Austin Journal of Obstetrics and Gynecology

Austin Publishing Group

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Research Article

Is There an Association Between Fetal Sex and Common Pregnancy-Induced Pathologies?

Gowda M, Kim Y, Bautista J and Tsai MC*
Department of Obstetrics and Gynecology, New York University School of Medicine, USA

***Corresponding author:** Tsai MC, Department of Obstetrics and Gynecology, Bellevue Hospital Center, New York University School of Medicine, 550 First Avenue, NBV 9E2 New York, NY 10016, USA, Tel: 212-263-3147; Fax: 212-263-825; Email: ming.tsai@med.nyu.edu

Received: July 30, 2014; **Accepted:** August 22, 2014; **Published:** August 25, 2014

Abstract

Objective: To investigate the possible correlation between fetal sex and obstetric outcome.

Materials and Methods: We performed a retrospective analysis of all singleton pregnancies delivered between April 2010 and November 2011. The incidences of pregnancy-induced pathologies as well as neonatal outcomes were compared based on fetal sex.

Results: Of the 2834 deliveries analyzed, fetal sex had no significant association with the development of preeclampsia, gestational hypertension, gestational diabetes, or intra hepatic cholestasis. However, when compared to female infants, male infants were significantly larger and more likely to be admitted to the intensive care unit.

Conclusion: Fetal sex does not appear to influence maternal susceptibility to common pregnancy- related pathologies; however, it may affect neonatal outcome. A clinically significant difference was noted in the correlation of fetal gender and admission to the neonatal intensive care unit.

Keywords: Fetal gender; Obstetrics outcome; Pregnancy induced pathology; Fetal sex

Abbreviation

NICU: Neonatal Intensive Care Unit; BMI: Body Mass Index; SRB: Sex Ratio at Birth; IUGR: Intra Uterine Growth Restriction

Introduction

Recent investigations suggest that fetal sex differences may play a role in both maternal and fetal pathophysiology. Overall, male fetuses have been associated with adverse pregnancy outcomes [1]. In the antenatal period, pregnancies carrying a male fetus had a higher incidence of fetal macrosomia, preterm birth, and preterm premature rupture of membranes [2,3]. Pregnancies with a male fetus are associated with arrest of labor; cord prolapsed, and increased frequency of cesarean section [4]. After controlling for potential confounding with birth weight and gestational age, male fetuses was predisposed to having lower Apgar scores at five minutes and non-reassuring fetal heart rate patterns [5]. Female neonates have better outcomes with lower neonatal intensive care unit (NICU) admissions.

Although meta-analysis confirmed the sex-specific difference as an independent risk factor for adverse pregnancy outcomes [1], the effect of fetal gender on pregnancy- induced maternal pathologies is less clear. A number of diagnoses during pregnancy have been noted to occur more frequently with a particular fetal sex; pregnant women with a diagnosis of hyper emesis gravid arum in the first trimester give birth to a higher proportion of females than do all mothers [6]. In a cohort analysis, Demissie et al. found that the male-to-female ratio at birth was significantly higher in pregnant women with placenta previa than in those without [7]. Contemporary literature failed to demonstrate a clear association between gender-related differences and preeclampsia. Conflicting observations of predominance of either male or female fetuses have been reported in mothers with preeclampsia [8-11], however, male infants appears to prevail over female infants in cases of gestational diabetes [1]. There is a paucity of literature currently available to address the correlation of gender-related differences linking other pregnancy-induced maternal pathologies, such as gestational hypertension and intra hepatic cholestasis. If the gender predilection theory is confirmed, then sex selection at the time of conception could have a potential application in modern obstetrics to significantly reduce pregnancy complications. In this study we aim to assess the effect of fetal gender on common pregnancy-induced disorders, including preeclampsia, gestational hypertension, intra hepatic cholestasis of pregnancy and gestational diabetes.

