AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

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

MYRTHE J.C.S. PEELEN[1], BRENDA M. KAZEMIER[1], ANITA C.J. RAVELLI[2], CHRISTIANNE J.M. DE GROOT[3], JORIS A.M. VAN DER POST[1], BEN W.J. MOL[4], PETRA J. HAJENIUS[1] & MARJOLEIN KOK[1]

[1]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, [2]Department of Medical Informatics, Academic Medical Center, Amsterdam, [3]Department of Obstetrics and Gynecology, VU Medical Center, Amsterdam, the Netherlands, and [4]The Robinson Research Institute, School of Medicine, University of Adelaide, The South Australian Health and Medical Research Institute, Adelaide, Australia

Key words
Fetal gender, morbidity, mortality, neonatal outcome, preterm birth, sex

Correspondence
Myrthe J.C.S. Peelen, Academic Medical Center, Department of Obstetrics & Gynecology, Room H4-232, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail: m.j.peelen@amc.nl

Conflicts of interest
The authors have stated explicitly that there are no conflict of interests in connection with this article.

Please cite this article as: Peelen MJCS, Kazemier BM, Ravelli ACJ, De Groot CJM, Van Der Post JAM, Mol BWJ, Hajenius PJ, *et al*. Impact of fetal gender on the risk of preterm birth, a national cohort study. Acta Obstet Gynecol Scand 2016; 95:1034–1041.

Received: 16 January 2016
Accepted: 18 May 2016

DOI: 10.1111/aogs.12929

Abstract

Introduction. Fetal gender is associated with preterm birth; however, a proper subdivision by onset of labor and corresponding neonatal outcome by week of gestation is lacking. *Material and methods.* Data from the Netherlands Perinatal Registry (1999–2010) were used to calculate relative risk ratios for gender by week of gestation and gender-related risk on adverse neonatal outcomes using a moving average technique. White European women with an alive fetus at onset of labor were included. Adverse neonatal outcomes were defined as neonatal mortality and a composite of neonatal morbidity. Onset of labor was categorized as spontaneous onset with intact membranes, premature rupture of membranes, and induction or elective cesarean section. *Results.* The study population comprised 1 736 615 singleton deliveries (25^{+0}–42^{+6} weeks). Male fetuses were at increased risk of spontaneous preterm birth with intact membranes compared with a female fetus with a peak between 27 and 31 weeks [relative risk (RR) 1.5; 95% CI 1.4–1.6]. Male fetuses were also at increased risk of preterm premature rupture of membranes between 27 and 37 weeks (RR 1.2; 95% CI 1.16–1.23). No gender effect was seen for medically indicated preterm birth. No significant differences were seen for neonatal mortality. Males were at significantly increased risk of composite neonatal morbidity from 29 weeks onwards (RR 1.3; 95% CI 1.3–1.4). *Conclusions.* Male fetal gender is a relevant risk factor for spontaneous preterm birth, both for intact membranes and for preterm premature rupture of membranes in white European women. In addition, male infants are at increased risk of neonatal morbidity.

Abbreviations: Perined, the Netherlands Perinatal Registry; RR, relative risk ratio.

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, especially important for spontaneous preterm birth, has not yet been resolved

Key Message

This study further expands on fetal gender as a risk factor for preterm birth by showing that male fetal gender is a relevant risk factor for spontaneous preterm birth, both for intact membranes and for preterm premature rupture of membranes, but not for medically indicated preterm birth.

(2,3). Because of its high impact on perinatal mortality and morbidity (4,5), much effort has been made to examine risk factors associated with preterm birth. Despite 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).

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 for preterm birth (range of odds ratios 1.1–1.3) (7–10). Recently, these findings have been confirmed in studies from non-Western countries (11,12). These studies show that fetal gender is a historically and geographically constant factor associated with preterm birth.

In the available studies, a proper subdivision by onset of labor in case 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 with intact membranes and preterm birth preceded by preterm premature rupture of membranes. This subdivision may contribute to further unravel the etiology of preterm birth, which could also be relevant in the light of the risk of recurrent preterm birth. If gender turns out to be relevant in one of the subgroups, this could influence treatment options and hence future management of preterm birth.

