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CHAPTER 4

Impact of fetal gender on the risk of preterm birth, a national cohort study

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ABSTRACT

Objective
To study the influence of fetal gender on preterm birth and neonatal outcome.

Study design
We performed a national cohort study using prospectively collected data from the Netherlands Perinatal Registry. The study population comprised 1,947,266 singleton deliveries (25^{+0} - 42^{+6} weeks) from white European women between 1999 and 2010 with an alive fetus at the onset of labor. Infants with congenital anomalies or in whom no gender was recorded were excluded. The relative risk ratios (RR) for gender per week of gestation were assessed as well as gender related risk on adverse neonatal outcomes. These outcomes were neonatal mortality and a composite of neonatal morbidity (defined as neonatal intensive care admission, sepsis, meconium aspiration, necrotizing enterocolitis, respiratory distress syndrome, Apgar score <7 at 5 min or intraventricular hemorrhage). Onset of labor was categorized in spontaneous onset with intact membranes, premature rupture of membranes or medically indicated (e.g. by induction of labor or an elective cesarean section). We used a moving average technique covering three weeks per measurement to correct for possible fluctuations due to the small number of events.

Results
Male fetuses were at increased risk of spontaneous preterm birth with intact membranes compared to a female fetus with a peak between 28 and 31 weeks (RR 1.5; 95% Confidence Interval (CI) 1.3-1.7). In addition, male fetuses were at increased risk of preterm premature rupture of membranes between 26 and 37 weeks (RR 1.2; 95% CI 1.16-1.23). No gender effect was seen for medically indicated preterm birth.

There were no significant differences between male and female infants born at comparable gestational ages regarding neonatal mortality. However, males were at significantly increased risk of composite neonatal morbidity compared to females from 29 weeks onwards with a peak at 37-38 weeks (RR 1.4; 95% CI 1.2-1.5).

Conclusions
Male fetal gender is an important risk factor for spontaneous preterm birth, both for intact membranes and for preterm premature rupture of membranes. In addition, male infants are at increased risk of neonatal morbidity.

INTRODUCTION

Preterm birth is one of the most serious obstetric complications affecting around 15 million pregnancies worldwide with over one million deaths each year due to its complications.(1) Preterm birth is a complicated syndrome with probably multiple etiologies and clinical manifestations and its pathogenesis has not yet been resolved.(2;3) Because of its high impact on perinatal mortality and morbidity(4;5), much effort has been put to examine risk factors associated with preterm birth. Despite the awareness of the consequences and the strenuous efforts in research, prediction of preterm birth remains a challenge. Proper risk assessment can help to select those women who will hopefully benefit from specific interventions.(6)

In the past decades, fetal gender has been examined as a risk factor for preterm birth in various populations. Most of the studies were executed in Western countries and found an association between women carrying a male fetus and their risk on preterm birth (range of odds ratios (OR) 1.1-1.3).(7-10) Recently, these findings have been confirmed in studies from non-Western countries (OR 1.1-1.2).(11;12) These studies show that fetal gender is historically and geographically a constant variable associated with preterm birth. Several hypotheses have been posed like hormonal differences between the sexes(7;8;13), relatively higher birth weight for males(8;14), infection related pathways(14-16) or an increased susceptibility for complications of pregnancy for women carrying a male fetus(13;17). On the other hand, conflicting results have been described regarding these hypotheses(18) and therefore the underlying mechanism still remains unclear.

In the available studies, a proper subdivision by the various clinical manifestations of preterm birth (spontaneous onset with intact membranes, premature rupture of membranes and medically indicated by inducing labor or an elective cesarean section) is lacking, especially the distinction between spontaneous preterm birth starting with intact membranes and preterm birth preceded by PPROM. Furthermore, the corresponding neonatal outcome conditional on gender has not been reported widely or has been limited by only reporting neonatal mortality and low Apgar scores. In this study, we examined in a large cohort of white European women not only the association between fetal gender and the various clinical manifestations of preterm birth but also neonatal outcomes both subdivided by week of gestation.

