Does Fetal Sex Influence the Risk of Preterm Delivery in Dichorionic Twin Pregnancies After Spontaneous Conception?

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Objective: The incidence of preterm delivery has been increasing, and our aim was to estimate the influence of fetal sex on the risk of preterm delivery in dichorionic twins after spontaneous conception. *Methods:* 125 spontaneously conceived dichorionic twin gestations, with viable fetuses, born after 24 weeks and delivered spontaneously before 37 weeks, were enrolled. The impact of fetal sex, previous preterm delivery, maternal age, body-mass-index, smoking, and parity on gestational age at birth were evaluated. *Results:* Despite similar baseline characteristics in all three groups, women with one or two male fetuses delivered significantly more often before 34 weeks than patients with two female fetuses, 48% (23/48) and 43% (19/44) vs 21% (7/33), $p = .04$. Regression analyses, including fetal sex, maternal age, maternal body-mass-index, smoking, previous preterm delivery and parity, revealed that only fetal sex was significantly associated with spontaneous preterm delivery ($p = .03$). *Conclusion:* Fetal sex appears to be a risk factor for preterm delivery in spontaneously conceived dichorionic twin gestations. Twin pregnancies with one or two male fetuses seem to be at higher risk for spontaneous preterm delivery than those with only females.

Keywords: fetal sex, preterm birth, spontaneous conception, chorionicity, twin pregnancy

Despite improvements in medical care, the incidence of preterm delivery, defined as birth before 37 weeks of pregnancy, has increased (Alexander & Slay, 2002; Goldenberg, 2002; Moutquin, 2003; Slattery & Morrison, 2002; Roberts et al., 2002). Preterm delivery is still the leading cause of perinatal mortality and morbidity in industrialized countries, accounting for 28% of neonatal mortality worldwide (Guyer et al., 1997; Menon, 2008). Nearly 50% of all children born before 26 complete weeks of gestation are severely disabled (Wood et al., 2000).

Though the pathophysiology of preterm delivery remains to be elucidated, data from animal experiments indicate that fetal gender could play a role in the etiology of preterm delivery (Challis et al., 2000). Epidemiological studies in humans appear to affirm these observations, reporting a higher rate of male fetuses among preterm deliveries (Astolfi et al., 1999; Zeitlin et al., 2002). Brettell et al., for instance, report that male singletons are more likely to deliver preterm when compared to females, particularly because of higher incidence of preterm labor and premature preterm rupture of membranes (PPROM) (Brettell et al., 2008). While some authors have attributed the higher risk of preterm delivery in male fetuses to higher weights of males at lower gestational ages compared to females, others have suggested possible immunological causes (Di Renzo et al., 2007; Gleicher, 2008; McGregor et al., 1992).

What causes labor is still, in principle, unknown (Muglia & Katz, 2010). Among many possible suggestions, Gleicher recently suggested that labor may be the consequence of a programmed, immunologically induced, graft-versus-host disease (GVHD) — like process, in which the fetal semi-allograft, after a period of pre-programmed pregnancy duration — that is, tolerance — is finally rejected, as previously reported (Gleicher, 2008). If one, indeed, assumes such an immunologically driven process of allograft tolerance during *normal pregnancy* and its termination with the onset of labor at term, the higher Y-chromosome-associated antigenicity of male pregnancies should lead to a stronger immune tolerance of the maternal immune system and, consequently, to a higher proportion of post-term pregnancies (Gleicher,

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2008; Piper et al., 2007; Vacchio & Hodes, 2005; Weghofer et al., 2009).

The better the immune tolerance of the fetal semi-allograft, the more significant will be any subsequent disturbance in normal immune tolerance on pregnancy outcome. The reported higher incidence of preterm births in male infants before 32 weeks, previously associated with specific placental lesions, has, for example, been suggested to be the consequence of an altered maternal immune response against the invading trophoblast (Ghidini & Salafia, 2005).

In multiple pregnancies, due to the increased allogenic antigen loads, immunological mechanisms should be even more apparent. The mother's immune system of allogen tolerance may, therefore, be particularly prone to disruptions in twin gestations and, consequently, cause premature labor and/or premature preterm rupture of membranes. In order to evaluate such a potential immune-mediated impact of fetal sex on preterm delivery pregnancies, we, in this study, investigated a cohort of patients with prematurely delivered twins after spontaneous labor and/or pPROM.

Materials and Methods

Over a period of 6 years, 775 twin gestations were delivered at the Department of Obstetrics and fetomaternal Medicine of the Medical University of Vienna, a tertiary care center serving high-risk pregnancies with different pregnancy-associated complications. Of those, only dichorionic (DC) twin pregnancies with viable fetuses (born after 24 weeks of gestation) that were delivered preterm (< 37 weeks), due to preterm onset of labor and/or rupture of membranes, were included in the study. The study was approved by the local research ethics committee.

