Exploring Fetal Sex as a Risk Factor for Sleep Disordered Breathing and Its Complications in Pregnancy

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Abstract

Sleep disordered breathing (SDB) is a common, yet under-recognized and undertreated condition in pregnancy. Sleep disordered breathing is associated with pregnancy complications including preeclampsia, gestational diabetes, preterm birth, as well as severe maternal morbidity and mortality. The identification of risk factors for SDB in pregnancy may improve screening, diagnosis, and treatment of SDB prior to the onset of pregnancy complications. The goal of this study was to determine whether fetal sex increases risk of SDB in pregnancy. A cohort of singleton (N = 991) pregnant women were recruited within 24 to 48 hours of delivery and answered questions regarding SDB symptoms by questionnaire. Women who reported frequent loud snoring at least 3 times a week were considered to have SDB. Hospital records were reviewed to extract information on fetal sex and pregnancy complications including preeclampsia, pregnancy-induced hypertension, gestational diabetes, preterm delivery, and low birth weight. Women carrying male fetuses were significantly more likely to have SDB (β = .37, *P* = .01, OR: 1.45 [95% CI: 1.09–1.94]). Fetal sex was associated with increased risk of hypertensive disorders of pregnancy (defined as preeclampsia and/or pregnancy-induced hypertension) among women with SDB in pregnancy (β = .41, *P* = .02, OR: 1.51[95%CI:1.08–2.11]).Fetal sex did not increase risk of preterm birth, low birth weight, or gestational diabetes among women with SDB in pregnancy. Women carrying male fetuses were approximately 1.5 times more likely to report SDB in pregnancy compared to women carrying female fetuses, and women with pregnancy-onset SDB

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carrying male fetuses were 1.5 times more likely to have hypertensive disorders of pregnancy compared to women with SDB carrying female fetuses. Confirmation of fetal sex as a risk factor may, with other risk factors, play a role in identifying women at highest risk of SDB complications in pregnancy.

Keywords

sleep disordered breathing; fetal sex; pregnancy; hypertensive disorders

Introduction

Maternal sleep disordered breathing (SDB), a condition in which pregnant women are affected by airflow limitation, recurrent arousals, and snoring during sleep, increases the risk of adverse perinatal outcomes, including hypertensive disorders,[1,2] gestational diabetes,[2,3] preterm birth,[4–6] and severe maternal morbidity,[2] and mortality.[1] Some form of SDB affects nearly 2 million pregnant women and infants in the United States each year, making SDB a major public health concern. The prevalence of SDB increases as pregnancy progresses, ranging from 4% to 11% in the first trimester, to 6% to 25% in the third trimester.[7] Sleep disordered breathing is even more common in women with complicated pregnancies, with prevalence rates that reach 50% to 75%.[8–10] However, despite the high prevalence of SDB in pregnancy and the increased risk of adverse pregnancy outcomes, SDB remains under-detected and undertreated in pregnant women.[2,11]

Fetal Sex and Pregnancy Complications

Past evidence demonstrates that fetal sex increases the risk of several adverse pregnancy outcomes that are also associated with SDB. Available data have examined the association of fetal sex with various perinatal outcomes but not in the context of SDB. Specifically, women carrying male fetuses are at increased risk of preeclampsia,[12] gestational diabetes,[13] preterm labor, uterine cord prolapse, and still birth.[14] In a meta-analysis that included more than 3 million pregnancies, male fetal sex was associated with a higher risk of preeclampsia in non-Asian populations.[12] Rates of gestational diabetes, a disease with high co-occurrence with SDB,[3] appear to be higher among pregnant women with male fetuses,[13] which may be due to poorer beta cell functioning among pregnant women with male fetuses.[13] Maternal systolic blood pressure is higher among women carrying male fetuses,[15] although observed sex differences in blood pressure were not replicated in a population-based study of pregnant women from Norway,[16] and women carrying male fetuses exhibit a more pro-inflammatory milieu in pregnancy.[17,18] Exposure to intermittent hypoxia and sleep fragmentation in pregnant animals shows epigenetic and metabolic changes in the offspring that appear to be sex-specific[19,20] such that male mice exposed to sleep fragmentation in utero had increased susceptibility to obesity and metabolic syndrome compared to females.[20]