Furthermore, in the previous studies on this subject 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 terms of counseling, it would be interesting to know whether a male infant born in a specific week of gestation would be at higher risk of mortality or morbidity compared with a female infant born in the same week.

In this study, we examined not only the association between fetal gender and the onset of preterm birth but also neonatal outcomes conditional on gender, both subdivided by week of gestation using a large cohort of white European women.

Material and methods

Data were derived from the Netherlands Perinatal Registry (Perined) between 1999 and 2010. The Perined database holds a validated linkage of three different national registries: the midwifery registry, the obstetrics registry and the neonatology registry of hospital admissions of newborns (13,14). The Perined registry contains prospectively obtained population-based data on pregnancies and provided care (interventions, referrals, deliveries and (re) admissions) of newborns of approximately 96% of all deliveries in The Netherlands. Data from individual caregivers are sent to this registry annually which is subjected to a number of range and consistency checks to ensure data quality. The data in the Perined registry are anonymous; therefore ethical approval was not needed for this study. The executive board of the Perined registry gave their approval for the use of their data for this study (approval number 13.63).

The study population comprised all singleton births from 25^{+0} weeks of gestation onwards of white European women with an alive fetus at the onset of labor and without congenital anomalies between 1 January 1999 and 31 December 2010. 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 antenatal fetal death and infants for whom no gender was recorded. We excluded women with other ethnicities to exclude potential confounding caused by the influence of ethnicity on preterm birth.

We obtained demographic and obstetric characteristics including maternal age, parity (categorized as nulliparous and multiparous women), socioeconomic status (categorized as 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), hypertensive disorder (defined as pregnancy-induced hypertension and/or (pre)eclampsia), onset of labor (categorized as spontaneous onset, induction of labor or elective cesarean section) and birthweight.

The initial analysis was performed for preterm birth defined as birth before 37 completed weeks of gestation. Preterm birth was subdivided into three subtypes of preterm birth: (i) spontaneous labor with intact membranes, (ii) premature rupture of membranes and (iii) 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 defined as intrapartum or neonatal mortality and neonatal morbidity. Intrapartum mortality was defined as fetal death occurring during labor, neonatal mortality was defined as death of live-born fetus within 28 days, and included both early neonatal mortality (death in the first 7 days) and late neonatal mortality (death between 7 days and 28 days of life). Composite neonatal morbidity included neonatal intensive care admission only or in combination with the diagnoses sepsis, meconium aspiration

syndrome, necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia, 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 study characteristics between male and female infants using a Student's *t*-test for the continuous values and a chi-squared test for binominal variables. The relative risk ratios (RR) for gender by week of gestation were estimated. We used a moving average technique covering 3 weeks per measurement to correct for possible fluctuations due to the small number of events, which was the case for extremely preterm birth. 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 gender remains associated with preterm birth before 37 and 34 completed weeks of gestation after correction for confounders. We corrected for hypertensive disorders, induction of labor and birthweight based on differences in population and clinical characteristics between the two groups.

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

Results

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 = 334 060; 16.1%) and with antepartum fetal mortality (n = 7582; 0.4%) and infants with no recorded gender (n = 70), the study population consisted of 1 736 615 fetuses alive at onset of labor; 892 023 male (51.4%) and 844 592 female (48.6%).

Study 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, males were more frequently induced, and their mean birthweight was higher. Females were more frequently born by an elective cesarean section.

Overall, out of 1 736 615 infants, 99 325 (5.7%) were born prematurely before 37 completed weeks; 55 247 (6.2%) males and 44 078 (5.2%) females (RR 1.19; 95% CI 1.17–1.20). 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.

