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Review Article

IS FETAL SEX ASSOCIATED WITH ADVERSE MATERNAL OUTCOMES IN TWIN PREGNANCY?

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A B S T R A C T

Aim: to estimate the relationship between fetal sex pairing on the risk of adverse maternal outcomes in twin gestation.
Methods: This study aimed at a retrospective analysis of all twin deliveries at British Columbia during a period of 10 years. This population-based study included 6,321 multiple-fetal gestations. The incidence of adverse maternal outcomes was described between three groups of fetal sex pairing: Male-male (2101 pairs, n=4,202), female-female (2053 pairs, n=4,106) and male-female (2,167 pairs, n=4,334) pairs. Regression analysis was used to predict the role of fetal gender on 16 adverse maternal outcomes.
Results: Association analysis suggest that length of stay in hospital, proteinuria, pregnancy induced hypertension, preeclampsia, antepartum haemorrhage, preterm birth, premature rupture of membrane and cesarean section were associated with sex pairing. Adjusting for confounding variables, multiple regression analysis substantiated these associations for postpartum length of stay longer than 3 days, proteinuria, pregnancy induced hypertension, preeclampsia and cesarean section.
Conclusions: Sex determination by ultrasound screening contributes to prediction of adverse maternal outcome and can improve clinical management of adverse maternal outcomes.

INTRODUCTION

The relationship between fetal sex and pregnancy outcomes was first described by Hall and Carr-Hill over 30 years ago in singleton pregnancies.[1] Evidence points towards an adverse effect of a male fetus on the outcome of pregnancy in terms of higher rates of eclampsia,[2]preeclampsia,[3] gestational diabetes,[4] and premature rupture of membrane.[5]

The literature regarding adverse maternal outcomes in relation to fetal sex in twin pregnancy is scarce. The available literature has several limitations and mostly compares outcomes of singleton pregnancies with those of twin pregnancies.[4,6] An older population-based study[7] obtaining data from the Danish National Birth Registry from 1980 to 1996 studied the association between sex discordance and maternal outcomes. Considering singleton healthy pregnancies with males as the reference group (n=36674), twin pregnancies had higher risks of hyperemesis: female-female twins (2.37, 95%CI 1.77-3.17), male-female twins (1.83, 95%CI 1.83-3.35) and male-male twins (1.75, 95%CI 1.13-1.26). The data suggested that the presence of at least one female in the twin pair increased the risk of hyperemesis.

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The risk of preeclampsia was also significantly associated with sex discordance: male-male twins (2.53, 95%CI 2.14-2.99), female-female twin pairs (2.47, 95%CI 2.09-2.92) and male-female twin pairs (2.23, 95%CI 1.89-2.68). Singleton male fetus is not a suitable reference category for comparing maternal outcomes among twin gestations.

Similarly, another study found that rates of both gestational hypertension and preeclampsia were significantly higher among women with twin gestations than among those with singleton gestations (2.04, 95%CI 1.60-2.59 and 2.62, 95%CI 2.03-3.38, respectively).[8] The study population consisted of healthy women with either singleton (n=2946) or twin gestations (n = 684) who were enrolled in two separate multicenter trials of low-dose aspirin for prevention of preeclampsia. Comparing male-male versus female-female twins within sex concordant twins showed a significantly higher risk of preeclampsia among mothers carrying female-female twins (7.6% vs. 3.6%, p=0.0005). Pre-existing hypertension was not taken into consideration as a potential confounder.

A Japanese population-based study[9] also found that the incidence of preeclamptic mothers with a female fetus was significantly higher than those with a male fetus (3.8% vs. 3.2%. $p<0.0001$) in singleton pregnancies. However, among sex-concordant twins, comparing male-male with female-female twins, a significantly higher risk of preeclampsia was

found among mothers carrying male-male twins (7.6% vs. 3.6%, p=0.0005). Potential confounders such as chronic hypertension were not taken into consideration.

No study to date has comprehensively assessed potential confounding factors such as a history of chronic hypertension, diabetes mellitus, number of antenatal visits, and maternal age. Furthermore, the role of fetal sex relative to maternal outcomes in several combinations of sex pairing has not been investigated. Our objective was to estimate the association between fetal sex pairing and adverse maternal outcomes in twin gestation.