Fetal Sex and SDB-Related Pathophysiology in Pregnancy

Differences in maternal levels of reproductive hormones by fetal sex[21–25] raise the question of whether fetal sex may play a role in the pathogenesis of SDB in pregnancy. In nonpregnant women, there is evidence that higher levels of testosterone increases risk of

SDB; women with polycystic ovarian syndrome (characterized by higher testosterone levels) have higher apnea/hypopnea index.[26] Male fetuses begin testosterone synthesis around gestational week 8, and secretion is high between weeks 10 and 20.[27] Human and animal studies indicate that testosterone is liposoluble and readily crosses the placental barrier.[28,29] There is also evidence of high concordance between maternal and fetal testosterone levels,[30] although results are inconsistent.[31,32] These findings suggest that women carrying males may have higher testosterone levels in pregnancy. Past findings evaluating weekly reproductive hormone levels have shown higher levels of estradiol in pregnancies carrying a female fetus in early pregnancy.[24] These findings have been demonstrated in other studies as well[25] where estradiol levels are 9% higher in pregnant women carrying a female fetus compared to those carrying a male fetus. In rhesus fetuses, progesterone levels were higher in umbilical artery and vein in pregnancies carrying a female fetus, suggesting sex-specific influence on biosynthesis and metabolism of progesterone.[33] As reproductive hormones have been implicated in upper airway patency and the pathogenesis of SDB,[34] and those same hormones may be impacted by fetal sex during pregnancy, we hypothesized that the risk of SDB may be higher among women carrying male fetuses.

Fetal Sex and Risk of SDB-Associated Pregnancy Complications

It is also biologically plausible that fetal sex may play a role in the association of SDB with adverse perinatal outcomes. The examination of fetal sex as a risk factor for SDB complications is predicated on differences in maternal physiology by fetal sex that may predispose women to adverse obstetric outcomes associated with SDB, and the reported differences by fetal sex in the development of these outcomes.[12–14,35] Moreover, there are fetal sex differences in biological pathways shared by SDB and perinatal outcomes such as preeclampsia. Several studies have demonstrated that pregnant women carrying a female fetus, in the absence of chromosomal abnormalities, have higher levels of free β-hCG and pregnancy-associated plasma protein A (PAPP-A).[21–23] It is also known that having low first trimester PAPP-A values is associated with increased risk of obstetric complications, such as preeclampsia and maternal long-term cardiovascular diseases,[36,37] and our own data have shown lower levels of PAPP-A in women with SDB compared to controls.[38]

Screening Algorithms for SDB in Pregnancy

In order to improve prediction of SDB in pregnancy, several groups have developed screening algorithms to identify women at risk of SDB. In the nuMoM2b study,[39] Louis et al found that age, body mass index (BMI), and frequent snoring predicted SDB in pregnancy.[40] Wilson et al determined that self-reported snoring, BMI, and tiredness at awakening were the strongest predictors of SDB. The screening algorithm developed by Facco et al[41] included self-reported frequent snoring, chronic hypertension, BMI, and age. Finally, Balserak et al[42] found that the Sleep Apnea Symptom Score + age, BMI, and bedpartner-reported snoring information demonstrated improved sensitivity and specificity to detect SDB in pregnancy. Given that the determination of fetal sex is clinically obtained regardless of women's desire to learn the sex of the baby, fetal genitalia are evaluated by routine second trimester fetal anatomy surveillance, and more recently, fetal sex is identified by first trimester fetal DNA testing, fetal sex could be incorporated into screening algorithms to

improve the identification of women at highest risk of SDB and associated complications in pregnancy.

Taken together, past findings support the biological plausibility of fetal sex leading to differences in maternal vulnerability for SDB, and maternal comorbidities associated with SDB in pregnancy. Therefore, the goals of the current study were to examine (1) the association between fetal sex and SDB and (2) the moderating role of fetal sex in the association between SDB and pregnancy complications. We hypothesized that women carrying male fetuses would be more likely to report SDB, and women with SDB would be more likely to experience pregnancy complications if they were carrying male fetuses.