To ensure maximal homogeneity of the study population, twin pregnancies conceived through assisted reproduction, preterm deliveries due to other than spontaneous onset of labor and preterm rupture of membranes (i.e., preeclampsia, reverse flow of the umbilical artery), pregnancies after fetal reduction, and pregnancies with fetal malformations, as well as monochorionic twin gestations, were excluded.

There were 23 twin pregnancies with unknown chorionicity, 178 monochorionic twins, three pregnancies after fetal reduction, and one case of conjoined twins that were excluded. Of the 582 remaining dichorionic twin pregnancies, we excluded 62 patients with an unknown mode of conception and 146 patients after assisted reproduction. Of the remaining 374 dichorionic twin pregnancies after spontaneous conception, we excluded those who delivered after 37 weeks of gestation (138 patients). Furthermore, we excluded 99 patients who were delivered preterm due to causes other than spontaneous onset of labor and preterm rupture of membranes (i.e., preeclampsia, reverse flow of the umbilical artery, IUGR, fetal malformations, questionable CTG pattern, and intrauterine fetal death).

Finally, 125 Caucasian women with DC twin gestations after spontaneous conception, who underwent prenatal care and delivery from 2003 to 2008, were included in the study. Gestational age was determined according to menstrual history and, if necessary, corrected by first-trimester measurement of the crown-rump length of the bigger twin. Chorionicity was determined sonographically in the first trimester in all study patients. Patients who had preterm rupture of membranes between 34 and 37 weeks of gestation were delivered shortly after confirmation of rupture. Patients who had a rupture of membranes before 34 weeks and who had no signs of infection were treated with tocolytics until fetal lung maturation was achieved.

The study cohort was evaluated for the impact of fetal sex on gestational age at birth, and included the following parameters: two male fetuses (M/M); twins of the opposite sex (F/M) versus two female fetuses (F/F); previous preterm delivery; maternal age; body-mass-index; smoking habits; and parity.

Data analyses of pregnancy- and delivery-related maternal and neonatal outcome data were based on retrospective chart reviews and computer-generated databases at the Department of Obstetrics and Gynecology at the Medical University Vienna. In order to exclude twin pregnancies after assisted reproduction, data linkage was performed with the computer-generated database at the IVF-Fonds.

Assuming the risk of preterm delivery before 34 weeks in twin pregnancies with male fetuses is double that of any other combination of twin fetuses, we calculated a sample size of 116 patients at a p-value of 0.05 and a power of 80 percent.

Statistical analyses were performed with SPSS software (version 15.0; SPSS, Chicago, IL). Normally distributed variables are summarized as means (± standard deviation), not as medians (minimum and maximum), and categorical data are expressed as percentages. Linear regression was used to identify weight discrepancy between male and female newborns. Logistic regression analysis was used to identify independent predictors of preterm delivery. For the logistic regression analysis, backward selection with a likelihood ratio test was used. The goodness-of-fit quality of the model was assessed using the Hosmer and Lemeshow test. Independent variables entered into the regression models were fetal sex, maternal age, maternal body-mass-index, smoking habits, previous preterm delivery, and parity. P values of < .05 were considered significant.

Results

Patient characteristics are shown in Table 1. There were 35.2% (44/125) patients who had twin gestations with two male fetuses (M/M), 26.4% (33/125) patients had two female fetuses (F/F), and 38.4% (48/125) carried twins of the opposite sex (F/M). Median gestational age at birth was 34.2 weeks for F/M, 34.3 weeks for M/M, and 35.1 weeks for F/F. Six

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women (4.8%) delivered before 28 weeks of gestation, 17 (13.6%) before 30 weeks, 28 (22.4%) before 32 weeks, and 42 (33.6%) before 34 weeks. Maternal age, body-mass-index, smoking habits, and parity did not differ significantly between the groups.

In our group, 41% (51/125) of all patients had preterm rupture of membranes. Of the pregnancies in our study population, 14% (18/125) had preterm premature rupture of membranes (PPROM) before 34 weeks of gestation. In the group of M/M fetuses, 16% (7/44) patients had PPROM, in the group of F/M fetuses, 15% (7/48) had PPROM, and, in the group of F/F fetuses, 12% (4/33) of the pregnancies were complicated by PPROM. Fetal outcome is shown in Table 2. Male newborns had a mean higher birth weight of 168 grams compared to females ($p < .05$). Pregnant women with one or two male fetuses delivered significantly more often before 34 weeks of gestation than patients with two female fetuses, 48% (23/48) and 43% (19/44) vs, 21% (7/33), $p = .04$. Regression analyses, including fetal sex, maternal age, maternal body-mass-index, smoking habits, previous preterm delivery, and parity, revealed that only fetal sex was significantly associated with spontaneous preterm delivery (see Table 3).