METHODS

We conducted a population-based retrospective cohort study of 6321 mothers and their twin gestations delivered in British Columbia for a 10-year period (2000-2010).[10]

The study variables included fetal sex pairing as the explanatory variable and eleven maternal outcomes as dependent variables: Antepartum, postpartum and total length of stay in hospital, proteinuria, Pregnancy induced hypertension (PIH), preeclampsia, antepartum haemorrhage < 20 weeks, antepartum haemorrhage ≥20 weeks, gestational diabetes, abnormal glucose factor in pregnancy, premature rupture of membrane, and prolonged rupture of membrane. We did not include in our analysis mothers who were re-admitted to the same or any other hospital within 30 days of discharge because such patients are likely to represent unusual cases.

We further excluded twins with conditions such as congenital anomalies, twin to twin transfusion syndrome (TTTs), birth weight less than 500 grams, and those who have had reduction procedures, to eliminate the potential interaction between sex pairing and growth discordance and to have consistency throughout our analytical approach. We also excluded cases with previous cesarean section.

A subgroup of women delivered in BC Children and Women (C&W) Hospital with pathology data were analysed separately.

Stepwise multiple regression analysis was employed to adjust for covariates and confounding variables based on the bivariate analysis. Binary adverse maternal outcomes were modeled using logistic GEE regression. Adjusted odds ratios for the final models (and 95% confidence interval [CI]) were then reported.

RESULTS

Of 13330 newborn twins, 14 twins were listed with unknown sex. These records were deleted from the study sample, leaving 13316 records of twins. After exclusion of cases described above, the final analytical data set included 6321 mothers (of 12642 individual twins) for analysis. Three groups of fetal sex pairing (male-male [n=2101], female-female [(n=2053] and male-female [n=2167] pairs) were compared for maternal characteristics and adverse maternal outcomes.

Effect of fetal sex pairing on maternal characteristics

We examined the maternal characteristics in relation to sex pairing (Table 1). Gestational age, maternal age, parity, years in school, maternal smoking habit and BMI were associated with fetal sex pairing. Female-male pairs had the longest gestational age. Mothers of sex-discordant pairs (female-male) were the oldest and had the highest BMI. Additionally, the frequency of primiparous gestations was highest amongst gestations carrying female-male pairs which is 5% higher than gestational age in mothers with male-male twin pairs. We did not find any association between any of the other maternal parameters and fetal sex.

Table 2 shows the frequency of adverse maternal outcomes in gestations carrying male-male, female-female and male-female twin pairs. We compared the three sex-pairing groups in terms of adverse maternal outcomes and found a significant association between fetal sex and the following parameters: antepartum and postpartum length of stay, proteinuria, PIH, use of antihypertensive medication, antepartum hemorrhage, preterm birth, premature rupture of membrane and cesarean section.

Total length of stay during the postpartum period was found to be statistically longer for female-female twins compared with male-male twins (4.10 days vs. 3.89 days, p=0.01), although clinically it is not significant. Proteinuria (5.3% vs. 3.8%, p=0.01), PIH (15.1% vs. 13.7%, p=0.05), preeclampsia (2.6% vs. 2.0%, p=0.05), preterm birth (62.4% vs. 59.7%), and cesarean section (67.3% vs. 64.4%) were more frequent in mothers with female-female gestations compared to mothers with male-male gestation, while frequency of premature rupture of membrane (76.8% vs. 79.6%, p=0.026) was higher amongst mothers with male-male twin pairs. We found a longer total length of stay in hospital for mothers carrying male-male twins than those carrying male-female twins (6.29 days vs. 5.94 days, p=0.03). This increase relates to antepartum stay rather than postpartum stay because the same finding was attributable to antepartum length of stay (p=0.01). Length of mother's stay in hospital was longer in mothers with female-female gestations compared to male-female gestations (6.31 days vs. 5.94 days, p=0.03). None of these numbers are clinically significant.

Mothers who were pregnant with male-female twins had a higher frequency of proteinuria (5.6% vs. 3.8%, p=0.05), PIH (16.2% vs. 13.7%, p=0.05), and abnormal glucose factor (2.8% vs. 2.0%, p=0.02) compared to mothers who were pregnant with male-male twins. The incidence of antepartum hemorrhage was higher in male-female gestations (2.9% vs. 2.1%, p=0.01) compared to the female-female gestations. Similarly, the frequency of premature rupture of membrane was significantly higher in male-female twins compared with female-female twins (79.2% vs. 76.8%, p=0.05).