Materials and Methods

A cohort of singleton pregnant women were recruited within 24 to 48 hours of delivery and answered questions regarding SDB symptoms by questionnaire. Participants were selected randomly from daily lists of all deliveries and recruited. Participants were included if they were English speaking and > 18 years old. Women with a fetal demise were excluded. Detailed methods were published elsewhere.[43] Women that reported frequent loud snoring at least 3 times a week on the multivariable apnea prediction index were considered to have SDB. Questions were as follows: in the last 3 months of your pregnancy, how often have you experienced (or were you told) about the following symptoms? (1) You snored loudly; (2) You snorted or gasped; (3) Your breathing stopped, you choked or you struggled for breath. Answers: (0) Never; (1) Rarely (less than once a week); (2) Sometimes (1–2 times a week); (3) Frequently (3–4 times a week); (4) Always (5–7 times a week). Women were also asked about SDB symptoms prior to pregnancy. Records of newborn infants were reviewed and neonatal biological sex at birth was recorded. Women with multiple gestations were excluded for the current analyses (N = 30) in order to isolate the effect of fetal sex. Charts were reviewed for maternal conditions including preeclampsia, pregnancy-induced hypertension, gestational diabetes, preterm delivery (< 37 weeks gestation), and low birth weight (<2500 grams) per guidelines at the time the study was conducted and initially reported. Preeclampsia and pregnancy-induced hypertension were classified based on the American Colleges of Obstetricians and Gynecologists definition, and gestational diabetes definition was based on Carpenter and Coustan criteria and the American Diabetes Association.[44–46] Preeclampsia and pregnancy-induced hypertension variables were combined to create a hypertensive disorders of pregnancy outcome variable. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the IRB (#254193 approved 8/12/2011, #792357 approved 6/12/2015). All women provided written consent prior to their participation.

Statistical Approach

IBM SPSS version 25 was used for statistical analyses. Descriptive statistics were performed to characterize the sample. Binary logistic regression analyses were used to determine whether fetal sex predicted SDB. Fetal sex was dummy coded in the models such that females were coded 0 and males were coded 1. Sleep disordered breathing and pregnancy complications were categorical and coded yes = 1 and no = 0. To determine whether fetal

sex moderated the association between SDB and adverse pregnancy outcomes, we calculated an interaction term by multiplying SDB status (yes/no) and fetal sex (male/female). The interaction term was then entered into the logistic regression model as an independent variable, along with SDB, fetal sex, and covariates. Pregnancy complications were entered into logistic regression models as dependent variables. We examined associations between SDB and fetal sex first in the whole sample, and next among women with SDB symptoms that began in pregnancy. Body mass index and maternal age were included in all analyses as covariates.

Results

A total of 1069 women were enrolled in the study, and 991 women were included in the current analyses after excluding for multiple gestations (N = 30) and the response "unknown" to self-reported snoring (N = 48). Women in this sample were, on average, 29 years old (SD = 10), BMI upon hospital admission for delivery was 32 (SD = 6), and racial/ ethnic composition of the sample was as follows: 70% White, 15% Hispanic, 11% Black, 4% Asian, 1% American Indian/Alaska Native, and 1% Native Hawaiian/Pacific Islander. Fifty-two percent of the neonates in the sample were male. Twenty-eight percent of the women reported SDB symptoms of frequent loud snoring in pregnancy (N = 279) and 72% of these women reported that SDB symptom onset began in pregnancy (N = 202; see Figure 1).

Fourteen percent of the women in this sample delivered preterm, 10% had hypertensive disorders of pregnancy, 9% had a diagnosis of gestational diabetes, and 9% delivered a low birth weight baby. Women who reported SDB symptoms were significantly older ($t=-3.37$, $P = .001$) and had higher BMIs upon hospital admission ($t = -7.84$, $P < .001$). Maternal age and BMI were therefore included as covariates in statistical models. See Table 1.

Fetal Sex and SDB

Women carrying male fetuses were significantly more likely to have symptoms of SDB in pregnancy ($\beta = .37$, $P = .01$, OR: 1.45 [95% CI: 1.09–1.94]). Among women with SDB, 55% of births were male versus 44% female births. This association dropped below significance when only women with SDB symptoms that began in pregnancy were included in analyses ($\beta = .26$, $P = .12$, OR: 1.30 [95% CI: 0.93–1.82]). Among women with SDB that began in pregnancy, 54% of births were to male infants versus 46% of births to female infants.

Fetal Sex as a Moderator of SDB and Adverse Pregnancy Outcomes

We evaluated the interaction between fetal sex and pregnancy-onset SDB on adverse pregnancy outcomes. The interaction between fetal sex and SDB significantly predicted diagnosis of hypertensive disorders of pregnancy ($\beta = .41$, $P = .02$, OR: 1.51 [95% CI: 1.08–2.11]) and marginally predicted diagnosis of gestational diabetes ($\beta = .34$, $P = .08$, OR: 1.41 [95% CI: 0.96–2.07]). The interaction between fetal sex and SDB did not predict preterm birth ($\beta = -.10$, $P = .62$, OR: 0.90 [95% CI: 0.60–1.35]) or low birth weight ($\beta = .94$, $P = .12$, OR: 2.55 [95% CI: 0.77–8.38]; see Table 2).