Materials and Methods

All singleton deliveries that occurred at Bellevue Hospital between April 2010 and November 2011 were identified using the Labor and Delivery Log Book. The corresponding charts were then retrospectively reviewed. A total of 2834 singleton pregnancies, resulting in the delivery of 1354 female and 1480 male infants, met inclusion criteria for this study. Clinical data collected for analysis included: induction of labor, mode of delivery, birth weight, sex, APGAR scores, neonatal intensive care unit (NICU) admission, and length of stay. Admission diagnoses for those neonates admitted to the NICU were recorded. Additional parameters explored antenatal maternal pathologies, including preeclampsia, gestational hypertension, intra hepatic cholestasis of pregnancy, and gestational diabetes. Maternal and neonatal morbidities were compared between the two infant gender groups using chi-squared and t-test analysis as appropriate. Differences were considered statistically significant at

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Citation: Gowda M, Kim Y, Bautista J and Tsai MC. Is There an Association Between Fetal Sex and Common Pregnancy-Induced Pathologies?. Austin J Obstet Gynecol. 2014;1(4): 5.

the P< 0.05 level. The significance of the odds ratio for gender and its 95% confidence interval were used to gauge the magnitude of the gender differences in the main study outcomes.

Results

A total of 2834 deliveries (1354 female fetuses, 1480 male fetuses) were included for analysis. Upon evaluation of maternal outcomes, fetal sex had no significant association with the development of maternal preeclampsia, gestational hypertension, diabetes, or intra hepatic cholestasis (Table 1).

With regard to hypertensive disorders of pregnancy, 82 of 1480 pregnancies carrying a male fetus were associated with preeclampsia, in comparison to 66 of 1354 pregnancies carrying a female fetus. The difference in the incidence of preeclampsia between mothers carrying male and female infants was not statistically significant, 5.5 vs 4.9% respectively (OR: 0.87, CI: 0.62-1.23). Similarly, there was no statistically significant difference in gestational hypertension between the two groups. 32 women with male fetuses (2.2%) and 37 with female fetuses (2.7%) developed gestational hypertension (OR: 1.27, CI: 0.77-2.12). Gestational diabetes was present in 96 pregnancies carrying male fetuses and 90 pregnancies carrying singleton female fetuses. The percentage of pregnancies with a diagnosis of gestational diabetes was nearly identical when comparing male and female fetuses, 6.5% and 6.6% respectively (OR1.03, CI 0.75, 1.40). The infrequency of intra hepatic cholestasis of pregnancy in the gravid female population was reflected in the low incidence of the disease in our study population. Only 28 patients with male fetuses (1.9%) and 20 patients with female fetuses (1.5%) were afflicted with this disorder (OR 0.78, CI 0.41, 1.44).

When stratified by infant gender, there did not appear to be any statistical difference in the frequency of preterm birth (p-value 0.840). Prematurity is defined as any delivery prior to completion of 37 weeks of gestation (Table 2). Male infants were found to be significantly larger as compared to female infants (p <0.0001). There was no statistically significant difference in term of mode of delivery between pregnancy bearing male and female infants. In analyzing neonatal outcomes, there appeared to be susceptibility differences between the sexes. Male fetuses had a statistically significant incidence of NICU admissions (17.6 %) as compared to female fetuses (14.8%), p= 0.04. There was a statistically significant need for specialized nursery services for male fetuses (Table 2). When the same comparison was grouped according to NICU admission diagnoses, the most common admission diagnosis were to rule out sepsis followed by respiratory distress syndrome. There were no significant differences in the incidence of meconium aspiration, intrauterine growth restriction, or cardiac anomalies between the two groups. Despite initial trends suggesting otherwise, statistically significant differences were again not apparent with regard to the following conditions: hyperbilirubinemia, respiratory distress syndrome (RDS), and sepsis (Table 3).

Discussion

While our study did not reflect any predilection for maternal illness in women carrying male fetuses, the literature had previously indicated a higher incidence of preeclampsia in this population [1,11-13]. However, not all the studies are supportive of the association between pregnancies with a male fetus and preeclampsia. Japanese's group had reported preeclampsia to be more associated with lower fetal sex ratio (female preponderance) compared to normotensive

Table 1: The association of fetal gender and pregnancy-induced pathology.

	Male fetus (n=1480)	Female fetus (n=1354)	OR (CI)	*P*- Value
Preeclampsia	82/1480 (5.5%)	66/1354 (4.9%)	0.87 (0.62, 1.23)	0.447
Gestational hypertension	32/1480 (2.2%)	37/1354 (2.7%)	1.27 (0.77, 2.12)	0.332
Gestational Diabetes	96/1480 (6.5%)	90/1354 (6.6%)	1.03 (0.75, 1.40)	0.87
Intrahepatic Cholestasis	28/1480 (1.9%)	20/1354 (1.5%)	0.78 (0.41, 1.44)	0.466

Table 2: Association of fetal gender and perinatal outcome.