Regression analysis

Table 3 shows regression analyses of regression analysis comparing maternal outcomes among twin pairs with different sex pairings. Female-female twins were considered as the reference category. We categorized length of stay to more or less than 3days stay in hospital. Compared with the reference category, the adjusted odds of a maternal stay longer than 3 days during the postpartum period for mothers carrying male-male fetuses was less than mothers who delivered female-female twins (0.86, 95%CI 0.76-0.96).

Odds of proteinuria (1.83, 95%CI 1.21-2.79) were higher in male-male pregnancies compared to female-female ones. Use of antihypertensive medication (0.33, 95%CI 0.15-0.73) was less likely to occur in mothers carrying male-male twins

compared to those carrying female-female twins. Similarly, mothers who were pregnant with male-male twins were less likely to undergo cesarean sections.

Mothers carrying male-female twins had higher odds of PIH than mothers carrying female-female twin pairs (2.28, 95%CI 1.27-4.11).

Table 1 Maternal characteristics of twin gestations according to sex combinations (6321 gestations)

*Kruskal Wallis Test, Wks: Weeks; SD: Standard deviation; Body mass index: BMI; Data for education, BMI, weight gain, and number of antenatal visits were collected after April 2007 only. 0.52% of data is missing, 24% of BMI and 13% of antenatal visits are missing.

	Female-Female (n=2053)	Female-Male (n=2167)	Male-Male (n=2101)	P
Gestational age, Wks, mean±SD	35.15±3.02	35.30±3.00	35.15±3.14	0.04
Maternal age, years, * mean±SD	31.25±5.68	32.35±5.67	31.26±5.72	0. 01
Education, years, mean±SD	14.79±2.87	14.75±2.81	14.32±2.85	0. 01
BMI, kg/m2,*mean±SD	24.26±4.99	24.60±5.25	24.20±4.92	0. 01
Pregnancy weight gain, kg, mean±SD	18.54±7.87	18.49±7.05	18.71±7.44	0.54
Number of antenatal visits, mean±SD	8.89±3.72	8.89±3.44	9.00±3.63	0.32
Primigravida, n (%)	2076(50.6%)	2236(51.6%)	1960(46.6%)	0. 01
Smoking, n (%)				
Current	368(27.1%)	404(27.8%)	426(32.2%)	
Former	286(21.1%)	292(20.1%)	280(21.1%)	0.02
Non-smoker	703(51.8%)	758(52.1%)	618(46.7%)	

Table 2 Comparing adverse maternal outcomes between male-male, female-femaleand male-female twin pairs using ANOVA and Post Hoc test

Maternal outcomes	FF Gestation n=2053	MM Gestation n=2101	MF Gestation n=2167	P	Posthoc test		
					P MM vs. FF	P MM vs. MF	P FF vs. MF
Total length of stay in hospital (in days), mean±SD*	6.31±8.28	6.29±8.20	5.94±7.12	0. 35	0.91	0.03	0.03
Antepartum length of stay, mean±SD	2.20±7.07	2.40±7.71	1.90±6.59	0.01	0.20	0.01	0.06
Postpartum length of stay, mean±SD	4.10±3.89	3.89±2.03	4.01±2.15	0.01	0.01	0.04	0.13
Current pregnancy related proteinuria	222(5.4%)	158(3.8%)	242(5.6%)	0. 01	0.05	0.01	0.66
Current pregnancy induced hypertension	622(15.1%)	574(13.7%)	704(16.2%)	0.01	0.05	0.01	0.22
On antihypertensive drugs during current pregnancy	36(0.9%)	64(1.5%)	52(1.2%)	0.02	0.01	0.19	0.12
Preeclampsia	212(5.2%)	148(3.5%)	230(5.3%)	0.01	0.05	0.09	0.94
Bleeding <20 weeks	118(2.9%)	148(3.5%)	132(3.0%)	0.21	0.09	0.90	0.39
Antepartum haemorrhage ≥20 weeks	88(2.1%)	124(3.0%)	126(2.9%)	0.03	0.02	0.21	0.01
Abnormal glucose factor	94(2.3%)	84(2.0%)	120(2.8%)	0.06	0.36	0.02	0.14
Any type of diabetes in the current pregnancy	412(10.0%)	450(10.7%)	492(11.4%)	0.14	0.31	0.34	0.06
Preterm	5562(62.4%)	2509(59.7%)	2625(60.6%)	0.03	0.01	0.41	0.09
Premature rupture of membrane	1872(76.8%)	2054(79.6%)	2024(79.2%)	0.04	0.01	0.50	0.05
Prolonged rupture of membrane	258(10.6%)	300(11.6%)	300(11.7%)	0.37	0.24	0.74	0.14
Cesarean section	1382(67.3%)	1353(64.4%)	1447(66.3%)	0.01	0.05	0.02	0.30

