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Is fetal gender associated with adverse perinatal outcome in intrauterine growth restriction (IUGR)?

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KEY WORDS
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Objective: The purpose of this study was to determine if there is a difference in perinatal outcome by gender among growth-restricted fetuses.
Study design: This was a retrospective cohort study of intrauterine growth restriction (IUGR) singleton pregnancies over a 5-year period. Clinical outcomes compared by gender included preterm delivery, perinatal mortality (PNM), respiratory distress syndrome (RDS), grade 3 or 4 intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and periventricular leukomalacia (PVL). Statistical analysis included bivariate and multivariable techniques.
Results: Seven hundred and twenty-seven singleton pregnancies with IUGR were identified. Three hundred and forty-six (47.6%) were males. Birth weight was similar between the groups. After adjusting for maternal demographics, medical history, gestational age, mode of delivery, and antenatal corticosteroids, adverse perinatal outcomes were similar between the groups. Severity of outcomes was also similar between males and females ($P = .66$).
Conclusion: Male fetuses with IUGR have similar outcomes when compared with female IUGR fetuses. Gender does not play a role in perinatal outcome in the setting of fetal growth restriction.

Gender differences in perinatal outcome and neonatal mortality have been described in the literature.[1,2] Male gender has been associated with an increased risk of diabetes-related morbidity[3] and preterm birth[4,5] among singleton and multiple gestations. An increased risk of respiratory distress syndrome–related mortality has also been described among male neonates,[6,7] suggesting that slower lung maturation among male fetuses may play a role in the gender differences seen in neonatal mortality.

Intrauterine growth restriction (IUGR) is defined as a manifestation of possible fetal and maternal disorders associated with a birth weight less than the 10th percentile for gestational age.[8] Risk factors for intrauterine growth restriction include smoking, low pre-pregnancy birth weight, and hypertension, among others. An Italian study evaluating gender in IUGR fetuses found that male gender interacted with the classic risk factors for growth restriction, such as smoking and low pre-pregnancy

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weight to increase the magnitude of risk for growth restriction.[9]

Although term and preterm IUGR neonates are at an increased risk of perinatal morbidity and mortality,[8,10] it is unclear whether male gender has a more pronounced effect on adverse perinatal outcome among growth-restricted fetuses. In order to further elucidate factors associated with perinatal outcome in growth restriction, we sought to investigate whether gender was an independent risk factor for adverse outcome among IUGR neonates.

Material and methods

To determine whether gender is independently associated with adverse perinatal outcome among growth-restricted fetuses, we performed a retrospective cohort study. We identified singleton pregnancies affected by IUGR over a 5-year period at the Hospital of the University of Pennsylvania. IUGR was defined as birth weight less than the 10th percentile for gestational age, as described by Brenner.[11] We identified patients with an obstetric database search and reviewed their medical records. Detailed information was collected, including demographics, medical history, obstetric history, gestational age at delivery, mode of delivery, neonatal birth weight, and neonatal outcome. Pregnancies complicated by multiple gestation, structural anomalies, or aneuploidy were excluded from the analysis because these conditions are associated with adverse outcome and are managed differently than singleton or nonanomalous pregnancies. Our institution's ethics committee approved the study.

The exposure of interest for this study is male gender. Clinical outcomes compared between males and females included preterm delivery (delivery at less than 34 weeks' gestation), perinatal mortality (PNM), respiratory distress syndrome (RDS), grade 3 or 4 intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and periventricular leukomalacia (PVL). RDS was defined as a persistent oxygen requirement of $\geq$25% fraction of inspired oxygen (FiO_2) for $\geq$24 hours along with a confirmatory chest radiograph. PVL was identified using standard transcranial ultrasonography diagnostic criteria. We defined perinatal mortality as death in the antepartum period at $\geq$24 gestational weeks or within the first 28 days of life. We constructed a composite major morbidity variable that included 1 or more of the following conditions: RDS, IVH, PVL, NEC, or perinatal death. We collected data on neonatal outcomes by reviewing the neonatal records. The attending neonatologists involved in the neonatal care assigned the diagnoses and outcomes.

For statistical analysis, we used Stata 8.0 SE software (College Station, Tex). Our analysis assessed whether gender was an independent risk factor for adverse perinatal outcome. We compared the study groups with the Student t test for continuous variables, and chi-square analysis or the Fisher exact test for categorical variables. We developed multivariable logistic regression models, controlling for potential confounders, to evaluate the effect of gender on perinatal outcome among growth-restricted neonates. We adjusted for the following potential confounders: maternal age, race (white vs other), smoking status, substance use, medical history, preeclampsia, gestational age at delivery, mode of delivery, and antenatal corticosteroid use. We report adjusted odds ratios (OR) and 95% CIs derived from the models.