MATERIAL AND METHODS

Database

Data were obtained from the Netherlands Perinatal Registry (PRN) between 1999 and 2010. The PRN database is obtained by a validated linkage of three different national registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns.(19;20) The PRN registry contains prospectively obtained population-based data on pregnancies and provided care (interventions, referrals, deliveries and (re)admissions) of newborns of ±96% of all deliveries in The Netherlands.

Inclusion and exclusion criteria
The study population comprised all singleton births of white European women with an alive fetus at the onset of labor and delivered an infant without congenital anomalies between January 1st, 1999 and December 31st, 2010 after 25^{+0} weeks of gestation. Pregnancy dating was performed by last menstrual period and/or the crown-rump length measured at the first trimester scan. We excluded pregnancies of women with other ethnicities, with an antenatal fetal death and of which no gender was recorded.

Population characteristic and clinical characteristics
We obtained demographic and obstetric characteristics including maternal age, parity (categorized in nulliparous and multiparous women), socio-economic status (categorized in high, middle and low, based on national governmental standards using the postal code of the women's address), mode of conception (spontaneous or artificial reproductive technology (ART)), hypertensive disorder (defined as pregnancy induced hypertension and/or (pre)eclampsia), onset of labor (categorized in spontaneous onset, induction of labor and elective cesarean section), birth weight and small for gestational age (below 2.3th centile).

Outcome measures
The initial analysis was done for preterm birth defined as a delivery before 37 completed weeks of gestation. Preterm birth was subdivided into three subtypes of preterm birth: (1) spontaneous labor with intact membranes, (2) premature rupture of membranes and (3) medically indicated by induction of labor or elective cesarean section. Subsequently, we looked at extremely preterm birth (<28 weeks), very preterm birth (28-32 weeks), moderate preterm birth (32-34 weeks) and late preterm birth (34-37 weeks).

We measured adverse neonatal outcomes, i.e. intrapartum or neonatal mortality and neonatal morbidity. Intrapartum mortality was defined as fetal death occurring during labor, neonatal mortality was defined as the death of live born fetus within 28 days, and included both early neonatal mortality (death in the first seven days) and late neonatal mortality (death between seven days and 28 days of life). Composite neonatal morbidity comprised neonatal intensive care admission, sepsis, meconium aspiration, necrotizing enterocolitis, respiratory distress syndrome, Apgar score <7 at 5 min, or intraventricular hemorrhage. All outcomes were reported for males and females by week of gestation.

Statistical analysis
We compared baseline characteristics between male and female infants with a t-test for the continuous values and a chi-square test for binominal variables. The relative risk ratios (RR) for gender by week of gestation were assessed. We used a moving average technique covering three weeks per measurement to correct for possible fluctuations due to the small number of events. A competing risk analysis was performed in which the remaining pregnant women in time are used as the denominator and the neonates born in a specific week of gestation were the numerator. We performed a multivariate logistic regression to study whether fetal sex remains associated with preterm birth before 37 completed weeks of gestation after correction for confounders. We corrected for parity, socio-economic status, mode of conception, induction of labor, premature rupture of membranes, and small for gestational age.

Data analyses were conducted with SAS (SAS institute Inc., Cary, NC, USA version 9.2). A p value <0.05 was considered statistically significant.

Ethical approval

The data in the PRN registry are anonymous; therefore ethical approval was not needed for this study. The executive board of the PRN registry gave their approval for the use of their data for this study (approval number 13.63).

RESULTS

Population

In the study period, 2,078,327 singletons were born between 25^{+0} and 42^{+6} weeks of gestation without congenital anomalies. After exclusion of women with other ethnicities than white European (n=123,549; 5.9%) and with antepartum fetal mortality (n=7,428; 0.4%) and of infants with no recorded gender (n=84), the study population consisted of 1,947,266 fetus alive at onset of labor; 999,978 males (51.4%) and 947,288 females (48.6%).