The relative risk ratios for male and female infants by onset of labor and by week of gestation are presented in Figure 1(a) and in the Supplementary material (Table S1). 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 27^{+0} and 31^{+6} weeks (RR 1.5 for male to female; 95% CI 1.4–1.6). Calculated for the total

Table 1. Study characteristics.[a]

	Male infant n = 892 023		Female infant n = 844 592		
		%		%	p-value
Maternal characteristics					
Maternal age at delivery, years (SD)	30.7 (4.6)		30.7 (4.7)		0.50
Nulliparous, n	425 186	47.7	401 485	47.5	0.09
Low socioeconomic status, n	171 977	19.3	162 334	19.2	0.32
Pregnancy and delivery					
Conception					0.43
Spontaneous, n	867 334	97.2	821 380	97.3	
Artificial reproductive technology, n	24 689	2.8	23 212	2.8	
Hypertensive disorder, n	83 706	9.4	76 680	9.1	<0.0001
Onset of labour					<0.0001
Spontaneous, n	702 957	78.8	664 676	78.7	
Induction of labour, n	138 784	15.6	129 538	15.3	
Elective caesarean section, n	50 282	5.6	50 378	6.0	
Neonatal outcome					
Mean birthweight (g) (SD)	3531 (586)		3407 (553)		<0.0001

[a]Study characteristics are shown for the total population and include pregnancies that resulted in a term birth.

Table 2. Preterm births.

	Male infant *n* = 892 023		Female infant *n* = 844 592				
	n	%	*n*	%	RR	95% CI	*p* value
Preterm birth < 37 weeks	55 247	6.2	44 078	5.2	1.18	1.17–1.19	<0.0001
Spontaneous with intact membranes	33 796	3.8	25 471	3.0	1.26	1.24–1.28	<0.0001
PPROM	8902	1.0	6637	0.8	1.19	1.16–1.23	<0.0001
Medically indicated	12 549	1.4	11 970	1.4	1.00	0.98–1.02	0.98
Preterm births							
34–37 weeks	41 308	4.6	33 453	4.0	1.17	1.15–1.19	<0.0001
32–34 weeks	7081	0.8	5378	0.6	1.25	1.20–1.29	<0.0001
28–32 weeks	5337	0.6	4077	0.5	1.24	1.19–1.29	<0.0001
<28 weeks	1521	0.2	1170	0.1	1.23	1.14–1.33	<0.0001

PPROM, preterm premature rupture of membranes; RR, relative risk ratio.

