least some of the studies means that the random-effects model should be preferred to the fixed-effect model. Therefore, the meta-analysis reported here does not by itself provide strong evidence of a relation between placenta previa and male sex.

It was difficult to assess the quality of most of the previous studies, because of the incompleteness of the information presented in the reports. The present study was based on a statewide database of all singleton births (the largest population of all reported studies on the subject) and investigated the potential role of confounding and effect-modifying variables. Moreover, the rates of placenta previa were consistent over the years studied (1989–1992) and were in agreement with published results (7, 13–15).

Our analyses used information routinely collected on the New Jersey state birth certificate, infant death certificate, and maternal and newborn hospital discharge claims data. We did not attempt to verify the data through medical chart review. The accuracy of the diagnosis of placenta previa based on administrative data sets is unknown. Studies conducted to assess the percentage of agreement between diagnoses on reabstracted records and original hospital records have shown a specificity of over 94 percent (mostly >99 percent) for 12 disease system categories (16). The sensitivity varied from 58 percent to 97 percent. On the other hand, placenta previa diagnosed early in pregnancy and resolved toward the end of pregnancy may be coded as present if placenta previa has been noted on the patient’s admission record (reducing specificity). In either case, we have no reason to believe that the misclassification would be differential by the infant’s sex. Furthermore, analyses restricting the definition of placenta previa to cases that also involved cesarean section delivery did not change our conclusions.

The correct diagnosis of placenta previa requires either documentation with ultrasound or a careful check and documentation at the time of cesarean section. We are uncertain of the proportion of this New Jersey cohort in which these criteria were used to define cases of placenta previa. Similarly, these criteria were unlikely to have been applied regularly in defining cases of placenta previa in the studies included in the meta-analysis, particularly because many of the older

TABLE 5. Summary odds ratios from meta-analysis of male sex in placenta previa

<table>
<thead>
<tr>
<th>All studies (2–8), plus present study</th>
<th>All studies (2–8), excluding present study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Peto's method</td>
<td>1.14</td>
</tr>
<tr>
<td>Bayes' method, with no random effects (no hierarchy)</td>
<td>1.14</td>
</tr>
<tr>
<td>Hierarchical Bayesian method (random-effects model)</td>
<td>1.15</td>
</tr>
<tr>
<td>DerSimonian and Laird method (random-effects model)</td>
<td>1.14</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
studies were conducted before the advent of obstetric ultrasound. Therefore, it is likely that patients with other causes of third trimester bleeding, such as placental abruption, may have been included in the definition of placenta previa, and the findings may represent the greater preponderance of male births among pregnancies with third trimester bleeding due to any cause.

Our finding of a greater preponderance of male births in pregnancies coded for placenta previa was based on those pregnancies that resulted in live births. The New Jersey linked birth certificate, infant death certificate, and maternal and newborn hospital discharge claims data do not contain any information on pregnancies that end in stillbirths and abortions. Findings obtained from the sexing of aborted fetuses by observation of external genitalia or the microscopic appearance of the gonads have been discordant. The most reliable investigation of anatomic sexing in abortions revealed a male:female sex ratio of 1.10 and 1.20 at different stages of gestation (17). Gonadal sexing is limited by the fact that most abortions occur before sex can be identified from the external genitalia, and also by the relative prominence of the female clitoris during gestation, which may result in overestimation of male sex. Findings based on sex chromatin analysis of spontaneous abortions have been equally conflicting. However, most have reported a high preponderance of males (17).

Jakobovits and Zubek (8) reported the male:female ratio at birth associated with placenta previa to be highest at the extreme ends of the maternal age range. However, their observation was based on a small number of women with placenta previa in the extreme reproductive age groups. For example, in the age groups 16–20 years and 36–40 years, the numbers of women with placenta previa were 11 and 17, respectively, where sex ratios of 2.67 and 4.67 were reported. We observed that the odds ratio for male sex associated with placenta previa was highest for the maternal age group <20 years but was not significantly different from the odds ratios obtained among other strata of maternal age (nonsignificant result of the Breslow test for homogeneity; see table 3).

In the study by MacGillivray et al. (7), the relation between placenta previa and the sex ratio at birth was found to be modified by parity. Among women without placenta previa, the male:female ratio decreased with increasing parity, whereas among women with placenta previa, the sex ratio increased with increasing parity. However, the latter trend did not achieve statistical significance. In our analysis, the odds ratio for male sex associated with placenta previa was higher among women with parity of ≥4, though it did not differ significantly from the odds ratios obtained in other strata of parity (table 3).

We examined the possibility that the excess of placenta previa with male births might be mediated through greater birth weight. Stratified analysis by birth weight showed a higher male:female ratio in babies weighing more than 4,000 g as compared with the other birth weight categories used. However, the increased male:female ratio was observed in both women without placenta previa (male:female ratio = 1.80) and women with placenta previa (male:female ratio = 2.02). The increased risk of placenta previa with male sex was present in all birth weight strata (table 3). Birth weight in pregnancies complicated by placenta previa tends to be lower than birth weight in other pregnancies (18). Therefore, it is difficult to disentangle the role of placenta previa in fetal growth and timing of delivery from the role of fetal weight in the occurrence of placenta previa.

The pathophysiologic mechanism explaining the association between placenta previa and male sex at birth is unknown. MacGillivray et al. (7) proposed that early and late insemination during the menstrual cycle may cause an increase in male conceptions and also lead to a change in the site of implantation. Other possible explanations include the preferential demise of female fetuses that implant in the lower segment of the uterus.

In conclusion, the evidence that seven of the eight studies examined (including the present study) had the same directionality of effect and that there was a 14 percent excess of placenta previa associated with male births in the present study makes it difficult to escape the conclusion that women carrying male fetuses have a higher risk of developing placenta previa. The mechanism for this association remains undetermined, but it may provide clues to the causes of low placental implantation.

ACKNOWLEDGMENTS

This study was supported by grant 5-T32-PE10011 from the Division of Medicine of the Health Resources and Services Administration, US Public Health Service.

The authors acknowledge the support of Maryanne Florio and Virginia Dato of the New Jersey Department of Health and Senior Services and the cooperation of the staff of the New Jersey Office of Telecommunications and Information Systems in the provision of data.

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