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Fetal gender of the first born and the recurrent risk of spontaneous preterm birth

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ABSTRACT

Objective: To study, in women with a spontaneous preterm birth (sPTB) in the first pregnancy, the effect of fetal sex in that first pregnancy on the recurrent sPTB risk.
Study design: A nationwide retrospective cohort study (data from National Perinatal Registry) on all women with two sequential singleton pregnancies (1999-2009) with the first delivery ending in sPTB <37 weeks. We used logistic regression analysis to study the association between fetal gender in the first pregnancy and the risk of recurrent sPTB. We repeated the analysis for sPTB<32 weeks.
Results: The overall incidence of sPTB <37 weeks in the first pregnancy was 4.5% (15,351/343,853). Among those 15,351 women, the risk of recurrent sPTB <37 weeks was increased when the first fetus was female compared when that fetus was male (15.8% vs 15.2%; aOR 1.2 (95% CI 1.05 to 1.3)). A similar effect was seen for sPTB <32weeks (8.2% vs 5.9%; aOR 4.5 (95% CI 1.5 to 13)).
Conclusion: Women who suffer sPTB of a female fetus have an increased risk of recurrent sPTB compared to women who suffer sPTB of a male fetus. This information provides proof for the hypothesis that sPTB is due to an independent maternal and fetal factor.

INTRODUCTION

Preterm birth (PTB) is the leading cause of neonatal morbidity and mortality in the Western world, being responsible for 75-90% of all neonatal deaths and a major cause of both short and long term neonatal morbidity.[1,2] Being born preterm predisposes infants to higher risks of chronic diseases and mortality later in life.[3,4] The incidence of PTB varies between countries, i.e. from 5-10% in European countries [5-7] and 11.4% in the USA[8].
The majority of women that deliver preterm do so after early spontaneous onset of labour. Spontaneous PTB (sPTB) can be caused by several different initiating factors, which have in common that they induce precocious inflammation in gestational tissues.[9] Numerous risk factors for PTB have been identified, both physiological and psychological, i.e. ethnicity, young maternal age, low socio-economic status, short pregnancy interval, poor access to prenatal care, infection, smoking, stress and ART. [10-12] The strongest predictor of PTB is a history of spontaneous preterm delivery.[10, 13-14]
It is known that fetal gender is a factor impacting likelihood of spontaneous PTB, with male fetal gender associated with an increased risk.[15] This could suggest that women who deliver a severely preterm female fetus, who is less likely to be born preterm then a male fetus, are themselves more likely to have an underlying maternal factor contributing to the PTB than women who deliver prematurely from a male fetus at the same gestational age. This is important, as it will point at a separate maternal and a separate fetal factor responsible for preterm birth. Since this maternal factor will remain present in the second pregnancy, women who delivered preterm from a female factor will have a higher risk of recurrent PTB in the second pregnancy. To test this hypothesis, we studied, in women with sPTB in the first pregnancy, the effect of fetal gender in the first pregnancy on the risk of recurrent sPTB in the subsequent pregnancy.

MATERIAL AND METHODS

Study population

We used data from the Perinatal Registry in the Netherlands (PRN) for our nationwide retrospective cohort study. The PRN consists of nationwide population-based data that contains information on pregnancies, deliveries ≥ 22 weeks of gestation and a birth weight of ≥ 500 grams and re-admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different

registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns.[16] The PRN registry covers approximately 96% of all deliveries in the Netherlands. For this study the longitudinal probabilistic linkage PRN dataset was used including the data of the first and second consecutive pregnancies of the same mothers between January 1, 1999 and December 31, 2009. The linkage is an addition of the longitudinal linkages as described by Schaaf et al. for the period 1999-2007.[17,18] Furthermore we have added more linkage possibilities in the linkage variables as compared to the former linkage procedure described by Schaaf et al. [17,18] because we have separated data variables in day, month and year of the date of birth of the woman and the child so in total 7 linkage variables.

As all data were registered anonymous, separate ethical approval was not needed for this study under Dutch law. The Netherlands Perinatal Registry gave permission for this study (approval number 11.44).