Baseline characteristics are presented in Table 1. No statistical significant differences were found in maternal characteristics. For pregnancy, delivery and neonatal characteristics the following significant differences were observed between males and females; in males the prevalence of maternal hypertensive disorders was higher, the onset of labor by induction of labor or by caesarean section was more frequent, and mean birth weight was higher.

Preterm birth

Overall, out of 1,947,266 infants 111,409 (5.7%) were born prematurely before 37 completed weeks; 61,762 (6.2%) males and 49,647 (5.2%) females (RR 1.18; 95% CI 1.17-1.19). Male infants were significantly more prevalent in two of the three subtypes of preterm birth (spontaneous with intact membranes and premature rupture of membranes), as in the various gestational age ranges (Table 2). No gender effect was seen for medically indicated preterm birth.

Table 1 | Baseline characteristics

	Male infant N=999,978	Female infant N=947,288	*p*-value
Maternal characteristics			
Maternal age at delivery, years (SD)	30.5 (4.8)	30.5 (4.8)	0.22
Nulliparous, N (%)	465,172 (46.5)	439,809 (46.4)	0.21
Low SES, N (%)	240,343 (24.0)	227,339 (24.0)	0.56
Pregnancy and delivery			
Conception			0.70
Spontaneous, N (%)	973,520 (97.4)	922,308 (97.4)	
ART, N (%)	26,458 (2.6)	24,980 (2.6)	
Hypertensive disorder, N (%)	90,161 (9.0)	82,746 (8.7)	<0.0001
Onset of labor			
Spontaneous, N (%)	790,027 (79.0)	747,886 (79.0)	0.35
Induction of labor, N (%)	154,754 (15.5)	144,243 (15.2)	<0.0001
Elective cesarean section, N (%)	55197 (5.5)	55,159 (5.8)	<0.0001
Neonatal characteristics			
Mean birth weight (gram) (SD)	3522 (586)	3398 (554)	<0.0001
SGA (<p2.3), N (%)	23,380 (2.3)	22,430 (2.4)	0.17

SD: standard deviation

ART: artificial reproductive technology

SES: Socio-economic status

SGA: small for gestational age

Table 2 | Preterm birth

	Male infant N=999,978	Female infant N=947,288	RR (95% CI)	*p* value
Preterm birth < 37 weeks, N (%)	61,762 (6.2)	49,647 (5.2)	1.18 (1.17-1.19)	<0.0001
Spontaneous with intact membranes, N (%)	37,598 (3.8)	28,618 (3.0)	1.25 (1.23-1.27)	<0.0001
PPROM, N (%)	10,018 (1.0)	7,507 (0.8)	1.19 (1.16-1.23)	<0.0001
Medically indicated, N (%)	14,146 (1.4)	13,522 (1.4)	1.00 (0.97-1.02)	0.74
34-37 weeks, N (%)	45,972 (4.6)	37,454 (4.0)	1.16 (1.15-1.18)	<0.0001
32-34 weeks, N (%)	7,902 (0.8)	6,044 (0.6)	1.24 (1.20-1.28)	<0.0001
28-32 weeks, N (%)	6,051 (0.6)	4,703 (0.5)	1.22 (1.17-1.27)	<0.0001
<28 weeks, N (%)	1,837 (0.2)	1,446 (0.2)	1.20 (1.12-1.29)	<0.0001

RR: relative risk ratio

CI: confidence interval

PPROM: preterm premature rupture of membranes

The relative risk ratios for male and female infants by onset of labor and by week of gestation are presented in Table 3. Male fetuses were at significant increased risk of spontaneous labor with intact membranes compared with female fetuses between 25^{+0} and 40^{+6} weeks. A peak was seen between 28^{+0} and 31^{+6} weeks (RR 1.5 for male to female; 95% CI 1.3-1.7). Calculated for the total population term versus preterm birth, males were at a significant increased risk for spontaneous preterm birth with intact membranes (RR 1.25; 95% CI 1.23-1.27). Furthermore, male fetuses were at increased risk of preterm premature rupture of membranes between 26^{+0} and 36^{+6} weeks (RR 1.2; 95% CI 1.16-1.23). These results are graphically displayed in Figure 1.

