Impact of sex on perinatal mortality and morbidity in twins

Elsmén, Emma; Källén, Karin; Marsal, Karel; Norman, Mikael; Hellstrom-Westas, Lena

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Emma Elsmén Steen*, Karin Källén, Karel Maršál, Mikael Norman and Lena Hellström-Westas

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Abstract

Objective: Twin studies offer opportunities to investigate mechanisms underlying sex-associated differences in perinatal outcomes. The objective of the study was to investigate sex-related differences in perinatal complications.
Study design: A cohort of 16,045 twin pregnancies – 32,090 twins – was explored for obstetric complications, perinatal and infant mortality, and neonatal morbidities.
Results: Twin pregnancies with a female fetus had an increased risk for preeclampsia, but otherwise there were no pregnancy complications associated with fetal sex. After birth, female-female twins had lower early neonatal and infant mortality, and lower risk for respiratory morbidities than male-male twins at all gestational ages. In unlike-sexed twin pairs, very preterm males had higher respiratory morbidity than females and, females were at higher risk for being growth restricted.
Conclusion: Male-male twins have higher respiratory morbidity and neonatal mortality than female-female twins. In unliked-sexed twin pairs, the males seem to be protected by having a female co-twin.

Keywords: Growth restriction; newborn; respiratory morbidity; preeclampsia; preterm.

*Corresponding author: Emma Elsmén Steen, MD, PhD, Department of Pediatrics, University Hospital, SE-221 85 Lund, Sweden, Tel.: +46-08-51770000, E-mail: emma.elsmen-steen@karolinska.se
Emma Elsmén Steen and Karel Maršál: Department of Clinical Sciences, Lund University, Lund, Sweden
Karin Källén: Tornblad Institute Reproductive Epidemiology Center, Lund University, Lund, Sweden
Mikael Norman: Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
Lena Hellström-Westas: Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

Introduction

Newborn males have higher neonatal morbidity and mortality than females, and they are more likely to develop neurological and developmental disabilities than females, particularly after preterm birth [17, 22, 30, 33].

We have previously shown that preterm males need more respiratory and circulatory support than females [10] and together with others, we have reported that respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and other respiratory diseases are more common in males than in females, both in singletons and twins [2, 3, 5, 18, 25, 31].

Studies of twins offer unique opportunities for investigating underlying causes of sex-related differences in perinatal outcomes. Genetic factors can be separated from early environmental influences both in term and preterm infants, not the least because twin pregnancies, more often than singletons, end before term [6, 13]. However, the twin approach is also challenging because outcomes are different for same-sex (mono- and dizygous) and sex-mixed (dizygous only) twins. Rydhström et al. showed that pregnancy loss is twice as high in like-sexed compared with unlike-sexed twins [27]. A small hospital-based study previously suggested that female-female (FF) twin pairs have longer gestation, lower mortality rate and lower incidence of BPD as compared to male-male (MM) twin pairs and sex-mixed (female-male, FM) twin pairs [5]. In a large population-based study, MM twins had increased neonatal and infant mortality risks as compared to other twin gender combinations [26]. Another population-based study of preterm twins showed that female twins in FM twin pairs had higher respiratory morbidity than other newborn females [29]. The authors suggested that the increased respiratory morbidity in the female twin could represent a "male disadvantage" acting through an intra-uterine paracrine effect.

The aim of the present study was to investigate effects of fetal and newborn sex on obstetric complications, perinatal mortality, and neonatal morbidity at different gestational ages in a large population-based study of twin pregnancies and twins.

Materials and methods

The study was based on data from the Swedish Medical Birth Register (MBR) held by the National Board of Health and Welfare. The MBR covers more than 98% of all deliveries and contains information on pregnancy, delivery, and neonatal conditions. Information

on infant mortality was obtained through national welfare statistics conducted by Statistics Sweden (SCB). For estimation of gestational age (GA), fetal ultrasound examinations are routinely performed at 16–18 weeks' gestation in about 97% of Swedish pregnant women. We included perinatal data from all newborn twins registered in the MBR during a 12-year period (January 1, 1996 to December, 2007), i.e., live-born twins of all gestations, and stillbirths of 28 weeks or more of gestation. Stillborn infants were excluded when analysing neonatal characteristics.