We excluded women with multiple pregnancies, women who delivered at a gestational age before 22 weeks or beyond 44 weeks, women who had inductions of labour < 37 weeks or elective/planned Caesarean sections <37 weeks, and women who suffered antenatal deaths, or congenital anomalies, leaving women with two subsequent singleton pregnancies with a spontaneous onset of birth if born <37 weeks. PTB was defined as a birth between 22 weeks and 37 weeks of gestation, while severe PTB was defined as a birth between 22 and 32 weeks of gestation. Calculation of gestational age (GA) was based on the women's last menstrual period and ultrasound dating.

Statistical analysis

Univariate analyses of the baseline characteristics were performed with the Student's *t* test for normally distributed continuous variables and chi-square test for categorical variables. Normality of continuous variables was assessed by visual inspection of Q-Q plots. All statistical tests were two-sided and a *P*-value of 0.05 was chosen as the threshold for statistical significance.

For our primary outcome, we used logistic regression to compare, in women with a previous sPTB <37 weeks, the impact of fetal gender in the first pregnancy on the risk of recurrent sPTB < 37 weeks in the second pregnancy. In a multivariate analysis, we adjusted for maternal age, low socio-economic status, artificial reproductive technology, interpregnancy interval, gestational age in the first pregnancy, fetal gender in the second pregnancy and birth weight in the second pregnancy. We measured the association between history of preterm birth and subsequent risk of spontaneous preterm birth by calculating an adjusted odds ratio (aOR).

Similar analyses were performed for spontaneous PTB <32 weeks. The data were analysed using SAS statistical software package version 9.3 (SAS Institute Inc, Cary, NC, USA).

RESULTS

After the longitudinal linkage procedure, we identified 390,269 women with two subsequent pregnancies between 1999-2009.

We excluded women with multiple pregnancies (n=11,038), women who delivered at a gestational age before 22.0 weeks or beyond 44.0 weeks onwards (n=115), women who had inductions of labour <37 weeks (n=7,378) or elective/planned Caesarean sections <37 weeks (n=5,988) and women who suffered antenatal deaths (n=3,806), or fetal congenital anomalies (n=18,091), leaving 343,853 women with two sequential singleton pregnancies with a spontaneous onset of birth if born <37 weeks for further analysis.

PTB <37 weeks

Incidence of PTB

The incidence of spontaneous PTB <37 weeks was 4.5% (15,351/343,853) in the first pregnancy, with 3.9% (6,595/167,630) in pregnancy with a female fetus versus 5.0% (8,756/176,223) when carrying a male fetus (Table 1 OR 0.78 (95% CI 0.76-0.81)).

Table 1: Chance of spontaneous PTB in first pregnancy overall and divided by gender of the fetus.

	PTB <37 weeks	Severe PTB <32 weeks
Overall (% (n/n))	4.5% (15,351/343,853)	0.50% (1,727/343,853)
Girl (% (n/n))	3.9% (6,595/167,630)	0.41% (692/167,630)
Boy (% (n/n))	5.0% (8,756/176,223)	0.59% (1,035/176,223)
Crude OR girls vs boys (95% CI)	0.78 (0.76-0.81)	0.70 (0.64-0.77)

PTB = preterm birth, OR= odds ratio, CI= confidence interval

Baseline characteristics

Baseline characteristics for the cohort with sPTB <37 weeks in the first pregnancy are shown in Table 2. Demographic characteristics of women suffering sPTB from a male or female fetus in the first pregnancy were comparable for mean maternal

age at delivery, non-white European ethnicity, low SES, pregnancy after ART and mean pregnancy interval between delivery and conception. The mean gestational age (GA) at delivery of the first pregnancy was 34 weeks + 5 days for female fetuses compared to 34 weeks +4 days for male fetuses (P=0.02) and the mean birth weight of girls born preterm in the first pregnancy was 2396 grams compared to 2453 grams for boys (P <0.001).

Table 2: Baseline characteristics of the cohort (n=15,351) with spontaneous PTB (<37 weeks) in the first pregnancy stratified by gender of the fetus in the first pregnancy

Characteristics	Female gender of fetus (n=6,595)	Male gender of fetus (n=8,756)	P value
Mean maternal age at delivery (years)	28,4	28,4	0.72
Non white European ethnicity (n (%))	679 (10.3%)	859 (9.8%)	0.32
Low SES (n (%))	1,464 (22.2%)	1,912 (21.8%)	0.59
Conception by ART (n (%))	1,572 (23.8%)	2,043 (23.3%)	0.47
Mean pregnancy interval (days)	705	702	0.76
Mean GA at delivery (weeks + days)	34+5	34+4	0.02
Birth weight 1st pregnancy (grams)	2396	2453	<0.0001