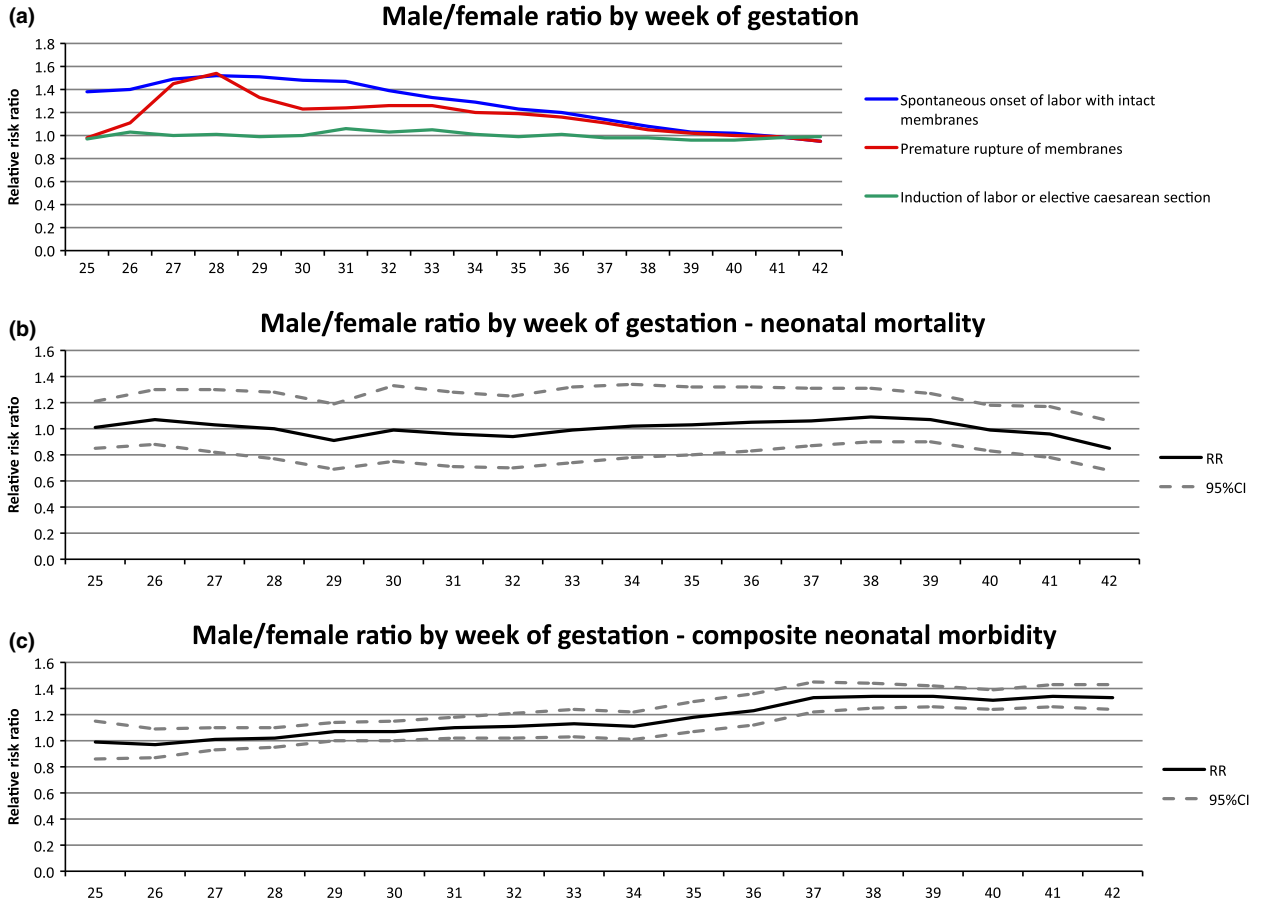

Figure 1. (a) Male/female ratio by week of gestation and onset of labor. Relative risk ratios for male infants vs. female infants are presented with a subdivision for spontaneous labor with intact membranes, premature rupture of membranes and induction of labor or elective cesarean section. (b) Male/female ratio by week of gestation for neonatal mortality. Relative risk ratios for male infants vs. female infants are presented with the 95% CI. (c) Male/female ratio by week of gestation for the composite neonatal morbidity. Relative risk ratios for male infants vs. female infants are presented with the 95% CI.

population term versus preterm birth, males were at a statistically significantly increased risk for spontaneous preterm birth with intact membranes (RR 1.26; 95% CI 1.24–1.28). Furthermore, male fetuses were at increased risk of preterm premature rupture of membranes between 27^{+0} and 36^{+6} weeks (RR 1.2; 95% CI 1.16–1.23).

In a multivariate logistic regression, with correction for hypertensive disorders, induction of labor and birthweight, male fetal gender still significantly increased the risk for preterm birth before 37 completed weeks (odds ratio 1.8; 95% CI 1.8–1.9) and before 34 weeks (odds ratio 1.9; 95% CI 1.9–2.0).

The male/female ratios for neonatal mortality and composite neonatal morbidity are graphically displayed in Figure 1(b,c) and Supplementary material (Table S2). Overall, male infants had a subtly increased risk for neonatal mortality compared with female infants (RR 1.1; 95% CI 1.1–1.2). However, when male and female infants born in the same week of gestation were compared, no significant differences were seen for neonatal mortality. Males were at significantly increased risk of composite neonatal morbidity compared with females from 29 weeks of gestation onwards with a peak at 37–38 weeks (RR 1.3; 95% CI 1.3–1.4).

Discussion

This national cohort study comprising white European women with an 11-year study period and data of 1 736 615 singleton births examined the influence of fetal gender on onset of preterm birth and neonatal outcomes subdivided by week of gestation. Our data show that male fetuses are at increased risk of spontaneous preterm birth with intact membranes and preterm premature rupture of membranes compared with a female fetus. We found no gender effect for medically indicated preterm birth or neonatal mortality. However, males were at significantly increased risk of composite neonatal morbidity compared with females from 29 weeks onwards. Multivariate analyses confirmed that male fetal gender was an independent risk factor for preterm birth.

A major strength of our study is the large national data set that 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 by onset of labor (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 associations on preterm birth in further detail. These analyses were combined with the neonatal outcomes by week of gestation from 25 weeks of gestation 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 $24^{0/7}$ and $25^{0/7}$ weeks (15). However, we do not think that this change of management influenced our study results.

