Fetal Sex as a Predictor of Sleep Disordered Breathing and Associated Pregnancy Complications: Analysis of a National Perinatal Cohort

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Abstract

Study objectives: We aimed to determine if fetal sex was associated with sleep disordered breathing (SDB) in pregnancy, and if fetal sex was associated with increased risk for adverse pregnancy outcomes among women with sleep disordered breathing. Methods: We analyzed 1,312,681 maternal-infant dyads from the National Perinatal Information Center database. This database includes discharge diagnosis and procedure codes based on the International Classification of Diseases, 9th Revision (ICD-9) from hospitals across the United States. We examined associations between fetal sex and SDB, gestational diabetes, gestational hypertension, preeclampsia, preterm birth, delivery type, and stillbirth. Results: Women were on average 30 years old (SD=6) and were 46% White, 18% Black, and 7% Hispanic. Logistic regression analyses revealed that carrying a male fetus was associated with increased risk for gestational diabetes (ORadj. 1.04, 95% CI 1.02-1.05, p-value <0.001), gestational hypertension (ORadj. 1.04, 95% CI 1.02-1.05, p-value =0.001), Cesarean delivery (ORadj. 1.17, 95% CI 1.16-1.19, p-value <0.001), and preterm birth (ORadj. 1.13, 95% CI 1.11-1.15, p-value <0.001). Fetal sex was not associated with SDB (ORadj. 0.99, 95% CI 0.89-1.12, p-value=.98), nor did fetal sex increase risk for adverse pregnancy outcomes among women with SDB (p-values > .09). Conclusions: Male fetal sex was associated with an increased risk for a number of adverse pregnancy outcomes, however fetal sex was not associated with SDB. Given the low rates of SDB discharge diagnoses in this cohort, future research is needed using objective measures of SDB to evaluate the association between fetal sex and SDB.

Introduction

Fetal sex has a profound effect on maternal health. In pregnancy, the fetal-placental unit allows for bi-directional communication between mother and fetus. Findings from both the human and animal literature demonstrate sexually dimorphic fetal-placental adaptations to signals from the maternal[1-3] and fetal environments[4, 5]. A recent review indicates that male fetal sex increases risk for a myriad of adverse perinatal outcomes, including preeclampsia[6], macrosomia, gestational diabetes, small for gestational age, stillbirth, Cesarean delivery, and preterm birth[7]. Male fetal sex also increases the odds of requiring insulin among pregnant women with gestational diabetes[8].

Despite accumulating evidence that male fetal sex is a risk factor for a host of adverse pregnancy outcomes, little is known about the impact of fetal sex and sleep disordered breathing. Maternal sleep disordered breathing (SDB), a condition in which pregnant women are affected by upper airway obstruction during sleep, affects 4-11% in first trimester and 6-25% by the third trimester, resulting in nearly two million

pregnant women and infants impacted by SDB in the United States each year[9]. SDB increases risk for adverse pregnancy outcomes that are also increased by male fetal sex, including hypertensive disorders[10], gestational diabetes[11, 12], and preterm birth[13, 14]. Prior studies suggest that the underlying pathophysiology of SDB may be impacted by fetal sex. Upper airway physiology including upper airway muscle function, nasal resistance and ventilatory control may be impacted by reproductive hormones. Progesterone, a respiratory drive stimulant that may be protective against the development of SDB[15], is lower across pregnancy among women carrying female fetuses[16]. Similarly, estradiol, an anti-oxidant hormone, is higher among women carrying female fetuses[17]. Finally, there is some evidence that pregnant women carrying female fetuses have lower weight gain in pregnancy relative to women carrying males[18]. This is important as obesity is a risk factor for SDB in pregnancy[19].