PTB = preterm birth, SES = social economic status, ART = artificial reproductive technology, GA= gestational age

Risk of recurrent PTB

In the second pregnancy the chance of recurrent sPTB <37 weeks was 15.5% (2,374/15,351). Of the 6,595 women who gave birth to a girl < 37 weeks in their first pregnancy 1,040 (15.8%) delivered prematurely (<37 weeks) again. The recurrent risk of sPTB after sPTB <37 weeks of a boy was 15.2% (1,334/8,756). For women who experience spontaneous PTB <37 weeks in the first pregnancy, carriage of a female fetus was therefore associated with an increased risk of recurrent sPTB in the second pregnancy (aOR 1.2 (95% CI 1.05-1.3), Table 3).

Table 3: Chance of recurrent spontaneous PTB weeks in the second pregnancy after spontaneous PTB in the first pregnancy of a girl compared to a boy in the first pregnancy

	PTB (<37 weeks)	Severe PTB (<32 weeks)
Girl (% (n/n))	15.8% (1,040/6,595)	8.2 % (57/692)
Boy (% (n/n)) (REF)	15.2% (1,334/8,756)	5.9% (61/1,035)
Crude OR (95% CI)	1.04 (0.95-1.14)	1.43 (0.99-2.09)
Adjusted OR (95% CI) *	1.2 (1.05-1.3)	4.5 (1.5-12.9)

PTB = preterm birth, CI = confidence interval

* Adjusted for: Gender in the second pregnancy, birth weight of the second pregnancy, pregnancy after ART, low SES, Non White European ethnicity, maternal age <25 year, interpregnancy interval (0-25 percentile,50-75 percentile,75-100 percentile), GA in first pregnancy.

PTB<32 weeks

Incidence of PTB

Amongst the original cohort of 343,853 women, 1,727 (0.50%) suffered severe spontaneous PTB <32 weeks in the first pregnancy (Table 1). Among these 1,727 women with sPTB <32 weeks in the first pregnancy, there were 692 women with a female fetus and 1,035 with a male fetus (corresponding spontaneous PTB rates <32 weeks female fetus 0.41% (692/167,630); male fetus 0.59% (1,035/176,223); OR 0.70 (95% CI 0.64-0.77)).

Baseline characteristics

The demographic and obstetric baseline characteristics of women delivering <32 weeks in the first pregnancy are shown in Table 4. Demographic characteristics were comparable for mean maternal age at delivery, low SES, pregnancy after ART and mean pregnancy interval between delivery and conception. There were significantly more women of non white European ethnicity delivering a girl preterm in the first pregnancy compared with a boy (18.8% vs 13.1% P < 0.001). The mean gestational age (GA) at delivery of the first pregnancy was 27 weeks + 6 days for female fetuses compared to 28 weeks + 1 day for male fetuses (P < 0.004) and the mean birth weight of girls born preterm in the first pregnancy was 1,126 grams compared to 1,258 grams for boys (P <0.001).

Table 4: Baseline characteristics of the cohort (n=1,727) with severe spontaneous PTB (<32 weeks) in the first pregnancy stratified by gender of the fetus in the first pregnancy

Characteristics	Female gender of fetus (n=692)	Male gender of fetus (n=1,035)	P value
Mean maternal age at delivery (years)	30.2	30.6	0.09
Non white European ethnicity (n (%))	130 (18.8%)	136 (13.1%)	0.001
Low SES (n (%))	194 (28.0%)	267 (25.8%)	0.30
Conception by ART (n (%))	155 (22.4%)	236 (22.8%)	0.84
Mean pregnancy interval (days)	625	644	0.44
Mean GA at delivery (weeks + days)	27+6	28+1	0.004
Birth weight (grams)	1126	1258	<0.0001

PTB = preterm birth, SES = social economic status, ART = artificial reproductive technology, GA= gestational age.

Risk of recurrent PTB

Of the 1,727 women with a previous spontaneous PTB <32 weeks, 118 (6.8%) delivered prematurely <32 weeks a second time (Table 3). The chance of recurrent severe sPTB after severe sPTB with a female fetus in the first pregnancy was 8.2% (57/692) compared to 5.9% (61/1,035) after severe sPTB of a boy in the first pregnancy (aOR 4.5 (95% CI 1.5-13)).