The investigated obstetric complications included: preeclampsia/eclampsia, polyhydramnios, infection, preterm prelabour rupture of membranes (PPROM) and prelabour rupture of membranes (PROM), abruption of the placenta, and twin-to-twin transfusion syndrome (TTTS). The investigated neonatal diagnoses were: transient tachypnea of the newborn (TTN), RDS, BPD, pneumothorax, intraventricular hemorrhage (IVH); any grade and grades 3–4 according to Papile [24], seizures and sepsis (culture proven). Collected neonatal data included: infant sex, GA, birth weight (BW), birth weight standard deviation score (BW SD-score), and presence of a low 5-min Apgar score (<7). Small for gestational age (SGA) was defined as a BW at or below −2 standard deviations (SD) of the expected BW for GA according to Swedish reference data, and large for gestational age (LGA) was defined as a BW at or above +2 SD [20]. The study was approved by the Regional Research Ethics Committee at Lund University and by the National Board of Health and Welfare.

Gestational age at birth was categorised in three groups: very preterm (GA<32 weeks), preterm (GA 32–36 weeks) and term (GA≥37 weeks). For most of the outcomes, the three gestational-age strata were analysed separately. Multiple logistic regression analyses were used for assessing odds ratios (OR) for dichotomous outcomes. All OR and 95% confidence intervals (95% CI) are presented after adjustment for GA (continuous variable) and BW SD-scores (continuous) unless stated otherwise. Non-parametric tests (Kruskal-Wallis/Wilcoxon) were used for comparisons of continuous data. The following comparisons were made: i) FF vs. MM pregnancies, ii) FF versus FM pregnancies, and iii) MM versus FM pregnancies. For the newborn twin infants: i) FF versus MM, ii) females in FM pairs (F/FM) versus males in FM pairs (M/FM), and for some estimates also iii) F/FM versus FF, and iv) M/FM versus MM. All statistical analyses were made using Gauss (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA, http://www.aptech.com).

Results

Obstetric complications

A total of 16,045 twin pregnancies and 32,090 infants (stillborn or live-born) were investigated. The distribution of pregnancies according to infant sex and GA at delivery is presented in Table 1. The median (interquartile range, IQR) GA was 261 (246–269) days for both FF and MM twin pregnancies, while FM pregnancies lasted on average 1 day longer, median 262 (250–270) days (P<0.001). There were no differences in mode of delivery, i.e., vaginal or cesarean section, between FF, MM and FM pregnancies.

Table 1 Numbers of twin pregnancies according to sex combinations and gestational age at birth.

Gestational age (weeks)	Female-Female, n (%)	Male-Male, n (%)	Female-Male, n (%)	Total, n (%)
<32	392 (7.8)	496 (9.4)	361 (6.4)	1249 (7.7)
32–36	1850 (36.6)	1861 (35.3)	1925 (33.6)	5636 (35.1)
>37	2817 (55.7)	2893 (55.2)	3438 (60.1)	9160 (57.1)
Total	5059 (100)	5262 (100)	5724 (100)	16,045 (100)

The prevalence of preeclampsia was significantly higher in FF pregnancies than in MM (OR 1.19; 95% CI 1.04–1.36) and also higher in FM as compared to MM pregnancies (OR 1.17; 95% CI 1.03–1.33) (Table 2). The risk for PPROM/PROM, infection, placental abruption and TTTS did not differ between FF and MM, FF and FM, or MM and FM pregnancies, respectively. The risk for polyhydramnios was increased in both FF and MM pregnancies as compared to FM, OR 2.80 (95% CI 1.30–6.04) and OR 2.93 (95% CI 1.37–6.24), respectively.

Fetal sex and obstetric complications stratified on gestational age

At <32 gestational weeks, the risk for preeclampsia was higher for FM as compared to MM pregnancies (OR 2.13; 95% CI 1.12–3.03). At 32–36 gestational weeks, the risk for preeclampsia was higher in FF pregnancies than in MM (OR 1.28; 95% CI 1.04–1.56). In term pregnancies there were no differences between FF and MM or FM for any of the investigated pregnancy complications.

Perinatal and postnatal mortality

The overall twin mortality, i.e., stillbirths, early neonatal deaths (END; 0–6 days), late neonatal deaths (LND; 7–28 days), postneonatal deaths (28 days–364 days) and infant mortality (0–364 days) is summarized in Table 3.