Results from a recently published study found that pregnant women carrying a male fetus were at increased risk of self-reported frequent loud snoring[20]; snoring is strongly associated with SDB in pregnancy[9]. Limitations of this study included the self-reported nature of symptoms of SDB and the relatively small sample size (approximately 1000 maternal-infant pairs). In addition, maternal and neonatal consequences of SDB may differ depending on fetal sex. In our previous study, among women who reported frequent loud snoring, male fetal sex increased risk for hypertensive disorders of pregnancy[20]. Exposure to intermittent hypoxia and sleep fragmentation in pregnant animals shows epigenetic and metabolic changes in the offspring that appear to be sex specific[21, 22]. Specifically, male mice exposed to sleep fragmentation in utero had increased susceptibility to obesity and metabolic syndrome and displayed increased body weight, food consumption, glucose tolerance, insulin resistance, and methylation of adipokines compared to female mice following sleep disturbances[22]. Thus, research on the association between fetal sex and SDB, as well as fetal sex as a moderator of the association between SDB and adverse pregnancy outcomes, is warranted.

In this study, we evaluated the association between fetal sex and maternal SDB, in addition to a number of adverse pregnancy outcomes that have been previously reported to differ according to fetal sex, using a national perinatal cohort database of over 1 million mother-infant dyads. We also evaluated if adverse maternal and neonatal consequences of SDB differed by fetal sex. We hypothesized that women carrying male fetuses would be at higher odds of having SDB in pregnancy, and the association between SDB and adverse pregnancy outcomes would be stronger among women carrying male fetuses compared to women carrying female fetuses.

Methods

To test our study aims, we analyzed data from the National Perinatal Information Center (NPIC). The dataset contains nearly 1.5 million de-identified linked maternal and neonatal records for deliveries from hospitals between 2010 and 2014. The dataset consists of maternal characteristics, billing information, and diagnosis and procedure codes based on the International Classification of Diseases, 9$^{\text{th}}$ Revision (ICD-9). NPIC is a membership organization consisting of perinatal centers from across all geographic census divisions of the U.S. (as defined by the American Hospital Association) that submit clinical and financial information for participation in the Perinatal Center Database (PCDB). Data are validated prior to being compiled into the PCDB, which consists of both maternal and neonatal hospital discharges, the latter occurring from birth to 28 days after birth. A validation report is communicated back to respective hospitals to address inconsistencies. Hospitals examine their metrics, address potential issues or discrepancies with provider documentation, coding, or quality, and correct their data prior to being included in the database for quarterly reporting. Multiple levels of comparison are provided for every metric reported. Hospital data are routinely compared to a peer subgroup, PCDB as a whole, a trend database, and other national benchmarks.

The neonatal record specifies neonatal sex and the maternal record has information on the exposure variable (maternal sleep disordered breathing) as well as adverse pregnancy outcomes (preeclampsia, gestational diabetes, gestational hypertension, stillbirth, preterm birth, delivery type). Other conditions that may influence our outcomes of interest, such as maternal obesity, smoking status, and medical conditions prior to pregnancy (such as diabetes and hypertension), were examined as covariates. The study was reviewed and approved by Institutional Review Boards of Women and Infants Hospital of Rhode Island (#881483,

04/27/2016) and Lifespan Hospital System (#894311, 05/10/2016).

Statistical Approach

All analyses were conduct in R version 3.6.0[23]. Our goal was to examine the association between 1) fetal sex and risk for adverse pregnancy outcomes including: SDB, gestational diabetes, gestational hypertension, preeclampsia, preterm birth, delivery type, and stillbirth, and 2) to examine the association between fetal sex and pregnancy complications among women with an SDB diagnosis. Only singleton pregnancies were included in the analyses in order to eliminate pregnancies carrying more than one fetal sex. Participants with a diagnosis of diabetes prior to pregnancy were excluded in order to examine the relation between fetal sex and diabetes onset in pregnancy.

We ran a series of Chi-square tests of independence between fetal sex and each of the pregnancy outcomes. We then conducted a series of logistic regression where fetal sex was treated as the predictor variable and the aforementioned pregnancy outcomes were the dependent variables in individual models. Fetal sex was dummy coded in the models such that females were coded 0 and males were coded 1. All of the dependent variables were categorical and coded yes=1, and no=0. Next, we selected only those women with a SDB diagnosis, and then repeated the series of logistic regression where fetal sex was treated as the predictor variable and the pregnancy complications were the dependent variables.