Using a national registry comes with some limitations. In the registry there are obligatory and non-obligatory fields. Unfortunately, some useful information regarding risk factors for preterm birth is listed in non-obligatory fields and is therefore limited or not recorded, for example smoking status, body mass index, periodontitis and bacterial vaginosis. The obstetric history is only globally recorded, so the number of deliveries is known but the gestational age at delivery of the previous pregnancies is not known. Therefore, we were not able to include previous preterm birth in the multivariate logistic regression analysis. In addition, misclassification cannot be ruled out in the registry, for example regarding premature rupture of membranes versus induction of labor. In our study, we kept 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 so resulted in an underestimation of cases with premature rupture of membranes. It is however very unlikely that this misclassification is dependent on fetal gender and influenced our results.

We confirmed that fetal gender is a risk factor for preterm birth, with a higher risk for male fetus than female (RR 1.19; 95% CI 1.17–1.20). Only a few other studies subdivided preterm birth by onset of labor (9,10,16–18), 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 studies (RR 1.24–1.31) (6,9,18). We also found a significant increased risk for preterm premature rupture of membranes for males, like one other study (18) out of three studies reporting on this subject (9,17). However, the latter two studies did find a nonsignificant trend for males. Both studies used a much smaller population and could have suffered a power problem (9,17). Furthermore, Harlow et al. only evaluated low-risk pregnancies and comprised different ethnicities (9). Regarding medically indicated preterm birth, our findings were consistent with those of other studies (9,10,16,18).

Some studies reported, like our study, that the increased risk for males is more prominent for very preterm birth (<32 weeks) (10,16,18,19). Zeitlin et al. analyzed only very preterm birth and found an obvious larger effect (RR 1.42; 95% CI 1.21–1.66) (17). However, as mentioned earlier, they may have suffered a power problem, as they only found a trend for preterm

premature rupture of membranes (RR 1.13; 95% CI 0.97–1.30). Our study is the only study that reports on the gender effect in a week-by-week analysis from 25 weeks of gestation onwards.

At present, one can only speculate on the mechanisms for gender-moderated differences in preterm birth risk. Several hypotheses have been posed, like hormonal differences between the sexes (7,8,20), relatively higher birthweight for males (8,21), infection-related pathways (21–23) or an increased susceptibility for complications of pregnancy for women carrying a male fetus (20,24). On the other hand, conflicting results have been described regarding these hypotheses (16) and therefore the underlying mechanism still remains unclear. The initiation of labor is known to be associated with placental corticotropin-releasing hormone production and corticotropin-releasing-hormone-binding proteins, and inflammatory processes or interactions between these mechanisms (25,26). Indeed, increased inflammatory markers have been found in male placentas compared with female placentas (22,27). Furthermore, differences in maternal salivary cortisol levels were observed between mothers 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 with placentas of a female fetus (27,29).

In our study we found that more female fetuses were delivered by elective cesarean section. This raises the question whether this fact influences the improved short-term outcomes for females. Our registry holds no information on the indication of the elective cesarean section. Absolute and relative indications for elective cesarean section are known, such as placenta previa, uterine fibroids, breech position, and cesarean section on request. For pregnancies complicated by a placenta previa, there is no proven increased prevalence for either males or females (30–32). For uterine fibroids there is no gender predominance known and for cesarean sections on request it is highly unlikely that gender plays a role. However, for breech position it is known that female fetuses have an increased risk to be in breech position (33,34). In The Netherlands, around 80% of women with a baby in breech position choose to have an elective cesarean section since the Term Breech Trial (35).

The reason for male infants to suffer more neonatal morbidity has been the subject of earlier research. Male fetal gender has been linked to higher rates of fetal distress, respiratory distress syndrome and low Apgar scores (36,37). The underlying mechanisms still remain unclear, although interesting suggestions have been made linking differences between placentas of males and females with adverse pregnancy outcome (27,29). Whether the larger size of male infants plays a role in the increased risk of neonatal morbidity will be the subject of our further research.

Identifying fetal gender as a risk factor for preterm birth will help further research to understand its complex etiology. In daily practice, clinicians should be more aware if a woman carrying a male fetus is admitted for preterm labor. Although the etiology of preterm birth is multifactorial, male gender has a consistent modest association with preterm birth. This additional increased risk could be decisive in women with other risk factors for preterm birth and could result in a clinical difference, especially keeping in mind that male infants are also more at risk for composite neonatal morbidity. However, change in clinical management based on fetal gender would be too early in our opinion, as fetal gender is currently not incorporated in, for example, clinical prediction models and is therefore of no clinical consequence.