Discussion

In this study, we found that pregnant women carrying male fetuses were more likely to report symptoms of SDB in pregnancy. Male fetal sex also was associated with increased risk of hypertensive disorders of pregnancy among women with SDB symptom onset in pregnancy. These results are the first, to our knowledge, to identify male fetal sex as a possible risk factor for SDB and SDB-associated complications in pregnancy. Results are consistent with, and build upon, prior studies indicating increased risk of adverse obstetric outcomes among women carrying male fetuses.[12–14,35]

The finding that fetal sex is associated with SDB-associated complications in pregnancy may have important clinical implications. Including fetal sex as one of the factors in a risk assessment model, may in fact improve identification of those women at highest risk of developing SDB in pregnancy. This will also improve identification of those women who would benefit from close maternal and fetal surveillance in order to prevent or decrease the incidence of SDB-associated complications. Prediction of risk of SDB in pregnancy has been challenging, and there is an interest in the field to develop algorithms to identify pregnant women at risk of SDB in order to maximize identification while minimizing demands on diagnostic resources and patient burden, such as polysomnography or in-home sleep apnea testing.[47] 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, it is possible to examine whether the addition of fetal sex to management decisions for screening for SDB and to identify women at highest risk of perinatal complications of SDB.

Pregnancies carrying male fetuses are at increased risk of a myriad of adverse perinatal outcomes, including preeclampsia,[12] gestational diabetes,[13] preterm labor, uterine cord prolapse, and stillbirth.[14] Increased risk for adverse obstetric outcomes among pregnant women carrying male fetuses may be due to physiological differences associated with male pregnancies. Past studies have found that the female placenta is more responsive to maternal stress signals in utero than the male placenta. Specifically, early intrauterine adversity may induce X chromosome inactivation in the female placenta yielding adaptive advantages for the female fetus,[48] and pregnant women with asthma carrying female fetuses displayed greater inflammation, reduced placental expression of 11βHSD2 (buffering the fetus from high levels of maternal cortisol), reduced fetal estriol, and lower birth weight.[49] There is also evidence that pregnant women carrying male fetuses have lower PAPP-A values compared to those carrying female fetuses.[21–23] Pregnancy-associated plasma protein A, a glycoprotein produced by the placenta and correlated with normal placental development, is recognized as a biomarker predicting poor obstetric outcomes. Low values are associated with increased risk of preeclampsia and fetal growth restriction.[50] Our group previously reported that pregnant women with obstructive sleep apnea have lower serum levels of PAPP-A compared to controls, and this result remained significant after adjusting for maternal BMI,[38] but the impact of fetal sex was not examined in this study.

In this study, the association between fetal sex and SDB was significant when the entire sample was tested but this association was attenuated when onset of SDB was restricted to pregnancy. This finding may have occurred due to the loss of statistical power to detect an

effect as the association approached significance (P = .12); the percentage of women carrying male fetuses among women with SDB with onset in pregnancy (54%) was comparable to the percentage of women carrying male fetuses in women with SDB with onset before or during pregnancy (55%). Another possibility is recall bias as women were asked toward the end of pregnancy to recall whether their symptoms started in pregnancy or prior to conception. When combined with other predictors of SDB, such as age and BMI, fetal sex may result in an improved ability to screen for SDB early in pregnancy. Future studies are needed that examine the sensitivity and specificity of SDB prediction when fetal sex is included in screening algorithms.