Relative risk ratios for male infants vs. female infants are presented with a subdivision for spontaneous labor with intact membranes, premature rupture of membranes and induction of labor or elective cesarean section.

Table 3 | Male/female ratio by onset of labor and weeks of gestation

	Spontaneous				**Medically indicated**	
	Intact membranes		**PROM**			
GA	RR	95% CI	RR	95% CI	RR	95% CI
25	1.36	(1.14-1.61)	0.97	(0.73-1.30)	0.88	(0.67-1.16)
26	1.37	(1.16-1.61)	1.07	(0.80-1.42)	1.01	(0.82-1.26)
27	1.44	(1.23-1.68)	1.35	(1.03-1.78)	0.97	(0.82-1.14)
28	1.46	(1.26-1.69)	1.45	(1.12-1.88)	1.00	(0.87-1.15)
29	1.47	(1.29-1.67)	1.33	(1.06-1.67)	0.98	(0.87-1.11)
30	1.44	(1.29-1.61)	1.27	(1.05-1.54)	1.00	(0.89-1.12)
31	1.45	(1.33-1.60)	1.26	(1.08-1.47)	1.05	(0.95-1.16)
32	1.39	(1.29-1.49)	1.25	(1.11-1.41)	1.02	(0.93-1.11)
33	1.32	(1.25-1.40)	1.27	(1.15-1.39)	1.03	(0.95-1.11)
34	1.28	(1.23-1.33)	1.20	(1.11-1.29)	1.00	(0.94-1.07)
35	1.22	(1.19-1.26)	1.19	(1.12-1.26)	0.99	(0.94-1.04)
36	1.19	(1.17-1.22)	1.15	(1.10-1.20)	1.01	(0.98-1.04)
37	1.13	(1.12-1.15)	1.10	(1.07-1.14)	0.98	(0.97-1.00)
38	1.07	(1.06-1.08)	1.05	(1.02-1.07)	0.98	(0.96-0.99)
39	1.03	(1.02-1.03)	1.02	(1.00-1.04)	0.96	(0.95-0.97)
40	1.02	(1.02-1.03)	1.00	(0.98-1.02)	0.96	0.95-0.97)
41	0.99	(0.99-1.00)	0.99	(0.98-1.00)	0.98	(0.97-0.99)
42	0.95	(0.94-0.96)	0.95	(0.92-0.98)	0.99	(0.99-1.00)

GA: gestational age (weeks)

RR: relative risk ratio

PROM: premature rupture of membranes

CI: confidence interval

In a multivariate logistic regression, with correction for nulliparity, low socio-economic status, ART, induction of labor, premature rupture of membranes, and small for gestational age, male fetal gender still significantly increased the risk for total preterm birth before 37 completed weeks (OR 1.19; 95% CI 1.18-1.20).

Neonatal outcomes

The male/female ratios for neonatal mortality and composite neonatal morbidity are displayed in Table 4 and graphically shown by Figure 2 and 3. There were no significant differences between male and female infants born at comparable gestational ages regarding neonatal mortality. However, males were at significantly increased risk of composite neonatal morbidity compared to females from 29 weeks onwards with a peak at 37-38 weeks (RR 1.4; 95% CI 1.2-1.5).