There were no differences in the risk for stillbirth that could be related to fetal sex, neither between FF and MM twins, nor between F/FM and M/FM. Infant mortality was lower in FF than in MM twins, OR 0.67 (95% CI 0.51–0.89), a result confined to END (OR 0.72; 95% CI 0.53–0.99). Male-male twin pairs had higher END and infant mortality than males in unlike-sex twin pairs (OR 1.8; 95% CI 1.21–2.91 and OR 1.55; 95% CI 1.09–2.23, respectively).

In preterm infants, infant mortality was lower in FF as compared to MM (for GA<32 weeks: OR 0.62; 95% CI

Table 2 Rates of preeclampsia in twin pregnancies according to gestational age and combinations of twin sexes.

Gestational age (weeks)	Female-Female, n/total (%)	Male-Male, n/total (%)	Female-Male, n/total (%)	Total, n/total (%)
<32	26/392 (6.6)	18/496 (3.6)	29/361 (8.0)	73/1249 (5.8)
32–36	267/1850 (14.4)	233/1861 (12.5)	263/1924 (13.7)	763/5636 (13.5)
>36	280/2817 (9.9)	271/2905 (9.3)	350/3438 (10.2)	901/9160 (9.8)
Total	573/5059 (11.3)	522/5262 (9.9)	642/5724 (11.2)	1737/16,045 (10.8)

Table 3 Perinatal and infant mortality according to combinations of twin sex in 32,090 twins (16,045 twin pregnancies).

	Female-Female, n (%)	Male-Male, n (%)	Female in FM, n (%)	Male in FM, n (%)	Total, n (%)
All twins	10,118 (100)	10,524(100)10,442	5724 (100)	5724 (100)	32,090 (100)
Live-born	10,044 (99.3)	(99.2)	5705 (99.7)	5700 (99.6)	31,890 (99.4)
Stillborn	74 (0.7)	83 (0.8)	19 (0.3)	24 (0.4)	200 (0.6)
Early neonatal death (0–6 days)	84 (0.8)	121 (1.2)	34 (0.6)	31 (0.5)	270 (0.8)
Late neonatal death (7–27 days)	21 (0.2)	26 (0.2)	4 (0.1)	11 (0.2)	62 (0.2)
Post-neonatal death (28–364 days)	7 (0.1)	17 (0.2)	4 (0.1)	6 (0.1)	34 (0.2)
Infant mortality (0–364 days)	112 (1.1)	164 (1.6)	42 (0.7)	48 (0.8)	366 (1.2)
Survivors at 365 days (% of live-born)	9932 (98.2)	10277 (97.7)	5663 (98.9)	5652 (98.7)	31,524 (98.2)

0.43–0.90; for GA 32–36 weeks: OR 0.51; 95% CI 0.29–0.89), but there was no difference in infant mortality between F/FM and M/FM. There were no other mortality differences related to sex in preterm infants. In term infants (GA 37 weeks and above), there were no differences in mortality for any of the comparisons.

Neonatal characteristics and morbidity

Neonatal characteristics

A low 5-min Apgar score was present in 5.5% of FF, in 6.1% of MM, in 4.8% of F/FM, and in 4.0% of M/FM twins (non-significant differences). The risk for a low Apgar score did not differ between the different twin combinations.

Female twins had significantly lower BW SD-scores than male twins; the median (IQR) BW SD-score in FF was –1.18 (–1.88 to –0.47) vs. MM –0.97 (–1.69 to –0.27) (P<0.001). Also, in unlike-sex twin pairs, the females had lower a BW SD-score than the males: F/FM –1.23 (–1.92 to –0.53) and M/FM –0.8 (–1.51 to –0.07) (P<0.001). The lower BW SD-scores in twin females were present and significant across all three GA strata. Furthermore, females in FM pairs had lower BW SD-scores than females in FF pairs (P=0.006). Correspondingly, M/FM twins had higher BW SD-scores than MM twins (P<0.001).