Results

Seven hundred and twenty-seven singleton pregnancies with IUGR were identified during the study period. Of these, 346 were males (47.6%). Tables I and II show the characteristics of the population by gender. Mean gestational ages for male and female fetuses were 36.9 weeks and 37.1 weeks' gestation, respectively (P = .49). No significant differences in demographics, medical history, or antenatal history were found in the population when compared by gender. The rates of cesarean delivery were similar between males and females. Among the growth-restricted fetuses delivered by cesarean section, 49% of males and 46% of females were delivered for nonreassuring testing (as defined by the treating obstetrician), respectively (P = .66). The rate of admission to the neonatal intensive care unit (NICU) was similar between males (40%) and females (37%, P = .42).

Unadjusted analyses showed no difference in the rate of the composite adverse perinatal outcome (PNM, RDS, IVH, NEC, and PVL) by gender. Perinatal mortality was similar between growth-restricted males and females; 13 stillbirths and 4 neonatal deaths occurred among the males, whereas 8 stillbirths and 7 neonatal deaths occurred among females (P = .52). Eighty-nine growth-restricted fetuses (12%; 44 males and 45 females) had 1 or more adverse perinatal outcomes. Among males, 33 (9.5%) had 1 adverse outcome and 11 (3.2%) had 2 or more adverse outcomes. Among females, 37 (9.7%) had 1 adverse outcome and 8 (2.1%) had 2 adverse outcomes. Severity of outcomes (defined as 1 vs 2 or more adverse outcomes) was similar between males and females (P = .66). Delivery gestational age was first categorized as delivery between 24 and 34 weeks' gestation, delivery between 34 and 36+6 weeks' gestation, and delivery after 37 weeks' gestation. No differences in individual or composite outcomes were noted between males and females when stratified by gestational age category (data not shown). Outcomes were also similar among preterm fetuses when

Table I Comparison of the IUGR population by gender

Characteristic	Males (n = 346)	Females (n = 381)	*P* value
Demographics			
Maternal age	25.9 ± 7.0	25.9 ± 7.0	.98
Gravidity	2.9 ± 2.2	3.14 ± 2.5	.31
Delivery gestational age (wk)	36.9 ± 3.4	37.1 ± 3.2	.49
Birth weight (g)	1357 ± 708	1402 ± 720	.58
Race (white vs other)	9.3	8.4	.68
Smoking	16.2	15.2	.72
Drug use*	7.3	8.2	.65
Medical history			
Chronic hypertension	5.8	8.4	.18
Pregestational diabetes	2.9	1.8	.35

Data are reported as mean ± standard deviation for continuous variables or percentage for discrete variables.

* Drug use includes the use of marijuana, cocaine, or intravenous drugs during pregnancy.

Table II Antenatal history of the IUGR population by gender

Antenatal history	Males (n = 346)	Females (n = 381)	*P* value
Gestational age at diagnosis of IUGR (wk)	31.2 ± 6.0	31.6 ± 5.9	.42
Previous preterm delivery	6.7	8.4	.43
IUGR in previous pregnancy	9.3	5.9	.11
Antenatal corticosteroids*	13	12	.71
Preeclampsia	17.4	15.6	.53
Cesarean section	33.3	32.3	.76
NICU admission	40	37	.42

Data are reported as mean ± standard deviation for continuous variables or percentage for discrete variables.

* Information not available for 25% of patients, 14% of which delivered before 34 weeks.

Table III Logistic regression models for the effect of gender on outcomes among growth restricted fetuses

Outcome	Males (n = 346)	Females (n = 381)	Adjusted OR (95% CI)
Delivery <34 weeks*	12.4	13.4	0.85 (0.52, 1.39)
PNM†	4.9	3.9	1.09 (0.32, 3.75)
RDS†	8.0	6.7	1.17 (0.54, 2.53)
IVH†	3.5	2.4	1.65 (0.57, 4.74)
NEC†	1.2	1.3	0.76 (0.16, 3.68)
PVL†	<1.0	0	—
Composite major morbidity	12.7	11.8	0.83 (0.41, 1.65)

Data are given as percentage.

* Model was adjusted for maternal age, race (white vs other), smoking status, medical history, preeclampsia, substance use, and mode of delivery.

† Models were adjusted for maternal age, race (white vs other), smoking status, medical history, preeclampsia, substance use, gestational age at delivery, mode of delivery, and antenatal corticosteroid use.

gestational age was categorized as delivery between 24 and 27+6 weeks' gestation, delivery between 28 and 32 weeks' gestation, and delivery between 32 and 34 weeks' gestation.

Logistic regression models were developed to determine the effect of gender on neonatal outcome controlling for potential confounders. Confounding variables were selected for their biologic significance. Preterm delivery rates were similar between the groups. After adjusting for maternal age, race (white vs other), smoking status, medical history, preeclampsia, substance use, gestational age at delivery, mode of delivery, and antenatal corticosteroid use, individual and composite outcomes for growth-restricted fetuses were similar between males and females (Table III).