For each model we derived a coefficient statistic, odds ratio, 95% confidence interval, unadjusted p-value, and adjusted p-value (to account for multiple models). The following variables were entered into each model as a priori covariates: race/ethnicity, age, obesity, pre-pregnancy hypertension, chronic renal disease, previous Cesarean section, tobacco use, alcohol use, and other drug use. All of the covariates were categorically coded yes=1, and no=0 except for age which was treated as a continuous variable. The race/ethnicity variable was recoded to contrast white individuals and all other racial/ethnic groups. Both the predictor variable (i.e., fetal sex) and covariates were entered simultaneously into the logistic regression models.

Results

1,312,681 maternal-infant dyads were included in analyses. In tables 1 and 2 we display maternal and fetal sample characteristics. We provide mean and standard deviations for all continuous variables and percentages for all categorical variables. Women in this study were, on average, 30 years old (SD=6), 46% were categorized as White race, 18% Black race, and 7% Hispanic ethnicity. Approximately 6% of women had a diagnosis of obesity. Women had, on average, one prior live birth (SD=1). According to hospital codes, 3.5% of participants used tobacco, 0.10% used alcohol, and 1.3% used drugs in pregnancy.

Approximately 7% of women in this sample were diagnosed with gestational diabetes, 5% with gestational hypertension, 4% with preeclampsia, and 0.10% with SDB. 33% of deliveries were Cesarean, and <.01% of births were stillbirths. 51% of the infants were male, and approximately 6% of births occurred prior to 37 weeks' gestation (i.e., preterm births).

Table 3 provides a summary of Chi-square statistics which examines the unadjusted association between fetal sex and pregnancy outcomes. Women carrying male fetuses were significantly more likely to be diagnosed with gestational diabetes (χ^2 =27.29, p<.001), and gestational hypertension (χ^2=20.26, p<.001) than women carrying female fetuses. Women carrying male fetuses were also more likely to have a Cesarean delivery (χ^2 =873.01, p<.001), and to deliver preterm (χ^2 =269.36, p<.001) than women carrying female fetuses. Women carrying females were more likely to be diagnosed with preeclampsia compared to women carrying male fetuses (χ^2 =4.04, p=.04). We did not observe differences in stillbirth or SDB diagnosis by fetal sex.

Logistic regression analyses, adjusting for covariates, revealed that pregnant women carrying male fetuses had approximately 4% higher odds of a diagnosis of gestational diabetes (OR_{adj}. 1.04, 95% CI 1.02-1.05, p-value <0.001), approximately 4% higher odds of a diagnosis of gestational hypertension (OR_{adj}. 1.04, 95% CI 1.02-1.05, p-value =0.001), approximately 17% higher odds of having a cesarean delivery (OR_{adj}. 1.17, 95% CI 1.16-1.19, p-value <0.001), and approximately 13% higher odds of having a preterm birth (OR_{adj}. 1.13, 95% CI 1.11-1.15, p-value <0.001) than pregnant women carrying female fetuses. We did not find

statistically significant effects on the association between fetal sex and preeclampsia, stillbirth, or SDB. See Figure 1.

Among only those women with an SDB diagnosis (n=1,333), fetal sex did not predict any pregnancy complications (p-values > .09), suggesting that fetal sex was not associated with risk for adverse pregnancy outcomes among women with SDB.

Discussion

Main Findings

Results from this study replicated findings from previous research that male fetal sex is associated with increased risk for adverse pregnancy outcomes including gestational diabetes, gestational hypertension, Cesarean delivery, and preterm birth[6, 24, 25] after adjusting for multiple confounding factors, but not with SDB. We observed very modest increased odds (4%) of gestational diabetes among women carrying males. Our findings are consistent with Jaskolka et al 2015[26] who also reported a 4% increased odds of gestational diabetes among women carrying male neonates. Others have not observed an association between fetal sex and gestational diabetes; however samples sizes were smaller than in the present study (n=20,000 vs. 1.3 million)[27]. We observed an increased rate of cesarean deliveries among male babies, which is consistent with previous studies, and has been attributed to larger fetal size[28] and greater fetal distress[29]among males. Male fetuses were at greater risk for preterm delivery, consistent with past epidemiologic studies[30, 31]. This association has been hypothesized to be driven by a greater pro-inflammatory fetal-placental environment[32].