Females were more often classified as SGA: 21.3% of FF vs. 16.4% of MM, and 22.3% of F/FM as compared to 12.9% of M/FM. The risks for FF being SGA as compared to MM were: OR 1.40 (95% CI 1.31–1.75), 1.41 (95%CI 1.26–1.59), and 1.37 (95% CI 1.24–1.51), respectively, for the three GA strata. The SGA risk for F/FM as compared to M/FM was higher in pregnancies ending moderately preterm and at term (OR 1.95; 95% CI 1.64–2.32 at 32–36 weeks, and OR 2.03; 95% CI 1.78–2.31 at 37 weeks and above).

Neonatal morbidity

Significant neonatal sex-related differences were seen in respiratory morbidities, whereas there were no sex-related differences between any of the comparisons for IVH (any grade or grades 3–4), seizures or sepsis. Neonatal morbidity is summarised in Table 4.

Infant sex and respiratory morbidity at different gestational ages

In very preterm twins (GA below 32 weeks), the risk for RDS, pneumothorax and BPD was lower in FF twins than in MM, with no differences between F/FM and M/FM twins (Table 5).

In moderately preterm infants (GA 32–36 weeks), the risk for TTN was lower for FF than for MM, and also lower for F/FM compared to M/FM. The risk for RDS did not differ between FF and MM, but was lower in F/FM as

Table 4 Neonatal morbidity in 31,890 live-born twins according to twin-sex combination and in relation to gestational age.

	Female-Female, n (%)	Male-Male, n (%)	Female, FM n (%)	Male, FM n (%)	Total, n (%)
Very preterm (<32 gestational weeks)					
Total	756 (100)	955 (100)	354 (100)	354 (100)	2419 (100)
TTN	164 (21.7)	173 (18.1)	70 (19.8)	65 (18.4)	472 (19.5)
RDS	273 (36.1)	424 (44.4)	143 (40.4)	155 (43.8)	995 (41.1)
Pneumothorax	23 (3.7)	59 (6.2)	10 (2.8)	18 (5.1)	115 (4.8)
BPD	37 (4.9)	77 (8.1)	23 (6.5)	27 (7.6)	164 (6.8)
IVH 3–4	31 (4.1)	47 (4.9)	17 (4.8)	18 (5.1)	113 (4.7)
Sepsis	75 (9.9)	116 (12.1)	33 (9.3)	36 (10.2)	260 (10.7)
Seizures	7 (0.9)	14 (1.5)	1 (0.3)	3 (0.8)	24 (1.0)
Preterm (32–36 gestational weeks)					
Total	3673 (100)	3687 (100)	1919 (100)	1920 (100)	11,199 (100)
TTN	396 (10.8)	549 (14.9)	223 (11.6)	300 (15.6)	1468 (13.1)
RDS	138 (3.8)	110 (3.0)	38 (2.0)	67 (3.5)	353 (3.2)
Pneumothorax	13 (0.4)	26 (0.7)	7 (0.4)	17 (0.9)	63 (0.6)
BPD	5 (0.1)	3 (0.1)	3 (0.2)	1 (0.1)	12 (0.1)
IVH 3–4	4 (0.1)	0 (0.0)	2 (0.1)	1 (0.1)	7 (0.1)
Sepsis	21 (0.6)	24 (0.7)	8 (0.4)	14 (0.7)	67 (0.6)
Seizures	7 (0.2)	11(0.3)	1 (0.1)	6 (0.3)	25 (0.2)
Term (≥37 gestational weeks)					
Total	5615 (100)	5799 (100)	3432 (100)	3426 (100)	18,272 (100)
TTN	91 (1.6)	168 (2.9)	57 (1.7)	81 (2.4)	397 (2.2)
RDS	5 (0.1)	3 (0.1)	2 (0.1)	5 (0.1)	15 (0.1)
Pneumothorax	5 (0.1)	14 (0.2)	5 (0.1)	7 (0.2)	31 (0.2)
BPD	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
IVH 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	5 (0.2)	3 (0.1)	1 (0.0)	2 (0.1)	11 (0.1)
Seizures	12 (0.2)	6 (0.1)	4 (0.1)	4 (0.1)	26 (0.1)

TTN=transient tachypnea of the newborn, RDS=respiratory distress syndrome, BPD=bronchopulmonary dysplasia, IVH=intraventricular hemorrhage.

compared to M/FM (Table 5). There were no gender differences in the risks for BPD.