Table 4 | Male/female ratio for neonatal outcomes by week of gestation

	Neonatal mortality		**Composite neonatal morbidity**	
GA	RR	95% CI	RR	95% CI
25	1.06	(0.90-1.24)	0.95	(0.83-1.10)
26	1.08	(0.90-1.30)	0.98	(0.87-1.09)
27	1.04	(0.84-1.29)	1.03	(0.94-1.12)
28	1.01	(0.80-1.28)	1.03	(0.95-1.10)
29	0.94	(0.72-1.21)	1.07	(1.00-1.15)
30	1.01	(0.78-1.32)	1.08	(1.01-1.17)
31	0.96	(0.73-1.26)	1.11	(1.03-1.21)
32	0.94	(0.72-1.24)	1.12	(1.03-1.23)
33	0.98	(0.75-1.28)	1.15	(1.05-1.26)
34	1.01	(0.78-1.30)	1.14	(1.03-1.26)
35	1.04	(0.82-1.31)	1.20	(1.08-1.34)
36	1.05	(0.85-1.30)	1.24	(1.10-1.39)
37	1.05	(0.87-1.27)	1.36	(1.22-1.52)
38	1.07	(0.90-1.27)	1.36	(1.24-1.50)
39	1.05	(0.89-1.23)	1.34	(1.24-1.46)
40	0.98	(0.83-1.15)	1.28	(1.18-1.38)
41	0.96	(0.79-1.15)	1.29	(1.19-1.41)
42	0.86	(0.70-1.06)	1.26	(1.15-1.39)

GA: gestational age (weeks)