	Male Infant	Female Infant	*P*- Value
Mean Birth weight (SD)	3344 ± 556	3223 ± 558	< 0.0001
Prematurity	141/1480 (9.5%)	126/1354 (9.3%)	0.840
Cesarean Section	457/1480 (30.8%)	406/1354 (29.9%)	0.601
NICU admission	261/1480 (17.6%)	200/1354 (14.8%)	0.04

Table 3: NICU Admission Diagnosis.

Diagnosis	Male Infant	Female Infant	*P*- Value
Cardiac anomaly	0.76 %	1.4 %	0.658
Hyperbilirubinemia	5.7 %	3.8 %	0.36
IUGR	1.5 %	1.9 %	0.735
Meconium aspiration	4.5 %	5.8 %	0.544
Preterm delivery	13.7 %	17.4 %	0.266
Respiratory distress Syndrome	27.0 %	20.3 %	0.092
Diabetes	12.9 %	17.9 %	0.14
Sepsis	46.9 %	46.6 %	0.941

Abbiviation: IUGR: Intra Uterine Growth Restriction.

pregnant women [8,9], but Makhseed's study did not confirm fetal gender association with preeclampsia [14]. Furthermore, another study reported a significantly lower rate of preeclampsia among women with male offspring in a cohort of singleton pregnancies delivered at <32 weeks gestation [15]. Evidence for this controversy can also be seen at the molecular level: Meta-analysis profiling of placental gene expression in preeclampsia indicates that up-regulation of the LHB cluster gene contributes to the gene expression signature of preeclampsia [16] and LHB is up-regulated in placental interface among pregnancies with a female fetus [17]. In contrast, other studies suggest that in pregnancies complicated by preeclampsia, micro vascular vasodilatation is reduced in women pregnant with a male fetus relative to normotensive women pregnant with a male fetus, with no difference observed in women pregnant with females [12]. These findings attribute the higher placental release of circulating anti-angiogenic products in the male fetus [18]. What if fetal sex association is a biased observation and the maternal pathology happens randomly regardless of fetal gender? It is plausible that other confounding factors such as birth sex ratio, ethnicity, obesity and environmental factors might play roles resulting in the perceived discrepancy of fetal gender preponderance in preeclampsia. In all studies, risk factors for preeclampsia such as maternal diabetes, obesity, weight gain, advanced maternal age, etc. are simply ignored and were not adjusted when calculating the correlation between fetal gender and preeclampsia. Thus, the observed gender association might be casual and this might account for the conflicting findings among different studies. In our study, almost 60% of the study population is Hispanic in origin, with a relatively higher body mass index (BMI) and prevalence of preeclampsia when compared to other patient populations. These factors might account for the lack of gender preponderance in our study. The sex ratio at birth (SRB) alone may be another plausible explanation of the discrepancy of fetal gender predilection in different ethnic groups. The sex ratio of males to females at birth is, on average, 1.03:1, favoring male preponderance. Asian/Pacific Islander newborns, as a group, have the highest male to- female ratio, 1.06:1. SRB of 1.04:1 for Hispanic newborns was intermediate between non-Hispanic white newborns, 1.05:1, and non-Hispanic black newborns, 1.03:1 [19-21]. SRB can be further influenced by sex selection abortion practice, environmental and socioeconomic factors [1]. The underlying reason behind the conflicting data reported in the published studies remains elusive, further studies are needed to gain better understanding.

Similarly, we were not able to replicate previous reports which described both increased incidence of gestational diabetes in pregnancies with a male fetus [1,11]. It is well know that glucose tolerance deteriorates in human pregnancy, but about 97-98% of all pregnant women retain a normal glucose tolerance and only 2-3% develop gestational diabetes [22]. Diabetes develops during pregnancy in women whose pancreatic function is insufficient to overcome the insulin resistance mediated by the placental secretion of diabetogenic hormones including growth hormone, corticotrophin-releasing hormone, placental lactogen, and progesterone [23]. Recent studies postulate an alternative theory linking a male fetus to maternal gestational diabetes with a significantly higher level of testosterone detected in cord blood in male infants compared to female infants [24-26]. Higher levels of testosterone in maternal and fetal circulations were positively associated with insulin resistance in pregnant women resulting in gestational diabetes [24,27]. One interesting observation of Morriset et al., study implied that maternal BMI, rather than the fetal sex, might be the culprit. When considering only male offspring, there was a trend for a positive association between maternal and fetal testosterone levels. When adjusting for maternal BMI, those associations were attenuated to near significant trends, suggesting that maternal BMI may explain in part these associations, confirming that maternal factors, rather than fetal gender, was responsible for the occurrence of gestational diabetes [24]. Our patient population in this study had a significantly higher BMI and incidence of gestational diabetes. We do believe that maternal obesity contributed significantly to the insulin resistance regardless of fetal gender. In addition, we found no fetal sex predilection to intra hepatic cholestasis and gestational hypertension in our study. The result is in concordance with previously published studies [9,14,28].