At term, the risk for TTN was lower in FF than in MM twins, but there were no differences between F/FM and M/FM twins (Table 5).

Discussion

The present population-based study – evaluating effects of fetal and neonatal sex on perinatal complications in a population-based study including 16,045 twin pregnancies (32,090 twins) – demonstrates that FF twins have lower mortality and morbidity than MM twins. Male twins in like-sexed twin pairs had the highest mortality risk and risks for respiratory morbidities, including a spectrum from RDS, pneumothorax and BPD in the most preterm twins to transient tachypnea in term twins. Previous studies have reported higher mortality in MM as compared to FF twins in twin populations from the 1980s and 1990s;

the present data demonstrate that such differences still persist [5, 26]. The increased risks for MM twins could not be explained by lower GA.

Preterm pregnancies containing a female fetus (FF or FM) had a higher risk for being affected by preeclampsia than MM twin pregnancies, otherwise there were no fetal-sex-associated risks for pregnancy complications. The association between female fetus and increased risk for preeclampsia leading to preterm delivery has previously also been found for singleton pregnancies [11]. The increased risk for polyhydramnios in both FF and MM pregnancies as compared to FM pregnancies most likely reflect cases of TTTS, which only occurs in same-sexed, monozygous, monochorionic pregnancies [16].

In unlike-sex twin pairs, sex-related differences in morbidity and mortality were much less pronounced: respiratory morbidity was lower only in moderately preterm females and there were no mortality differences between females and males. However, males in unlike-sex twin pairs had significantly lower END and infant mortality than MM, while there were no differences between

Table 5 Risk for neonatal respiratory morbidity according to gestational age and combinations of sex in twins.

		Unadjusted			Adjusted		
		OR	95% CI	P-value	OR	95% CI	P-value
<32 gestational weeks							
TTN	FF vs. MM	1.25	0.99–1.59	NS	1.27	0.99–1.64	NS
	FM:F vs. M	1.1	0.75–1.60	NS	1.14	0.77–1.69	NS
RDS	FF vs. MM	0.71	0.58–0.86	<0.001	0.68	0.55–0.84	<0.001
	FM:F vs. M	0.87	0.65–1.17	NS	0.84	0.61–1.16	NS
Pnthx	FF vs. MM	0.58	0.37–0.93	0.022	0.54	0.33–0.87	0.011
	FM:F vs. M	0.54	0.25–1.19	NS	–	–	–
BPD	FF vs. MM	0.59	0.39–0.88	0.010	0.54	0.36–0.83	0.004
	FM:F vs. M	0.84	0.47–1.50	NS	0.80	0.44–1.48	NS
32–36 gestational weeks							
TTN	FF vs. MM	0.69	0.60–0.79	<0.001	0.67	0.58–0.78	<0.001
	FM:F vs. M	0.71	0.59–0.86	<0.001	0.77	0.63–0.94	0.009
RDS	FF vs. MM	1.27	0.98–1.64	NS	1.25	0.96–1.62	NS
	FM:F vs. M	0.56	0.37–0.84	0.005	0.55	0.36–0.84	0.006
Pnthx	FF vs. MM	0.50	0.36–0.97	0.042	0.52	0.27–1.016	NS
	FM:F vs. M	0.41	0.17–0.99	0.048	–	–	–
≥37 gestational weeks							
TTN	FF vs. MM	0.55	0.43–0.72	<0.001	0.55	0.42–0.71	<0.001
	FM:F vs. M	0.70	0.50–0.98	0.039	0.74	0.52–1.05	NS
Pnthx	FF vs. MM	0.37	0.13–1.02	NS	–	–	–
	FM:F vs. M	0.71	0.23–2.25	NS	–	–	–

Unadjusted odd ratios (OR) and OR adjusted for gestational age and birth weight SD scores are presented.
95% CI=95% confidence interval, RDS=respiratory distress syndrome, TTN=transient tachypnea of the newborn, Pnthx=pneumothorax, BPD=bronchopulmonary dysplasia.

females in unlike-sex twin pairs and female-female twin pairs, indicating a protective effect on male twins of having a female co-twin. It has been suggested that a female co-twin improves outcome for the male twin in unlike-sexed twin pairs by increasing pregnancy duration and BW [8]. Other studies have discussed the possibility of a masculinizing effect of the male twin on his female co-twin, resulting in increased BW of the female twin [4, 14]. The current data from a national cohort of infants do not support earlier findings; mean pregnancy duration was only 1 day longer for unlike-sexed twins as compared to same-sex twin pairs. In addition, the current data demonstrate that the females in unlike-sexed twin pairs have the lowest BW SD-score and the highest risks for being SGA. The sex difference in BW SD-scores increases with increasing duration of the pregnancy indicating that male twins in unlike-sexed twin pairs have an advantage of having a female co-twin, but that the female twin has a disadvantage of the male co-twin.