RR: relative risk ratio

CI: confidence interval

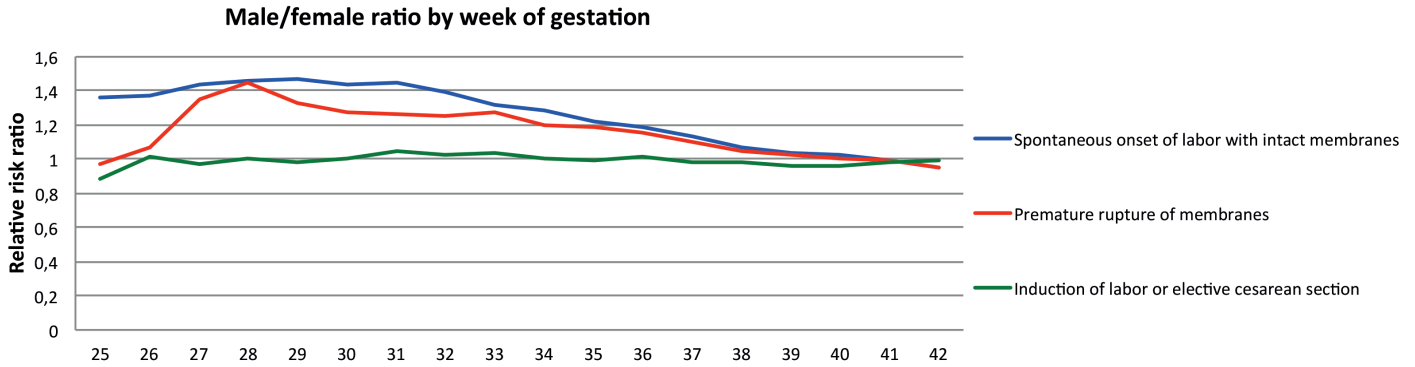

Figure 1 | Male/female ratio by week of gestation and onset of labor

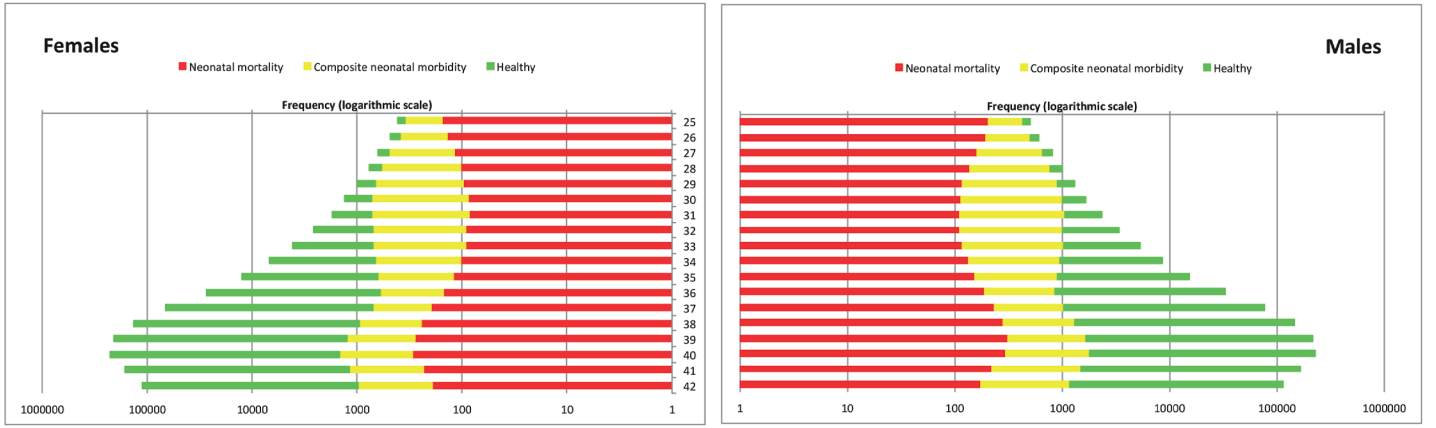

Figure 2 | Neonatal outcome for males and females by week of gestation

Neonatal outcome is presented with a subdivision of neonatal mortality, composite neonatal morbidity and healthy infants expressed with a logarithmic scale for every week of gestation.

Figure 3 | Neonatal outcome for males and females by week of gestation

Neonatal outcome is presented with a subdivision of neonatal mortality, composite neonatal morbidity and healthy infants expressed in percentages for every week of gestation.

COMMENT

Main findings

This national cohort study comprising white European women with an 11-year study period and data of 1,947,266 singleton births examined the influence of fetal gender on various subtypes of preterm birth and on neonatal outcomes subdivided by week of gestation. Our data show that male fetuses were at increased risk of spontaneous preterm birth with intact membranes compared to a female fetus with a peak between 28 and 31 weeks (RR 1.5 for male to female; 95% CI 1.3-1.7). In addition, male fetuses were at increased risk of preterm premature rupture of membranes between 26^{+0} and 36^{+6} weeks (RR 1.2; 95 CI 1.16-1.23). We found no gender effect for medically indicated preterm birth or neonatal mortality. Furthermore, males were at significantly increased risk of composite neonatal morbidity compared to females from 29 weeks onwards (RR 1.4; 95% CI 1.2-1.5). Multivariate analyses confirmed that male fetal gender was a strong independent risk factor for preterm birth.

Strengths and Limitations

A major strength of our study is the large national dataset we were able to use for our analyses with coverage of around 96% of all pregnancies in The Netherlands over an 11-year study period. Furthermore, we subdivided preterm birth into its various clinical manifestations (spontaneous labor with intact membranes, premature rupture of membranes and medically indicated preterm birth) and examined the week-by-week male/female ratios to study gender effects on preterm birth in further detail. These analyses were combined with the neonatal outcomes by week of gestation from 25 weeks onwards. During the study period, there was a change in clinical practice regarding the management of extremely premature infants. Before 2010, infants born $<25^{0/7}$ weeks were not actively managed unless their clinical condition at birth was optimal. A national multidisciplinary guideline was implemented in 2010 by obstetricians and neonatologists to allow active management of premature infants born between $24^{0/7}$-$25^{0/7}$ weeks.(21) We do not think however that this change of management was of influence on our study results.