*Kruskal Wallis test;
OR: Odds ratio,
AOR: Adjusted odds ratio,
95%CI: 95% confidence interval;
MM: male-male,
FF: female-female,
MF: male-female

Table 3 Unadjusted and adjusted OR (95%CI) of maternal outcomes in relation to sex discordance in mothers delivered in BC (6321 gestations, n=12642)

	OR 95%CI MM vs. FF Gestation	AOR 95%CI MM vs. FF Gestations	OR 95%CI MF vs. FF Gestation	AOR 95%CI MF vs. FF Gestations
Total length of stay in hospital > 3 days	0.98(0.68-1.39)	3.46(0.72-16.71)	1.07(0.95-1.20)	1.15(0.60-2.20)
Antepartum length of stay > 3 days	1.05(0.91-1.20)	1.00(0.84-1.05)	0.93(0.81-1.07)	0.88(0.74-1.05)
Postpartum length of stay> 3 days	0.86(0.77-0.97)	0.86(0.76-0.96)	0.95(0.84-1.06)	0.88(0.78-1.00)
Current pregnancy related proteinuria	1.93(1.30-2.88)	1.83(1.21-2.79)	1.40(0.56-3.53)	1.56(0.58-4.23)
Current pregnancy induced hypertension	1.19(0.87-1.63)	1.17(0.85-1.61)	2.03(1.17-3.52)	2.28(1.27-4.11)
On antihypertensive drugs during current pregnancy	0.89(0.69-1.14)	0.33(0.15-0.73)	1.13(0.89-1.44)	0.72(0.46-1.11)
Preeclampsia	1.63(1.00-2.65)	1.63(0.99-2.70)	1.88(0.55-6.36)	2.65(0.74-9.52)
Antepartum haemorrhage ≥20 weeks	1.39(0.84-2.29)	1.47(0.89-2.41)	1.22(0.89-1.67)	1.20(0.86-1.66)
Abnormal glucose factor	0.90(0.56-1.44)	0.92(0.57-1.48)	0.44(0.13-1.51)	0.53(0.15-1.81)
Any type of diabetes in the current pregnancy	0.89(0.68-1.17)	0.94(0.71-1.23)	1.04(0.51-2.11)	1.08(0.52-2.24)
Preterm	0.92(0.77-1.09)	0.90(0.75-1.07)	0.60(0.38-0.97)	0.59(0.37-0.94)
Premature rupture of membrane	0.78(0.35-1.76)	2.09(1.50-2.92)	0.52(0.21-1.29)	0.34(0.11-1.07)
Prolonged rupture of membrane	0.71(0.19-2.60)	0.46(0.11-1.81)	0.65(0.20-2.72)	0.53(0.14-1.96)
Cesarean section	0.87(0.80-0.96)	0.86(0.77-0.96)	0.93(0.84-1.04)	0.87(0.78-0.98)

OR: Odds ratio,
AOR: Adjusted odds ratio,
95%CI: 95% confidence interval;
MM: male-male,
FF: female-female,
MF: male-female

Table 4 Unadjusted and adjusted OR (95%CI) of maternal outcomes in relation to sex discordance in mothers delivered at C&W hospital (1493 gestations)