Data on the use of antenatal corticosteroids were unavailable for 25% of patients, 14% of which delivered before 34 weeks' gestation (equally distributed between male and female fetuses). Sixty percent of patients who delivered before 34 weeks received antenatal steroids, whereas 25% did not. We performed our primary analysis assuming that patients without documentation of antenatal steroids did not receive steroids. Excluding these patients or assuming that they received steroids in secondary analyses did not alter the results of our models (data not shown).

Comment

In our cohort, growth-restricted male fetuses have perinatal outcomes similar to growth-restricted female fetuses. Our data suggest that gender is not an independent risk factor for adverse perinatal outcome in the setting of fetal growth restriction.

Male gender in earlier studies, not specifically addressing growth restriction, has been linked to adverse perinatal outcome.[1,6,7] A study on neonatal morbidity and mortality statistics for Wisconsin from 1979 through 1982 found that deaths secondary to RDS were greater for males regardless of Apgar scores, delivery mode, maternal age, or ancillary diagnosis.[7] A 1985 study using linked birth and death certificates from infants born in Georgia between 1974 and 1977 noted a higher mortality rate in males than in females.[6] An excess in neonatal mortality rates among males was noted for almost all causes of death, but it was most pronounced for RDS, suggesting that slower lung maturation among male fetuses contributes to gender differences in neonatal mortality. Data from the National Institute of Child Health and Human Development (NICHHD) Neonatal Research Network evaluating the effects of mechanical ventilation among

extremely premature infants (501-800 g) in 1994 and 1995 found that females had an advantage in survival with mechanical ventilation equivalent to an increase in birth weight of 90 g.[12] Recent data from Sweden (1999-2000) noted a gender difference in neonatal mortality within the first week of life for infants born between 24 and 32 gestational weeks, 6.3% for males versus 3.7% for females.[1] The limitation of interpreting data from earlier studies is that antenatal corticosteroids were not routinely used during those time periods. Data on antenatal corticosteroids are not mentioned in the Sweden review by Ingemarsson. However, data suggest a greater effect of betamethasone prophylaxis in RDS prevention in female infants when compared with male infants.[13-15] The study from NICCHD showing a female advantage in survival with mechanical ventilation did not specifically address growth restriction and only evaluated extremely preterm infants.[12]

Our study findings suggest that in the setting of IUGR, the proposed slower lung maturation in males is not a major contributing factor in developing an adverse outcome. Earlier data suggested that growth restricted neonates had better outcomes and less RDS caused by stress-induced fetal maturity.[16,17] One may hypothesize that males in our cohort did not have worse outcomes when compared with females because of stress-induced maturation effects of fetal growth restriction. However, recent data do not support the notion that growth-restricted neonates have improved outcomes.[10,18] We conclude from our results that the failure of a fetus to achieve his or her growth potential adversely impacts perinatal morbidity and mortality independently of gender,[8] but we are unable to determine whether a stress-induced "maturity" conferred by fetal growth restriction alters the relationship between fetal gender and neonatal outcome.

One of the limitations of our study is that information on the use of antenatal corticosteroids was unavailable for 14% of patients who delivered before 34 weeks' gestation. However, we performed our analysis assuming that patients without documentation of antenatal steroids did not receive steroids. Excluding these patients or assuming that they received steroids in a sensitivity analysis did not alter our results. Significant differential information bias on the administration of steroids is unlikely to have occurred by gender.

We also do not have complete information on the etiology of IUGR in these structurally normal fetuses, but because antenatal history and perinatal outcomes are similar between males and females, it is unlikely that the etiologies of IUGR would be markedly different by gender. We excluded fetuses with congenital anomalies and aneuploidy to minimize heterogeneity in the study population that might mask differences between the study groups.

Length of stay in the NICU was not available for the entire cohort. Although information on NICU stay is undoubtedly clinically important, we were interested in evaluating well-defined neonatal outcomes such as RDS, IVH, NEC, and PVL. Apgar scores were available for most patients but were not analyzed in our study because several of the Apgar score components are subjective and factors such as gestational age and low birth weight may affect the score.[19] In addition, we feel that the Apgar score is a less important surrogate outcome since its predictive ability for most concrete neonatal outcomes is limited.

Because our results showed no difference in growth-restricted fetuses by gender, we performed a post-hoc power analysis to evaluate whether our sample size had enough power to detect a difference in perinatal outcomes. We found that our retrospective cohort study had 80% power to detect an OR of at least 1.8 for the composite outcome in males when compared with females.

In conclusion, male fetuses with IUGR have similar outcomes to female IUGR fetuses. Although our study findings may not directly impact clinical management of an IUGR pregnancy, they help in further understanding the morbidity and mortality risks in growth-restricted fetuses and may be used in prenatal patient counseling. The concept that preterm males do not perform clinically as well as females does not seem to apply in the setting of growth restriction. Factors other than gender play a role in the perinatal outcome of these pregnancies.

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