Using a national registry such as PRN comes with some limitations. In the registry there are obligatory and non-obligatory fields. Some useful information regarding risk factors for preterm birth is not recorded at all or in the non-obligatory fields and therefore limited recorded and not available for analysis, for example information on body mass index and smoking status. After correcting for possible and available confounders however, fetal gender remained significantly associated. Furthermore, misclassification cannot be ruled out in the registry, for example regarding premature rupture of membranes or induction of labor. In our study, we remained premature rupture of membranes classified as such, even if subsequent augmentation of labor was started for instance for signs of intrauterine infection being an inherent consequence of ruptured membranes. However, it cannot be ruled out that some of the cases with premature rupture of membranes were recorded as an induction of labor and thus resulted in an underestimation of cases with premature rupture of membranes. But it is very unlikely that this misclassification is dependent on fetal gender and influenced our results.

Interpretation
We confirmed that fetal gender is a risk factor for preterm birth, with a higher risk for male fetus than female (RR 1.18; 95% CI 1.17-1.19). Only a few other studies subdivided preterm birth in various clinical manifestations of preterm birth(9;10;18;22;23), but none studied this gender effect in a week-by-week analysis.

The relative risk we found for spontaneous preterm birth with intact membranes was comparable with earlier reported (RR 1.24 - 1.31(6;9;23)). We also found a significant increased risk on preterm premature ruptures of membranes for males as one other study(23) reported, but this was not described in other studies.(9;22) This could be explained by the fact that Harlow *et al.* only used low-risk pregnancies and comprised different ethnicities.

Regarding medically indicated preterm birth, our findings were consistent with that of other studies.(9;23) Some studies reported, like our study, that the increased risk for males is more prominent for very preterm birth (< 32 weeks).(10;18;23;24) Zeitlin *et al.* analyzed only very preterm birth (<33 weeks) and found an obvious larger effect (RR 1.42).(22) However, she studied a much smaller population and maybe suffered a power problem, as they did found a non-significant trend for males compared to females for preterm premature rupture of membranes (RR 1.13; 95% CI 0.97-1.30). Our study excels by reporting the gender effect in a week-by-week analysis from 25 weeks onwards.

At present, one can only speculate on the mechanisms for gender moderated differences in preterm birth risk. The initiation of labor is known to be associated with placental CRH production and CRH binding proteins, and inflammatory processes or interactions between these mechanisms.(25;26) Indeed increased inflammatory markers were found in male compared to female placentas.(15;27) Furthermore, differences in maternal salivary cortisol levels were observed between mother's carrying a male versus female fetus throughout pregnancy with a cross-over at 30 weeks of gestation.(28) In addition, placentas of a male fetus were found to react differently to adverse events compared to placentas of a female fetus.(27;29)

Proposals for future research
Once a pregnancy is established, obviously fetal gender cannot be changed. But, identifying fetal gender as a risk factor for preterm birth will help further research to understand its complex etiology and create awareness for clinicians in daily practice when a woman carrying a male fetus is admitted with signs of preterm labor. Especially because not only the risk for preterm birth is increased, but male infants are also more at risk for composite neonatal morbidity.

Although earlier studies were carried out in different parts of the world, only some studies reported on ethnicity within their population.(7;9;18) Schaaf *et al.* showed that African and South Asian ethnicities have increased rissk for preterm birth.(30) Future research should focus on this subject to investigate if fetal gender remains an important risk factor compared to the white European population or could even be an effect modifier for other ethnicities.

Furthermore, it would be interesting to study subsequent singleton pregnancies within the same mother and also multiple pregnancies with different combinations (male-male, male-female and female-female) to see how fetal gender further influences the risk on preterm birth. Moreover, instead of studying a single risk factor for preterm birth, it would be interesting to put further effort in combining known risk factors for preterm birth in a large cohort and developing a prediction model resulting in individualized risk assessment.[6]

In summary, we found male fetuses to be at increased risk of spontaneous preterm birth with intact membranes compared to a female fetus with a peak between 28 and 31 weeks. In addition, male fetuses were at increased risk of preterm premature rupture of membranes between 26 and 37 weeks. We found no gender effect for medically indicated preterm birth.

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