Discussion

Our data support the hypothesis that fetal sex might be an independent risk factor for spontaneous preterm delivery in dichorionic twins after spontaneous conception. Two male twins and opposite-sex twins present with a higher risk for preterm birth than twin gestations with exclusively female fetuses.

These results are only partly in accordance with Tan et al., who reported the highest rate of preterm birth in twins with exclusively male fetuses, followed by intermediate prematurity risk in F/F pregnancies and the lowest preterm birth rates in opposite-sex twins (Tan et al., 2004). These authors included monochorionic and dichorionic twin pregnancies. Monochorionic twins are usually same-sex twins, while dichorionic might be either of the same or the opposite sex. Monochorionicity is, however, associated with significantly higher risks for preterm birth than dichorionicity. One can, therefore, assume that opposite sex-twins would have presented with a higher prematurity risk compared to same sex twins, if only dichorionic twins had been considered for analysis, as demonstrated by Cooperstock et al. (Cooperstock & Campbell, 1996; Cooperstock & Bakewell, 1998).

Table 1

Patient Characteristics of Women with Prematurely Delivered (24–37 weeks of gestation) Dichorionic Twin Gestations After Spontaneous Conception

	All patients ($n = 125$)	M/M* ($n = 44$)	M/F* ($n = 48$)	F/F* ($n = 33$)
Maternal age (years [mean ± SD])	29.5 ± 5.2	28.7 ± 5.0	30.7 ± 5.5	28.7 ± 4.8
BMI (kg/m²)[median, range]	22.6 (15.0;35.5)	22.1(15.0–30.5)	23.4 (17.9;35.5)	22.4 (17.6;30.1)
Smoking (%,n)	14.4 (18/125)	18.1 (8/44)	12.5 (6/48)	12.1 (4/33)
Primiparae (%,n)	28.0 (35/125)	29.5 (13/44)	35.4 (17/48)	15.2 (5/33)
Multiparae (%,n)	72.0 (90/125)	70.5 (31/44)	64.6 (31/48)	84.4 (28/33)
Previous preterm delivery (%,n)	3.2 (4/125)	2.3 (1/44)	4.1 (2/48)	3.0 (1/33)

Note: *There are no statistically significant differences between groups. M/M: patients with 2 male fetuses, M/F: patients with 1 male and 1 female fetus, F/F: patients with 2 female fetuses, SD: standard deviation, BMI: Body-Mass-Index.

Table 2

Fetal Outcome of Women With Prematurely Delivered (24–37 Weeks of Gestation) Dichorionic Twin Gestations After Spontaneous Conception

	All patients ($n = 125$)	M/M* ($n = 44$)	M/F* ($n = 48$)	F/F* ($n = 33$)
Birth weight twin I (gram) [mean, SD]	1954 (567)	1996 (588)	1891 (551)	1986 (571)
Birth weight twin II (gram) [mean, SD]	1935 (603)	2000 (570)	1832 (648)	1997 (574)
Weight discrepancy (gram) [median, range]	9, (0;59)	11 (0;59)	13 (0;57)	8 (2;29)
Arterial pH value twin I [median, range]	7.28, (6.93;7.47)	7.29 (7.05;7.45)	7.28 (6.93;7.47)	7.28 (7.11–7.38)
Arterial pH value twin II [median, range]	7.27 (6.89;7.43)	7.27 (6.89;7.43)	7.26 (7.10;7.37)	7.28 (6.89;7.40)
APGAR 5 minutes twin I [median, range]	9.5 (0;10)	10 (0;10)	9 (7;10)	10 (5;10)
APGAR 5 minutes twin II [median, range]	9.0 (6;10)	9 (7;10)	9 (7;10)	9 (6;10)
Transfer to the NICU twin I (%,n)	50 (63/125)	45 (20/44)	50 (24/48)	57 (19/33)
Transfer to the NICU twin II (%,n)	46.4 (58/125)	43 (19/44)	44 (21/48)	18/33)

Note: *There are no statistically significant differences between groups. M/M: patients with 2 male fetuses, M/F: patients with 1 male and 1 female fetus, F/F: patients with 2 female fetuses, SD: standard deviation, NICU: Neonatal intensive care unit.