Although earlier studies were carried out in different parts of the world, only some studies reported on ethnicity within their population (7,9,16). Schaaf et al. showed that African and South Asian ethnicities have an increased risk for preterm birth (38). Future research should focus on this subject to investigate if fetal gender remains an important risk factor compared with the white European population or could even be an effect modifier for other ethnicities. Furthermore, it would be interesting to study 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, further effort can be put into 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 in white European women to be at increased risk of spontaneous preterm birth with intact membranes compared with a female fetus with a peak between 27 and 31 weeks. In addition, male fetuses were at increased risk of preterm premature rupture of membranes between 27 and 37 weeks. We found no gender effect for medically indicated preterm birth.

Acknowledgments

We thank all Dutch midwives, obstetricians, neonatologists and other perinatal healthcare providers for the registration of perinatal information and the Foundation of The Netherlands Perinatal Registry (www.perinatreg.nl) for permission to use the registry data.

Funding

None.

References

1. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Howson CP, Kinney MV, Lawn JE (eds). Geneva: World Health Organization, 2012.
2. Gotsch F, Gotsch F, Romero R, Erez O, Vaisbuch E, Kusanovic JP, et al. The preterm parturition syndrome and its implications for understanding the biology, risk assessment, diagnosis, treatment and prevention of preterm birth. J Matern Fetal Neonatal Med. 2009;22(Suppl. 2): 5–23.
3. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG. 2006;113(Suppl. 3):17–42.
4. Slattery MM, Morrison JJ. Preterm delivery. Lancet. 2002;360:1489–97.
5. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med. 2004;9:429–35.
6. Schaaf JM, Ravelli AC, Mol BW, Abu-Hanna A. Development of a prognostic model for predicting spontaneous singleton preterm birth. Eur J Obstet Gynecol Reprod Biol. 2012;164:150–5.
7. Cooperstock M, Campbell J. Excess males in preterm birth: interactions with gestational age, race, and multiple birth. Obstet Gynecol. 1996;88:189–93.
8. Hall MH, Carr-Hill R. Impact of sex ratio on onset and management of labour. Br Med J (Clin Res Ed). 1982;285:401–3.
9. Harlow BL, Frigoletto FD, Cramer DW, Evans JK, LeFevre ML, Bain RP, et al. Determinants of preterm delivery in low-risk pregnancies. The RADIUS Study Group. J Clin Epidemiol. 1996;49:441–8.
10. Zeitlin J, Saurel-Cubizolles MJ, De Mouzon J, Rivera L, Ancel PY, Blondel B, et al. Fetal sex and preterm birth: are males at greater risk? Hum Reprod. 2002;17:2762–8.
11. Khalil MM, Alzahra E. Fetal gender and pregnancy outcomes in Libya: a retrospective study. Libyan J Med. 2013;8. DOI: 10.3402/ljm.v8i0.20008.
12. Lao TT, Sahota DS, Suen SS, Law LW. The impact of fetal gender on preterm birth in a southern Chinese population. J Matern Fetal Neonatal Med. 2011;24:1440–3.
13. Meray N, Reitsma JB, Ravelli AC, Bonsel GJ. Probabilistic record linkage is a valid and transparent tool to combine databases without a patient identification number. J Clin Epidemiol. 2007;60:883–91.
14. Tromp M, Ravelli AC, Meray N, Reitsma JB, Bonsel GJ. An efficient validation method of probabilistic record linkage including readmissions and twins. Methods Inf Med. 2008;47:356–63.
15. Dutch Society of Obstetrics and Gynaecology [NVOG]. Practice guideline 'Perinatal management of extremely preterm delivery'. Available online at: www.nvog.nl//Sites/Files/0000001346_Richtlijn Perinataal beleid bij extreme vroeggeboorte.pdf (accessed July 16, 2013).
16. Brettell R, Yeh PS, Impey LW. Examination of the association between male gender and preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2008;141:123–6.
17. Zeitlin J, Ancel PY, Larroque B, Kaminski M. Fetal sex and indicated very preterm birth: results of the EPIPAGE study. Am J Obstet Gynecol. 2004;190:1322–5.
18. Melamed N, Yogev Y, Glezerman M. Fetal gender and pregnancy outcome. J Matern Fetal Neonatal Med. 2010;23:338–44.
19. Vatten LJ, Skjaerven R. Offspring sex and pregnancy outcome by length of gestation. Early Hum Dev. 2004;76:47–54.
20. MacGillivray I, Davey DA. The influence of fetal sex on rupture of the membranes and preterm labor. Am J Obstet Gynecol. 1985;153:814–5.
21. McGregor JA, Leff M, Orleans M, Baron A. Fetal gender differences in preterm birth: findings in a North American cohort. Am J Perinatol. 1992;9:43–8.
22. Ghidini A, Salafia CM. Gender differences of placental dysfunction in severe prematurity. BJOG. 2005;112:140–4.
23. Goldenberg RL, Andrews WW, Faye-Petersen OM, Goepfert AR, Cliver SP, Hauth JC. The Alabama Preterm Birth Study: intrauterine infection and placental histologic findings in preterm births of males and females less than 32 weeks. Am J Obstet Gynecol. 2006;195:1533–7.
24. Campbell DM, MacGillivray I, Carr-Hill R, Samphier M. Fetal sex and pre-eclampsia in primigravidae. Br J Obstet Gynaecol. 1983;90:26–7.
25. Kim SH, Shim SH, Sung SR, Lee KA, Shim JY, Cha DH, et al. Gene expression analysis of the microdissected trophoblast layer of human placenta after the spontaneous onset of labor. PLoS ONE. 2013;8:e77648.
26. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med. 2010;362:529–35.
27. Clifton VL. Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival. Placenta. 2010;31(Suppl):S33–9.
28. DiPietro JA, Costigan KA, Kivlighan KT, Chen P, Laudenslager ML. Maternal salivary cortisol differs by fetal sex during the second half of pregnancy. Psychoneuroendocrinology. 2011;36:588–91.
29. Challis J, Newnham J, Petraglia F, Yeganegi M, Bocking A. Fetal sex and preterm birth. Placenta. 2013;34:95–9.
30. Walfisch A, Sheiner E. Placenta previa and immediate outcome of the term offspring. Arch Gynecol Obstet. 2016; 293:1365. DOI: 10.1007/s00404-016-4044-1
31. Demissie K, Breckenridge MB, Joseph L, Rhoads GG. Placenta previa: preponderance of male sex at birth. Am J Epidemiol. 1999;149:824–30.