	OR 95%CI MM vs. FF Gestation	AOR 95%CI MM vs. FF Gestations	OR 95%CI MF vs. FF Gestation	AOR 95%CI MF vs. FF Gestations
Total length of stay in hospital >3 days	0.75(0.56-0.99)	2.36(0.59-9.38)	0.83(0.62-1.11)	0.66(0.19-2.33)
Antepartum length of stay	1.05(0.48-2.31)	1.13(0.39-3.26)	0.72(0.32-1.62)	1.41(0.50-3.90)
Postpartum length of stay	0.86(0.64-1.16)	0.77(0.51-1.16)	0.94(0.47-1.87)	0.92(0.46-1.82)
Current pregnancy related proteinuria	1.23(0.71-2.12)	0.95(0.53-1.71)	0.47(0.17-1.31)	0.29(0.09-0.92)
Current pregnancy induced hypertension	0.54(0.24-1.24)	0.84(0.55-1.28)	0.88(0.43-1.80)	0.62(0.29-1.32)
Bleeding <20 weeks	1.07(0.54-2.12)	0.82(0.38-1.75)	4.29(0.89-20.75)	4.93(0.75-32.08)
Antepartum haemorrhage ≥20 weeks	1.65(0.83-3.28)	1.77(0.75-4.16)	1.01(0.24-4.15)	1.86(0.28-12.29)
Abnormal glucose factor	0.73(0.35-1.54)	0.65(0.30-1.35)	2.06(0.36-11.51)	1.42(0.22-9.01)
Any type of diabetes in the current pregnancy	0.63(0.52-2.89)	1.22(0.48-3.06)	1.41(0.63-3.15)	2.09(0.48-3.06)
Preterm	1.14(0.59-2.17)	0.97(0.49-1.93)	1.03(0.56-1.90)	1.32(0.70-2.52)
Premature rupture of membrane	0.82(0.58-1.14)	1.03(0.70-1.52)	2.07(0.94-4.55)	2.59(1.17-5.72)
Cesarean section	0.84(0.61-1.17)	0.82(0.56-1.18)	0.47(0.24-0.89)	0.38(0.18-0.80)

OR: Odds ratio,
AOR: Adjusted odds ratio,
95%CI: 95% confidence interval;
MM: male-male,
FF: female-female,
MF: male-female

An OR of 0.59 (95%CI 0.37-0.94) indicated a 41% decrease in the odds of having a preterm birth if mothers were pregnant with male-female twins compared with those pregnant with female-female twins, after adjustment for confounders. Similarly, a reduced adjusted odds of cesarean section was found in male-female gestations compared to the reference gestation (0.87, 95%CI 0.78-0.98).Twin sex pairing was not associated with any other adverse maternal outcomes during pregnancyunderstudy after adjusting for potential confounding variables.

Subgroup analysis adjusting for chorionicity

A group of women delivered in C&W Hospital with pathology data were analysed separately to adjust for the impact of chorionicity (Table 4). The number of gestations included 1493 pregnancies (n=2986 twins). Three sex pairing groups were identified (489 female-female pairs, n=978; 508 male-male pairs, n=1016; 496 male-female pairs, n=992). Regression analysis suggested that the odds of premature rupture of membrane were 2.59 (95%CI 1.17-5.72) for male-female pregnancies compared to female-female pregnancies while the odds of cesarean section were 62% lower (95%CI 0.18-0.80) in male-female gestations compared to the reference category (female-female gestations). No other maternal adverse outcomes were significantly associated with sex pairing.

DISCUSSION

Considering pregnancies with female-female twin pairs as the reference category, our regression analysis found the following:

1. Lower odds of a longer than 3 days' postpartum maternal stay in hospital for male-male pregnancies.
2. Mothers carrying male-female twins had higher odds of PIH, and lower odds of preterm birth and cesarean section compared to the reference gestations. Moreover, adjusted odds for cesarean section was lower in male-male gestations compared with female-female pregnancies.
3. Regression analysis found that sex has no influence on postpartum stay in hospital, antepartum hemorrhage, abnormal glucose factor, gestational diabetes, or premature or prolonged rupture of membrane after adjusting for confounding variables.
4. A reduced odds of cesarean section in male-female gestations was reproduced in a subsample analysis controlling for chorionicity. Higher odds of premature rupture of membrane were found in male-female gestations compared to female-female gestations. No other comparison was found to be significant in our subgroup analysis.

Length of stay in hospital

The study of length of maternal stay in hospital has great implications for defining resource requirements and cost implications of such hospitalizations. No study has attempted to identify the association between fetal sex pairing and length of antenatal or postnatal hospital stay. More importantly, our findings will help to support or refute the male "contribution" to adverse maternal complications.