Shinwell et al. suggested that a masculinizing effect from the male increased respiratory morbidity in the female co-twin in very low BW (VLBW) unlike-sexed twin pairs [29]. Their study included 2448 VLBW twins, which compares well to the 2419 twins with GA below 32

weeks in the current study. The study by Shinwell et al did not include the diagnosis TTN, which was a diagnosis in almost 20% of our infants, and their rate of RDS was higher, around 70% vs. 40% in the present study. The differences in respiratory morbidity diagnoses probably reflect differences in diagnostic criteria, but taken together the total respiratory morbidities are very similar in the two studies. The present data support the results of Shinwell et al., i.e., the lower respiratory morbidity in FF twins as compared to MM twins is not accompanied by a comparable difference in respiratory morbidity between females and males in unlike-sexed twin pairs, which indicates a disadvantage for a female twin with a male co-twin.

The association between the presence of a female fetus and increased risk for early preeclampsia has been described before, but not in twins [11, 19, 32]. Immunological factors have been proposed to be involved in the pathophysiology of preeclampsia. Testosterone, which is also an immunomodulator, is higher in male fetuses and in pregnant women developing preeclampsia and carrying male fetuses [1, 28]. It has previously been suggested that increased testosterone levels could contribute to a dampened immunological response to the male fetus. We hypothesise that androgen effects on the immune system

contribute to the decreased risk for preeclampsia in pregnancies with male fetuses but also to the increased risk for respiratory morbidity in the newborn male infant [7]. Moreover, animal models have shown that estrogens are critical for alveolar development, and also for development of epithelial sodium channels that are important for absorption of fetal lung fluid after birth [21, 25].

Sex differences in perinatal and infant mortality seem to decrease with advancing socioeconomic conditions and improved medical care [9]. Consequently, we were recently unable to demonstrate sex differences in perinatal mortality and morbidity in a national cohort of extremely preterm infants, including both singletons and multiple pregnancies [12]. However, in moderately preterm infants we found that male sex was a risk factor for neonatal respiratory morbidity [2] and the current population-based data, ranging from 1996 to 2007, also shows that perinatal sex differences in mortality and morbidity among twins is still a matter of concern.

A strength of this study is that data were extracted from a quality-assured large population-based register. The large sample size allows the population to be investigated in GA strata without losing power. A limitation in the present investigation is that the MBR during the study period did not register stillborns before 28 weeks of gestation. Consequently, it is not possible to accurately evaluate the risks for stillbirth at extremely low gestations. Another limitation is the lack of information on twin zygosity and chorionicity, as monochorionic twins have higher mortality than dichorionic twins [15, 26]. In a study by Melamed et al. of 2704 dichorionic twin pregnancies, female-female twin pairs had longer gestation than males, and females in unlike-sexed twin pairs had higher respiratory and neurologic morbidity [23]. In the same study and similar to the present data, MM twin pairs had lower growth rate than males in unlike-sexed twin pairs. These investigators concluded that pregnancy outcome in dichorionic twins is better when there is at least one female twin present. However, almost 70% of the dichorionic twin pairs in the study by Melamed et al. were unlike-sexed twin pairs, and consequently the number of same-sex twin pairs were probably underrepresented, also indicating the difficulties in estimating chorionicity in twin studies. Consequently, future studies should focus on evaluating whether same-sex dizygotic twin pairs have similar outcomes to unlike-sexed twin pairs.

In conclusion, the current study clearly demonstrates the increased risk for perinatal mortality and morbidity in MM twins as compared to FF twins. The male twin in unlike-sexed twin pairs seems to have a significant advantage of having a female co-twin, while the female co-twin seems to have a minor disadvantage of having a male co-twin.

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