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Table 3

Predictors of Spontaneous Preterm Delivery Before 34 Weeks in Women with Prematurely Delivered (24–37) Weeks of Gestation) Dichorionic Twin Gestations After Spontaneous Conception

Model	OR	CI	*p* value
1 (Constant)	2.44		0.69
Age	0.95	0.85–1.07	0.41
Parity	0.89	0.53–1.48	0.65
Body-mass-index	0.99	0.98–1.01	0.13
Smoking	1.24	0.34–4.54	0.75
Previous preterm delivery	4.02	0.24–66.14	0.33
Fetal sex			0.03
Fetal sex (F/F versus M/M)	10.47	1.18–93.19	0.03
Fetal sex (F/F versus F/M)	19.46	2.14–176.82	0.008
2 (Constant)	2.57		0.68
Age	0.95	0.85–1.07	0.39
Parity	0.90	0.54–1.49	0.68
Body-mass-index	0.99	0.98–1.00	0.14
Previous preterm delivery	4.05	0.25–65.5	0.32
Fetal sex			0.03
Fetal sex (F/F versus M/M)	10.72	1.21–94.79	0.03
Fetal sex (F/F versus F/M)	19.49	2.15–176.77	0.008
3 (Constant)	2.50		0.69
Age	0.95	0.85–1.06	0.34
Body-mass-index	0.99	0.98–1.00	0.13
Previous preterm delivery	3.42	0.34–49.40	0.37
Fetal sex			0.02
Fetal sex (F/F versus M/M)	11.25	1.29–98.73	0.02
Fetal sex (F/F versus F/M)	20.41	2.27–183.90	0.007
4 (Constant)	2.18		0.73
Age	0.96	0.86–1.07	0.43
Body-mass-index	0.99	0.97–1.00	0.10
Fetal sex			0.02
Fetal sex (F/F versus M/M)	11.82	1.36–103.12	0.02
Fetal sex (F/F versus F/M)	22.10	2.47–197.59	0.006
5 (Constant)	0.76		0.88
Body-mass-index	0.99	0.97–1.00	0.06
Fetal sex			0.02
Fetal sex (F/F versus M/M)	12.02	1.38–104.72	0.02
Fetal sex (F/F versus F/M)	20.65	2.33–182.83	0.007

Note: Dependent variable: Spontaneous preterm delivery before 34 weeks; OR: odds ratio; CI: confidence interval; F/F: 2 female fetuses; M/M: 2 male fetuses; F/M: One female and one male fetus. Logistic regression analysis with backward selection with a likelihood ratio.

In view of the hypothesis that the onset of labor may be triggered by immunological mechanisms, comparable to acute GVHD-like processes, preterm labor would present the premature termination of maternal immune tolerance of the fetal (semi)allograft (Gleicher, 2008).

In accord with this consideration, it is understandable that recipients of organ transplants who receive lifelong immune suppression to preserve allograft tolerance are at increased risk for preterm delivery (Mastrobattista & Gomez-Lobo, 2008). The literature suggests that maternal immune activation in pregnancy is in response to the HY protein, encoded by the Y chromosome (Piper et al., 2007). Since it is known from organ transplant experiences that allograft tolerance can fail, leading to GVHD and rejection processes, increased initial activation of the maternal immune tolerance, due to the presence of a male fetus, would be expected to be more vulnerable to malfunctions of tolerance, and, therefore, more vulnerable to preterm birth (Toubai et al., 2008; Weghofer et al., 2009).

Confirming a potential immunological etiology for early labor, other pregnancy-related complications, which have been suggested to be based on abnormal immunological allograft tolerance of the fetus such as preeclampsia, also support such a hypothesis (Gleicher, 2007). For example, a higher incidence of preeclampsia was reported in male fetuses compared with females in very preterm births (gestational age at birth below 32 weeks), but the risk for preeclampsia was reported to be, overall, lower for the male gender (Elsmén et al., 2006).

It has also been hypothesized that the higher incidence of preterm birth for male fetuses may be linked to the relatively greater weight at lower gestational age of male fetuses compared to females (Di Renzo et al., 2007) We, indeed, have consistently found a significant higher birth weight in male newborns compared with females.

We have evaluated other, different risk factors that are known to be associated with preterm delivery,

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such as smoking, parity and BMI. Neither of these risk factors appeared to have a significant influence on preterm birth in our study. This might be due to the fact that our study population included mainly non-smoking women of normal weight. Parity has been reported to be associated with preterm labor (Erez et al., 2008).

In our study, women with twin pregnancies with one or two male fetuses were more often Primiparae than those with two female fetuses, but this difference was not statistically significant.

Patients with previous preterm delivery had a higher risk for delivery before 34 weeks, although not reaching statistically significance (Robinson & Norwitz, 2010). For the given proportions of preterm deliveries before 34 weeks, we have calculated a sample size of 300 patients to show a significant influence of a previous preterm delivery.

The major strength of this study is its homogeneity of the study population, since the study focused on dichorionic twin pregnancies after spontaneous conception with spontaneous preterm delivery in Caucasian women. All women underwent close prenatal monitoring at a high-risk maternity unit and were delivered by highly experienced obstetricians, thus eliminating, to a large degree, iatrogenic, genetic, and/or social factors in explaining our findings.

In conclusion, our data support fetal sex as an independent risk factor for preterm birth in dichorionic twin pregnancies after spontaneous conception.

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