Sex of the First-born and Risk of Preterm Birth in the Subsequent Pregnancy

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Background: Recent data suggest that the chance of successfully maintaining a pregnancy may be influenced by the sex of previously born children. We explored a possible relation between sex of the first-born infant and the risk of preterm birth in the second pregnancy.

Methods: Using data from the National Medical Birth Registries in Denmark 1980–2004 and Sweden 1980–2001, we selected all women whose first and second births were singleton and who had information on sex of first-born infant and gestational age for the second (Denmark, n = 393,686; Sweden, n = 603,282). Cox proportional hazards regression analysis was used to estimate the hazard ratio of preterm birth in the second pregnancy according to the sex of the first-born infant.

Results: Compared with women whose first baby was a girl, women with boys had an increased risk of preterm birth in a second pregnancy (hazard ratio = 1.10 [95% confidence interval = 1.07–1.13]). This result was consistent in the 2 populations. The association was not confounded by maternal age, interpregnancy interval, or sex of the second infant or by maternal characteristics that do not vary from one pregnancy to the next.

Conclusions: Exposure to a male fetus may increase a woman's risk of preterm delivery in the next pregnancy. While the findings have no direct public health relevance, they may suggest new pathways by which preterm birth can occur.

(*Epidemiology* 2011;22: 000–000)

Studies based on clinical populations suggest that having given birth to a boy in the first pregnancy increases the risk for recurrent miscarriage.[1,2] In large population-based studies, the birth of a boy in first pregnancy has been associated with increased stillbirth risk and decreased birth weight in subsequent pregnancies.[3,4] It is possible that similar associations can be observed for other reproductive outcomes such as preterm birth.

There are several possible mechanisms by which sex of the first-born might affect birth outcomes in subsequent pregnancies. One is that a male fetus may alter the immune response to subsequent pregnancies in susceptible women. Because half of all fetal tissue antigens are paternal in origin, immune reactions must be suppressed or tolerated to maintain the pregnancy.[5–8] When carrying a male fetus, the maternal immune system is exposed to male cells that may result in long-lasting immunity against male-specific (H-Y) antigens.[9] Immunity against H-Y antigens is found to be responsible for a higher risk of graft-versus-host disease in the nonphysiologic situation of stem-cell transplantation with female donors to male recipients.[10,11] Immunologic priming against H-Y antigens in one pregnancy may also affect subsequent pregnancies. Alternative explanations include unobserved confounding from innate maternal factors[12] or changes in the family environment or maternal behavior after the birth of a boy.

We explored the association between sex of the first-born and risk of preterm birth in the second pregnancy, using data from the population-based Danish and Swedish Medical Birth Registries.

METHODS

We used the population-based Medical Birth Registries of Denmark and Sweden to identify women who gave birth to a first and second singleton infant during the period 1980–2004 (Denmark) and 1980–2001 (Sweden). Correct record linkage between the first and second pregnancy was ensured by using the unique personal identification number assigned to each Danish and Swedish resident and recorded in the registries. We included only births with information on sex of the first infant and gestational age of the second. In both countries information on gestational age was missing for fewer than 1% of the eligible second births. The resulting datasets included 393,686 women from Denmark and 603,282 women from Sweden. In Denmark, gestational age was estimated in the beginning of the study period predominantly from the date of last menstrual period, in the mid of the study period predominantly by ultrasound examination around pregnancy week 22, and in the last part of the study period mostly by first-trimester ultrasound scanning. In Swe-

Submitted 8 April 2010; accepted 8 October 2010.

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ISSN: 1044-3983/11/2203-0001
DOI: 10.1097/EDE.0b013e31820e8600

TABLE 1. Selected Characteristics of Second-born Children According to Sex of the First-born

	Sex of First-born	Sex of Second-born	Number	Second-born Preterm[a] (%)	Interpregnancy Interval (Years)	Maternal Age at Second-birth (Years)
Denmark	Girl	Girl	92,752	3.39	3.7	29.4
		Boy	98,443	3.84	3.7	29.4
		All	191,195	3.63	3.7	29.4
	Boy	Girl	98,317	3.57	3.7	29.4
		Boy	104,174	4.25	3.7	29.4
		All	202,491	3.92	3.7	29.4
Sweden	Girl	Girl	141,865	3.59	3.1	29.0
		Boy	151,230	3.94	3.1	29.0
		All	293,095	3.77	3.1	29.0
	Boy	Girl	150,621	3.73	3.1	29.0
		Boy	159,567	4.30	3.1	29.1
		All	310,188	4.02	3.1	29.1

Data from the Danish (1980–2004) and Swedish Medical Birth Registries (1980–2001).
[a]Preterm was defined as being born before 37 completed weeks of gestation.

den, gestational age was estimated by early-second-trimester ultrasound dating when available; otherwise, the last menstrual period was used. Ultrasound scanning became increasingly common in Sweden during the 1980s, and beginning in 1990 all women were offered an early ultrasound investigation; 95% of women in Sweden accept this offer.[13] Gestational age was recorded in full weeks. Preterm birth was defined as a gestational age of less than 37 completed gestational weeks.