We did not replicate previous research indicating an increased risk for stillbirth in male neonates; however, others have also failed to find an association between fetal sex and rates of stillbirth[33, 34]. We also did not observe previously-reported differences in preeclampsia by fetal sex[6], however, we did find that rates of gestational hypertension were higher among women carrying male fetuses, as has been demonstrated in past literature[35]. Greater rates of gestational hypertension among women carrying male fetuses has been attributed to higher cardiovascular and metabolic demands on women carrying male fetuses[35].

Contrary to our hypothesis, we did not find an association between fetal sex and SDB diagnosis. As well, we did not find an association between fetal sex and pregnancy complications among only those women with an SDB diagnosis. This is in contrast to recently published findings showing that women carrying male fetuses were more likely to report frequent loud snoring (a key symptom of SDB), and pregnant women with frequent loud snoring carrying male fetuses were also more likely to experience hypertensive disorders in pregnancy[20]. We surmise that the lack of association between fetal sex and SDB in this database may have been driven by the potential underreporting of SDB in hospital diagnosis and procedure codes, due in large part to under-diagnosis of the condition in this population. Specifically, only 0.1% of women in this sample had an SDB diagnosis on their hospital record. The prevalence of SDB in this sample is substantially lower than the national averages (4-25%[9]). We suggest that future studies, using improved objective assessment of SDB, examine the association between fetal sex and prevalence of this condition.

Interpretation

SDB remains under-detected and under-treated in pregnancy. Surveys of obstetric providers indicate a lack of institutional guidelines for SDB screening in pregnancy, and low screening rates[36-38]. The most commonly used self-report questionnaires for screening for SDB in pregnancy include the Berlin Questionnaire and the Epworth Sleepiness Scale, neither of which demonstrate adequate predictive value in pregnancy, particularly in the 1sttrimester[39-44]. For this reason, there is an interest in the field to develop screening algorithms to identify pregnant women at risk for SDB. Maternal characteristics including age, BMI, self-reported and/or bedpartner-reported snoring, tiredness at awakening, diagnoses of chronic hypertension, pre-gestational diabetes, history of preeclampsia have been included in past algorithms to determine SDB risk[45-48]. As fetal sex is now being identified earlier in pregnancy than in the past, given the advent of cell free DNA as a screening test, future research is needed to examine whether the addition of fetal sex to previously developed SDB screening algorithms improves sensitivity, specificity, and predictive value of SDB

in pregnancy.

Strengths and Limitations

Results from this study should be interpreted in light of several limitations. First, given the low prevalence of SDB in this sample, it is likely that hospital discharge diagnosis and procedure codes underreported women who experienced SDB in pregnancy. This was not the case for other pregnancy outcomes including gestational diabetes, gestational hypertension, and cesarean delivery, which were comparable to national rates in the United States[49]. However, rates of preterm birth in this sample (approximately 6%) were lower than national averages. In addition, we did not have information on whether women received treatment for SDB, which could have impacted our examination of fetal sex as a moderator of the association between SDB and adverse pregnancy outcomes. We were also unable to examine if rates of cesarean section differed by male sex due to indicators such as fetal distress, as has been shown in past studies [8, 29]. Strengths of this study include the large sample size, the inclusion of pregnancies from across the United States, and adjustment for multiple confounding factors.

Conclusion

In this national cohort of over 1.3 million mother-infant dyads, we found that women carrying male fetuses were at increased risk for gestational hypertension, gestational diabetes, cesarean delivery, and preterm birth. Women were not more likely to have a diagnosis of sleep disordered breathing, however, rates of SDB were significantly lower in this sample than national averages, suggesting that SDB was underreported. These findings are in contrast to a recent paper that observed increased risk for self-reported symptoms of SDB among women carrying male fetuses. Taken together, future research using objective measures of sleep disordered breathing is needed to test the association between fetal sex and SDB.

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Figure Legend

Figure 1. Odds ratios of fetal sex and pregnancy complication

Note. Increased odds indicate increased risk among women with male fetuses. Logistic regression models adjusted for race/ethnicity, age, obesity, pre-pregnancy hypertension, chronic renal disease, previous C-section, tobacco use, alcohol use, and other drug use. GDM = gestational diabetes. GHTN = gestational hypertension. PTB = preterm birth. PEC = preeclampsia. SDB = sleep disordered breathing.

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