Although our study did not reveal any particular male vulnerability to preterm labor, previous investigations have reported a higher incidence of preterm birth and preterm premature rupture of membranes in women carrying males. Shorter intrauterine gestations in male fetuses may be a correlate of their greater weight at earlier gestational ages [3]. Another theory links the increased infection rate (in women with male fetuses) to increased incidence of preterm labor and preterm premature rupture of membranes. A third theory implicates the higher androgen levels in males as the mechanism of preterm labor [29]. Our study confirmed a statistically higher number of male neonates required NICU admission. Upon further data stratification based on infant gender, no statistically significant differences were seen based on admission diagnosis (Table 3). For instance, we were not able to draw any definite conclusions based on increased susceptibility to infection or meconium aspiration for male neonates; but as a group, male neonates had a predisposition for critical care referral. Although male infants were larger in size and more likely to be admitted to NICU, we were not able to observe a correlation between male infant weight and NICU admission.

The results of our research support our hypothesis that male sex may be an independent risk factor for adverse neonatal outcomes. Although the exact mechanisms have not been defined, several studies have suggested that differences in metabolism may play a significant role in intrauterine growth, development, and response to stress. Bovine studies show that total glucose metabolism was doubled in male embryos, in comparison to female embryos at the same gestational age [30]. The higher metabolic rate may contribute to accelerated growth and development with a correspondent increase in birth weight. This might explain why the male infants in our study are significantly larger than the female infants. Human studies have demonstrated elevated glucose levels at birth in male neonates [31]. In the same study sample, umbilical cord arterial blood was analyzed in term deliveries, immediately after birth and the majority of male newborns had serum glucose levels above the 95th percentile. Additionally, metabolic variation may account for adaptive response to stress. The same study also measured sex differences in response to labor stress via differences in cord blood pH values. In the group of neonates exposed to labor, there were significantly more male than female neonates with academia (pH < 7.10). Additionally, 7 of 9 cases in the severe acidemia subgroup were

males. There were no differences in cord artery blood pH in neonates who underwent planned Cesarean section. The sexual dimorphism of perinatal outcome can be related to the sex-biased gene expression in the placental interface [17]. Female fetuses invest more in extra-embryonic tissue development than males. Since mothers can allocate limited resources to a fetus in utero, male fetuses invest more resources in body growth and development (embryonic tissue) at the expense of investing less in the development of extra-embryonic tissues [32,33]. This may account for a male bias in the incidence of placental dysfunction [34] and in pregnancy complications where placental pathology is implicated [1,16 19].

We recognize the limitations of our study--a retrospective chart review with a relatively low number of pregnancies enrolled could account for the lack of statistical significance between gender difference and pregnancy-induced maternal pathology. Other reports on the same topic have examined similar sample sizes but the current subject number should nevertheless be taken into account. Despite these limitations, we were able to observe a significant association between male fetal sex and poorer perinatal outcome and higher NICU admission. The strength of this study is that it is one of few studies to investigate the correlation of fetal gender and pregnancy-induced pathologies other than preeclampsia and diabetes. Further studies are needed using different ethnic populations and controlling for confounding factors for maternal pathologies to validate the fetal gender association.

Conclusion

Our study found no association between fetal sex and maternal preeclampsia, gestational hypertension, diabetes, or intra hepatic cholestasis. Male infants are at significantly increased risk of higher birth weight and perinatal complication except preterm birth. One particularly significant finding of this study was the predisposition of males with regard to neonatal intensive care unit admissions.

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Citation: Gowda M, Kim Y, Bautista J and Tsai MC. Is There an Association Between Fetal Sex and Common Pregnancy-Induced Pathologies?. Austin J Obstet Gynecol. 2014;1(4): 5.