Previously, epidemiological data have been examined in an attempt to determine which variables bear the greatest influence on antenatal and postnatal length of stay. We used the available information in the literature to identify the confounding variables hindering the relation between fetal sex and maternal hospital stay. For example, complications arising from pre-existing medical conditions can increase prenatal length of stay.[11] Maternal postnatal length of stay can also be influenced by parameters such as neonatal mortality, method of delivery, post-delivery complications, and hospital discharge policies.[12] The Perinatal Statistics Report 2007 on perinatal events in Ireland suggests that the mothers' mean postnatal length of stay was 3 days for live born multiple births.[13] About 48% of mothers carrying multiple gestations remained in hospital for less than 3 days and a further 48.8% were discharged between 3 to 5 days, identifying with variation in hospital discharge policies.

Antenatal hospitalization in women has been examined by Brooten *et al*. on high risk pregnancies.[14] Women with pre-gestational diabetes had the greatest length of hospitalizations

whereas those with gestational diabetes had the shortest. Other major reasons for hospitalization were preterm labour, glucose control, and preeclampsia. In our study, maternal postpartum hospitalization was found to be of shortest length among mothers carrying male-male twins compared with mothers carrying opposite-sex twins. Total hospital stays or postnatal length of stay, however, did not differ between the different sex-paring groups. Adjusting for medical conditions (pre-existing gestational diabetes, hypertension, preeclampsia), type of delivery, and neonatal mortality, we did not find any statistically significant difference between the comparison groups for total length of hospital stay or antepartum stay. While the postpartum length of stay was associated with sex in one group (male-male compared to the reference group), this association was not confirmed by the adjusted analysis in the comparison between male-female twins and the reference category. This could be due to lack of re-admission data. It is possible that our analysis has not captured the full postnatal length of stay in hospital, leading to an insignificant result for part of our comparison. Moreover, postpartum discharge has been declining significantly during last decade in Canada due to availability of home care and intentional early discharge of mothers during the postpartum period.[15] Our study results could help health care provider who visit mothers at home to pay more attention to mothers who delivered female-female infants. Future longitudinal studies can investigate the postpartum length of stay during last decade to reflect upon change in practice pattern over time.

Preeclampsia/PIH

A Japanese study on 10025 twin gestations from 125 hospitals (2001 through 2005) found that mothers of female-female twins had the highest preeclampsia rate (5.2%), mothers of male-female pairs had an intermediate rate (4.6%), and the mothers of male-male twins had the lowest rate (3.9%).[9] The authors also reported a higher risk of preeclampsia among mothers carrying female-female twins than those carrying male-male twins (p=0.0005). This result is consistent with our findings. We found an increased rate of preeclampsia in mothers who carried female-female twins compared with those who were pregnant with male-male twins (5.2% vs. 3.5%, p=0.01). However, the regression analysis did not confirm such findings after adjusting for confounding variables.

The Shiozaki *et al*. study[9] introduced earlier also showed that, compared with mothers carrying male–male fetuses, those carrying female-female fetuses had significantly lower incidences of PIH (7.3% vs. 4.9%, p=0.04). We found a similar result but our finding was not statistically significant (1.17; 95%CI 0.85-1.61).

We also observed that pregnancies with opposite-sex twins had a higher frequency of PIH, compared with pregnancies with female-female twins (2.28; 95%CI 1.27-4.11). The physiological justification of these findings remains obscure and work on the aetiology is insufficient. It may be speculated that immune incompatibility between mother and fetus contributes to the pathogenesis of preeclampsia. The fetus brings the paternal gene pool to the mother's body, which may stimulate a maternal immune reaction. If this theory is correct, male-female twins with two sets of genes would have higher rates of preeclampsia. In other words, having two sets of different gene pools would trigger more immune incompatibility between the mother and the fetus than two sets of similar gene pools. We found higher incidences of adverse maternal outcomes during pregnancy (proteinuria, PIH, preeclampsia) in mothers who carried male-female twins compared with other twin pairs. Moreover, gender similarity could be the result of having identical twins where one egg, with less gene diversity, is divided into two, producing male-male or female-female twin pairs. This means that twins with similar gender, if identical, carry less gene diversity, hence less of maternal complications. This hypothesis should be tested in the presence of zygosity variable.

Gestational diabetes

The relationship between fetal sex and gestational diabetes is a complicated issue because many confounding factors can impact the disease.[16] In the literature related to singleton pregnancies, male sex is association with increased rates of gestational diabetes.[6] We did not find similar incidences of gestational diabetes among three sex-pairing groups (p=0.14). Melamed *et al.* detected a statistically significant higher incidence of gestational diabetes in mothers with female-female (6.9%) gestations than those with male-male (3.6%, P=0.06) gestations.[17] These results might be limited due to lack of adjustment for maternal body mass index or maternal weight gain during pregnancy. We controlled for these variables and did not find any association between sex pairing and gestational diabetes. Cardiovascular comorbidities, neuroendocrine signalling and metabolism or other unknown variable may contribute in association between gestational diabetes and gender in twin gestation that we have not accounted for.