Statistical analysis

Cox proportional hazards regression analysis was used to model the relationship between sex of the first-born and risk of preterm birth in the second. Gestational age was used as the underlying time-scale. We censored all ongoing pregnancies at a gestational age of 37 completed weeks. The proportional-hazards assumption was assessed graphically by plotting the Schoenfeld residuals against gestational age.[14] The combined estimates were calculated as averages of the beta estimates for Denmark and Sweden weighted by the inverse of the standard errors of the estimates. *P*-values for the combined estimate were calculated using a Wald test. A χ^2 test was used to examine the association between a first preterm birth and the sex of the second born infant.

To examine the role of selection to a second pregnancy among women with a first live-born child, we examined the chances of having a second pregnancy that resulted in a live birth in the period of observation, conditional on each combination of sex and preterm status of the first born child. We then used the inverse of these 4 probabilities as propensity-weights in a logistic regression model, and analyzed the association between sex of the first-born and the risk of preterm birth (gestational age $<$ 37 completed weeks). We compared the resulting estimates with those obtained without weighting.

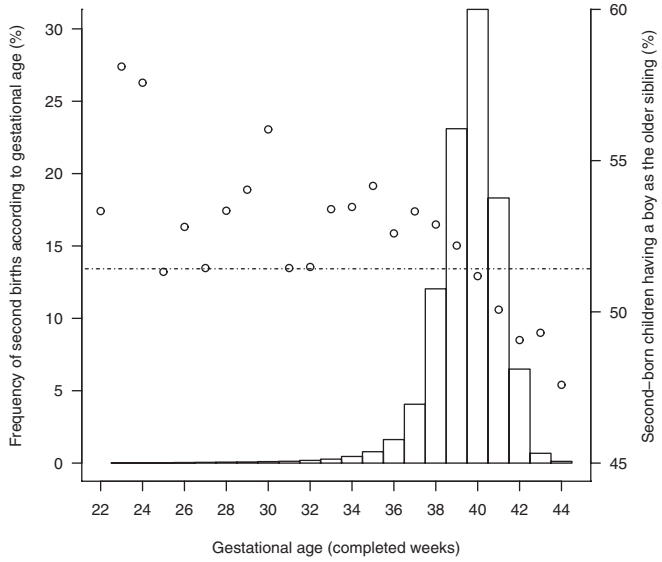

FIGURE 1. Distribution of gestational ages (histogram, right axis) and the percentage of second-born children having a boy as the older sibling (dots, left axis). The dotted line represents overall percentage of boys as the older sibling (51.4%).

RESULTS

In Denmark, the proportion of second births born preterm after birth of a girl was 3.6%, while the corresponding figure after a boy was 3.9%. In Sweden, the proportion of second births being preterm was 3.8% after birth of a first-born girl and 4.0% after the birth of a first-born boy (Table 1). Interpregnancy interval and maternal age at the second birth did not appear to be related to sex of the first-born infant. The distribution of gestational age among live-born second births is shown in Figure 1, along with the percentage of second-born children having a boy as the older sibling (ie, the

TABLE 2. Hazard Ratios of Preterm Birth for the Second-born if the First-born was a Boy in the Danish and Swedish Medical Birth Registries 1980–2003

Data	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Denmark	1.11 (1.06–1.16)	1.11 (1.06–1.16)
Sweden	1.09 (1.06–1.13)	1.09 (1.06–1.13)
Combined[b]	1.10 (1.07–1.13)	1.10 (1.07–1.13)

[a]Adjusted for maternal age, interpregnancy interval and sex of the second-born infant.
[b]The combined estimates were calculated as a precision-weighted average of the log-hazard ratios.