32. D'Souza D. Fetal growth and sex related to placenta praevia. J Obstet Gynaecol. 2000;20:382–4.
33. Zsirai L, Csakany GM, Vargha P, Fulop V, Tabak AG. Breech presentation: its predictors and consequences. An analysis of the Hungarian Tauffer Obstetric Database (1996–2011). Acta Obstet Gynecol Scand. 2016;95:347–54.
34. Fruscalzo A, Londero AP, Salvador S, Bertozzi S, Biasioli A, Della Martina M, et al. New and old predictive factors for breech presentation: our experience in 14 433 singleton pregnancies and a literature review. J Matern Fetal Neonatal Med. 2014;27:167–72.
35. Molkenboer JF, Bouckaert PX, Roumen FJ. Recent trends in breech delivery in the Netherlands. BJOG. 2003;110:948–51.
36. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med. 2007;4:19–30.
37. Bekedam DJ, Engelsbel S, Mol BW, Buitendijk SE, van der Pal-de Bruin KM. Male predominance in fetal distress during labor. Am J Obstet Gynecol 2002;187:1605–7.
38. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Ethnic disparities in the risk of adverse neonatal outcome after spontaneous preterm birth. Acta Obstet Gynecol Scand. 2012;91:1402–8.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Male/female ratio by onset of labour and weeks of gestation. Male/female ratios were calculated using a moving average technique covering 3 weeks per measurement. Neonates born in a specific week were the numerator and the remaining pregnant women in time were the denominator.

Table S2. Male/female ratio for neonatal outcomes by week of gestation.