COMMENT

Main Findings

We studied the effect of fetal gender and spontaneous preterm birth in the first pregnancy on the recurrent risk of sPTB in the second pregnancy. We found an increased risk of both recurrent severe sPTB <32 weeks and sPTB <37 weeks after sPTB of a girl compared to sPTB of a boy in the first pregnancy (aOR 4.5 (95% CI 1.5-13) and aOR 1.2 (95% CI 1.05-1.3) respectively).

Strengths and Limitations

Our study is based on data lodged in a large population-based national data system from the Perinatal Registry the Netherlands, which comprises nearly all pregnancy and births in the Netherlands. The 4% missing birth data are due to non-reporting general practitioners and midwives. However, pregnancies with preterm birth are unlikely to have been missed because of non-reporting midwives and general practitioners, since PTB is an indication for referral to an obstetrician.

We used a probabilistic linkage method to link the first and subsequent pregnancy. Non-linkage was possible due to missing values of linkage variables and the small number of linkage variables. Zipcode of the mother was one linkage variable, but in the event of women moving address over time, or if the date of the last child was not recorded in the national registry, most woman could be linked based on the two other linkage variables. A more common reason for non-linkage was women having their first birth before 1999 or their second birth after 2009. Since in this case the reason for non-linkage was not related to the primary outcome measures, it is not likely that non-linked pregnancies would have influenced our results to a significant degree. Furthermore we have added more linkage possibilities in the linkage variables as compared to the former linkage procedure described by Schaaf et al. (Schaaf et al., 2012) because we separated data variables into day, month and year of the date of birth of the woman and the child, providing in total 7 linkage variables.

Since our study is based on data of the National Perinatal Registry of the Netherlands, only data provided in the system could be taken in account, i.e. no information on cervical length was available.

Interpretation

It is well described that male fetal gender increases the risk of spontaneous PTB in any given pregnancy, and this was indeed the case in our cohort. However, to our knowledge, no other studies have assessed the chance of recurrent sPTB in relation to fetal sex of the first pregnancy when sPTB has occurred in the first pregnancy. We found an increased risk of both recurrent severe sPTB <32 weeks and sPTB <37 weeks after sPTB of a girl compared to sPTB of a boy in the first pregnancy, with the association being much stronger in women suffering severe sPTB <32 weeks. This suggests that when women deliver severely preterm with a female fetus, that is by virtue of gender less likely to be born preterm then a male fetus, it is more likely that there is an underlying maternal factor contributing to the PTB. Maternal factors underlying PTB include parameters of the maternal immune response that act to protect the fetus from the aberrant inflammatory response leading to premature parturition[19,20] We cannot exclude the possibility that gender of the first fetus interacts with maternal immune parameters in such a way as to affect the likelihood of a second PTB. It seems reasonable that because of greater antigenic stimulation, carriage of a male fetus activates a stronger memory immune response to provide more robust T cell-mediated immune tolerance[21] that in turn provides stronger protection against preterm birth in a subsequent pregnancy, than does carriage of a female fetus.

We hypothesized that women delivering preterm of a female fetus, that is by virtue of gender less likely to be born preterm then a male fetus, might have a maternal factor that makes them vulnerable to deliver preterm. The fact that our findings point to a maternal factor contributing to PTB, has implications for research in PTB. Most trials nowadays, which evaluate the effectiveness of treatment to prevent (recurrent) PTB, do not differentiate for this underlying maternal factor. Therefore future trials to evaluate the effectiveness of treatment should record and take into account threatening PTB of a boy compared to a girl or threatening recurrent PTB after PTB of a boy or a girl, since it seems likely that different mechanisms play a role in the cascade that leads to PTB based on maternal factors versus fetal factors.

Furthermore, since this maternal factor will still be present in a subsequent pregnancy, there could be a potential option for intervention to prevent recurrent PTB. We therefore suggest further research to find common factors in women with sPTB of a female fetus to give more insight in the underlying maternal factor leading to sPTB and then potentially find new treatments options to be able to prevent recurrent sPTB. This could be genetic research, or assessment of underlying infections.

CONCLUSION

We found that women who suffer spontaneous PTB while being pregnant from a female fetus have an increased risk of recurrent spontaneous PTB as compared to women who suffer spontaneous PTB of a male fetus. This adds to the hypothesis that fetal and maternal factors contribute independently to the risk of initial and recurrent PTB.

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