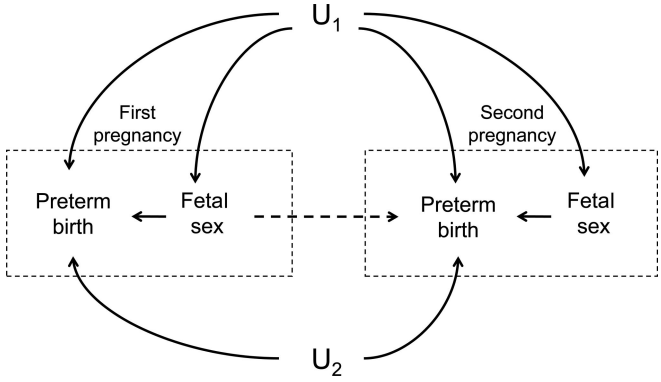

FIGURE 2. Diagram showing how 2 sets of unobserved variables (U_1 and U_2) may influence sex and preterm birth in 2 subsequent pregnancies. The dotted arrow represents the association of interest.

percentage exposed). This figure shows that the percentage declines steadily with increasing gestational age, and this trend was present even after 36 completed weeks. This suggests that a first-born boy decreases the length of the next pregnancy.

Compared with women whose first-born infant was a girl, women with a boy faced a 10% higher risk of preterm delivery in a second pregnancy (Table 2). An examination of the Schoenfeld residuals suggested that the magnitude of the association between sex of the first-born and risk of preterm birth in the second-born was consistent across all preterm gestational ages. Adjustment for interpregnancy interval, maternal age, and sex of the second birth did not alter the findings. To examine whether changes in gestational age estimation practices or other period-related factors accounted for the finding, we repeated the analyses separately for second births occurring before 1991 and from 1991 onwards, with similar estimates (likelihood ratio test of no interaction: Sweden, $P = 0.64$; Denmark, $P = 0.27$).

The main analyses are based on women with 2 live births. Women who had only their first birth in the period of observation did not contribute to the analyses. If the propensity to have a second pregnancy is dependent on the sex of the first child and on the risk of preterm birth, this could lead to selection bias (selective fertility[15]). Using the combined Danish and Swedish data, we examined whether the sex of the first-born was associated with the chance of giving birth to a second in the period of observation. If the first-born was a boy, 63.5% of the women had a second pregnancy that resulted in a live birth in the period of observation. If the first-born was a girl, the corresponding number was 63.3%. This small difference (0.2%) suggests little selection based on sex of the first-born. We calculated the inverse probability of having a second live birth in the period of observation for each combination of sex and preterm status of the first born, and we used these weights for a separate set of analyses. The results after inverse-probability-weighting were nearly identical to the unweighted results (data not shown).

We examined whether the observed associations were a result of confounding by unobserved maternal factors (represented by U_1 in Fig. 2) present at both the first and second pregnancy that affect sex ratio and the risk of preterm birth (eg, genes or innate sex hormone levels). We tested whether preterm birth in the first pregnancy predicted sex of the second-born infant, and whether sex of the first live birth predicted the sex of the second-born child. A first preterm birth was associated with an odds ratio (OR) of 1.00 (95% CI = 0.99–1.02) for the second-born to be a boy. If the first-born was a boy, the OR for a second-born boy was also 1.00 (95% CI = 0.99–1.00). Whatever is causing the association between the sex of the first-born and preterm birth in the next pregnancy, it does not appear to be a factor that is present in both pregnancies.

The mechanism need not be intrinsically biologic; it could involve behavioral changes in response to the sex of the first-born child. For example, baby boys may induce more family stress than girls. This may in turn affect the risk of preterm birth in subsequent pregnancies (by stress-related psychoneuroendocrine mechanisms, or by changes in factors such as maternal smoking and alcohol use). To examine whether the associations could be due to differences in the family environment or in maternal behavioral risk factors related to sex of the first-born, we looked at a subset of 4450 women whose first and second babies were part of the National Danish Birth Cohort. These women had provided detailed information on various risk factors in a computer-assisted telephone interview around the 30th week of their pregnancy with their second child (Olsen et al[16]). We examined whether the distribution of life stress and emotional symptoms,[17] current smoking,[18] and alcohol binge-drinking[19] during pregnancy differed according to sex of the first-born. There were only very small and unsystematic differences (data not shown). In the full Danish data where the identity of the juridical father was known, we also examined whether partner change between a first and second live birth was associated with sex of the first-born. The chance of having

different fathers for the first and second live births was slightly lower when the first-born was a girl (OR = 0.98 [95% CI = 0.96–1.00]).

DISCUSSION

Women whose first-born child was a boy had a 10% higher risk of preterm birth in the next pregnancy. The association did not appear to be confounded by unobserved maternal factors present at both first and second pregnancy or by maternal age, interpregnancy interval, or sex of the second child.