Rupture of membrane

Premature rupture of membrane has been reported among mothers of male newborns compared with mothers of females.[4] The higher incidence in pregnancies with a male fetus has been linked to the relatively greater weight at a lower gestational age of male newborns versus female infants. Others have suggested that the higher incidence of premature rupture of membrane is caused by an increased predisposition to infection in mothers carrying male fetuses.[18] It has been speculated that the blood of male fetuses mounts a larger pro-inflammatory response to cytokine, promoting premature rupture of membrane.[19] Future studies can verify these hypotheses by measuring cytokines, utilized as biomarkers in the diagnosis of intrauterine infections. The hypothesis of males being more responsive to PROM is consistent with our finding of a higher rate of premature rupture of membrane in mothers carrying male-male twin pairs (79.6%) compared with mothers in the female-female group (76.8%, Table 12-2). Cytokines, a marker of inflammation/infection, measuredin amniotic fluid samples collected from 15 singleton pregnancies did not show any different patterns regarding fetal sex,[20] although small sample size is a limitation for this finding.

Prolonged rupture of membrane is associated with increased maternal morbidity and adverse perinatal outcomes.[21] Asymptomatic term infants born to mothers with prolonged rupture of the membranes longer than 24 hours should be closely observed for the first 12 hours of age. Our data did not indicate any association with fetal sex pairing and prolonged rupture of membrane. This means that fetal sex is not a predictive variable for prolonged rupture of membrane.

Preterm birth

A retrospective large study of 148243 live-birth twin pairs has found an association between male sex and increased preterm birth. Unlike this study, we found the highest proportion of preterm births belonged to female-female gestations. Moreover, our adjusted regression analysis did not find any role for sex in determination of preterm birth even after adjustment for cesarean section. Unlike our findings, a study of 9993 twin pregnancies foundthat the male-male twins had the highest preterm rate, opposite-sex twins had an intermediate rate, and the female-female twins had the lowest rate.[22] These findings were significant and the authors concluded that fetal sex influences the pathogenies of preterm birth through an unknown mechanism. This study failed to adjust for any confounder or conduct regression analysis.

Cesarean section

A higher rate of cesarean section in twin gestations is an established fact in the literature[23] given higher rates of delivery complications such as higher rates of placenta previa,[24] malpresentation,[25] fetal growth discordance. Moreover, higher rate cesarean section could be due to male macrosomia which in turn is the result of higher fetal malemetabolic rate,[26] endocrine factors (such as gestational diabetes). Other contributing factor in higher rate of cesarean section in male relates to higher birth weight of males, and clinicians' preference.[27]

In singleton pregnancies, earlier studies have shown an association between fetal sex and rates of cesarean section.[28,29] This association has been attributed to males' larger size at birth[29], fetal presentation,[30] and variances in levels of corticosteroids and estrogen precursors that may influence the onset of labor.[23]

We found the highest incidence of cesarean sections in female-female gestations compared to male-male and male-female gestations. Similarly, a study of twin gestations of 8858 very low birth weight (500–1500 grams) infants of 24-34 weeks' gestation found the highest rate of cesarean section amongst female-female pregnancies (67.5%) compared to male-male (65.6%) and male-female (65.1%) twins.[31] Another study investigating the role of fetal sex in relation to maternal outcomes found the highest rate of cesarean section in female-female pregnancies (FF:86.2% vs. MM: 82.6%, MF:81.4%), although the difference was not found to be significant (p=0.06).[17] A higher rate of cesarean section has been attributed to BWD.[32] We adjusted for BWD and still found an association between fetal sex and this method of delivery. Other contributing factors such as iatrogenic cesarean section should be taken into account in future studies.

In conclusion, on the basis of our results and review of earlier studies, our findings suggest that sex discordance relates to adverse maternal outcomes such as preeclampsia, PIH, antepartum hypertension and premature rupture of membrane. These findings provide clues for future studies to find mechanisms by which maternal complications are related to sex pairing in twin gestation. Clinical relevance and importance of determining sex during ultrasound screening may provide for better clinical management.

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