The data for this study came from 2 large population-based registries, with consistent results in both populations. The unique personal identifier system used in both Denmark and Sweden ensures correct linkage of first and second pregnancies. The analyses of successive births also adjust for unmeasured maternal or environmental confounders shared over pregnancies. Having information on gestational age at the first birth allows us to examine the role of confounding from maternal factors present at both pregnancies. We found no indication that such confounders could explain the findings. The fact that the associations were similar in 2 independent data sources reduces the risk that our findings are due to chance or artifactual biases specific to one of the data sources. Gestational age is subject to measurement error, but it seems unlikely that misclassification of gestational age of the second-born would be differential with regard to sex of the first-born. If anything, such misclassification would likely bias the estimates towards the null. While the registries record all live births regardless of gestational age, stillbirths are recorded only from the 28th completed week onwards. This represents a selection of pregnancies because fetal losses are not counted. However, such a mechanism would bias the findings only if the association between sex of the first-born infant and risk of preterm birth in the subsequent pregnancy depended on the gestational age at which the association was evaluated. We did not observe gestational-age dependence of the association in the 2 datasets when examining the proportional-hazards assumption.

There was little evidence to suggest that sex of the first-born influenced the chance of a second child during the period of observation. The main findings could be entirely explained if, among the 37% of women who did not have a second child in the period of follow-up, the rate ratio of preterm birth was 20% lower in pregnancies following a first-born boy. While this seems unlikely, it is not observable. Weighting the observed data according to the inverse of the sex- and preterm birth-specific chances of having a second pregnancy did not alter the findings. However, this strategy works only if selection occurs at random, conditional on sex and preterm birth in the first pregnancy; this is unverifiable and perhaps unlikely. For example, conditioning on preterm birth in the first pregnancy may introduce bias from unobserved common causes of preterm birth in the first and second pregnancy (U_2 in Fig. 2) as preterm birth in the first pregnancy is a collider on an otherwise closed pathway between the exposure and the outcome. It seems unlikely that this type of selection could explain the observed data, particularly as first-born boys also seem to increase other types of pregnancy failure (recurrent miscarriage, stillbirth)[1,4] that would reduce the chance of experiencing a second live birth in the period of observation. This suggests that—if anything—this type of selection would bias the main findings towards the null.

Male fetuses are at higher risk of preterm birth,[20] birth complications,[21] and cesarean delivery.[22] The mechanisms responsible are largely unknown, but may share pathways with the association reported in this study. The association between male fetal sex and adverse birth outcomes, coupled with the tracking of adverse birth outcomes over pregnancies, means that conditioning on outcomes in the first pregnancy will likely bias the results.

We have previously reported that birth of a boy is associated with increased risk of recurrent miscarriage,[1] a small decrease in birth weight,[3] and a small increase in stillbirth risk[4] in subsequent pregnancies. Whatever causes these associations, the mechanism must be something that happens during or after the first pregnancy. One possible mechanism is that women change behavior as a consequence of the sex of the first-born. We did not observe any association between the sex of the first-born and a set of potentially mediating risk factors for preterm birth related to family environment and maternal behavior. These findings are corroborated by previous findings that sex of the first-born child is not associated with changes in risk factors for preterm birth.[3]

The maternal immune system may be involved in this mechanism. Maternal priming against male-specific minor H-Y antigens in the first pregnancy is one possible mechanism. Usually, fetal antigens are presented to the maternal immune system under noninflammatory conditions, resulting in tolerance against these antigens.[23] If the maternal immune system becomes sensitized to H-Y antigens in the first pregnancy, the second exposure (next pregnancy) may invoke stronger immune responses to H-Y antigens. Such immune response may promote liberation of inflammatory cytokines, causing increased prostaglandin production in the uterus that could shorten gestation.[24] In support of this hypothesis, patients with secondary recurrent miscarriage and with H-Y-presenting human leukocyte antigen alleles had a lower chance of having a live birth after the miscarriages if the infant born prior to the miscarriages was a boy. There was no difference in live-birth rates according to sex of the first child in patients without H-Y-presenting human leukocyte antigen.[25] Although our findings are in concordance with an abnormal H-Y-immunization primed in the first pregnancy, we cannot prove this hypothesis or exclude other biologic

mechanisms. Further exploration of these mechanisms may provide new insights regarding biologic pathways leading to preterm delivery and other unfavorable outcomes of pregnancy.

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