Strengths of this study include the robust sample size and the ability to obtain maternal diagnoses and pregnancy outcomes from the medical records. Another strength is the examination of fetal sex as a risk factor for SDB, as this line of inquiry has not been conducted in the past research. Limitations from the study include the evaluation of SDB symptoms using a self-report tool based on snoring status. While snoring in pregnancy is strongly associated with SDB,[7] women may be unaware, or fail to report, snoring in pregnancy. As previously mentioned, recall bias for onset of symptoms may play a role in our findings. We were also not able to evaluate SDB symptoms prospectively and at different gestational time periods to determine whether the association between SDB and adverse pregnancy outcomes differs according to the timing of symptom onset. Finally, maternal physiological mechanisms, such as inflammation and progesterone, were not assessed. Therefore, we were unable to examine whether fetal sex is associated with biological pathways that may increase vulnerability for SDB. In addition, although no neonatal genetic features were described in our cohort, results of neonatal genetic testing were not available for review. Future studies should investigate whether the role of fetal sex in predicting SDB is affected by presence of genetic syndromes, given the fact that some genetic syndromes may affect levels of certain placental biomarkers, such as PAPP-A, which may be related to the pathogenesis of SDB and other obstetric conditions.[23]

Conclusion

In this cohort of approximately 1000 women, we found that women carrying male fetuses were approximately 1.5 times more likely to report symptoms of SDB in pregnancy compared to women carrying female fetuses; however, this was not true when only women with pregnancy-onset SDB were included. Women with SDB onset in pregnancy were also more likely to have hypertensive disorders of pregnancy if carrying a male fetus. Future studies are needed to confirm these findings using objective sleep assessments. Future studies are also needed that examine the biological pathways that could explain the increased risk of SDB among women carrying male fetuses. If confirmed, fetal sex may be important to consider when assessing maternal risk of the development of SDB in pregnancy.

Acknowledgments

References

1. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998–2009. Sleep. 2014;37(5):843–849. [PubMed: 24790262]

2. Bourjeily G, Danilack VA, Bublitz MH, et al. Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. Sleep Med. 2017;38:50–57. [PubMed: 29031756]

3. Facco FL, Parker CB, Reddy UM, et al. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. Obstet Gynecol. 2017; 129(1):31–41. [PubMed: 27926645]

4. Chen YH, Kang JH, Lin CC, Wang IT, Keller JJ, Lin HC. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am J Obstet Gynecol. 2012;206(2):136, e131–e135. [PubMed: 22000892]

5. Bin YS, Cistulli PA, Ford JB. Population-based study of sleep apnea in pregnancy and maternal and infant outcomes. J Clin Sleep Med. 2016;12(6):871–877. [PubMed: 27070246]

6. Felder JN, Baer RJ, Rand L, Jelliffe-Pawlowski LL, Prather AA. Sleep disorder diagnosis during pregnancy and risk of preterm birth. Obstet Gynecol. 2017;130(3):573–581. [PubMed: 28796676]

7. Izci Balserak B. Sleep disordered breathing in pregnancy. Breathe (Sheff). 2015;11(4):268–277. [PubMed: 27064321]

8. Pamidi S, Marc I, Simoneau G, et al. Maternal sleep-disordered breathing and the risk of delivering small for gestational age infants: a prospective cohort study. Thorax. 2016;71(8): 719–725. [PubMed: 27084956]

9. Reutrakul S, Zaidi N, Wroblewski K, et al. Interactions between pregnancy, obstructive sleep apnea, and gestational diabetes mellitus. J Clin Endocrinol Metab. 2013;98(10):4195–4202. [PubMed: 23966237]

10. Wanitcharoenkul E, Chirakalwasan N, Amnakkittikul S, et al. Obstructive sleep apnea and diet-controlled gestational diabetes. Sleep Med. 2017;39:101–107. [PubMed: 29157580]

11. Bourjeily G, Raker C, Paglia MJ, Ankner G, O'Connor K. Patient and provider perceptions of sleep disordered breathing assessment during prenatal care: a survey-based observational study. Ther Adv Respir Dis. 2012;6(4):211–219. [PubMed: 22556123]

12. Jaskolka D, Retnakaran R, Zinman B, Kramer CK. Fetal sex and maternal risk of pre-eclampsia/ eclampsia: a systematic review and meta-analysis. BJOG. 2017;124(4):553–560. [PubMed: 27315789]

13. Retnakaran R, Kramer CK, Ye C, et al. Fetal sex and maternal risk of gestational diabetes mellitus: the impact of having a boy. Diabetes Care. 2015;38(5):844–851. [PubMed: 25693837]

14. Mondal D, Galloway TS, Bailey TC, Mathews F. Elevated risk of stillbirth in males: systematic review and meta-analysis of more than 30 million births. BMC Med. 2014;12:220. [PubMed: 25428603]

15. Retnakaran R, Wen SW, Tan H, et al. Maternal blood pressure before pregnancy and sex of the baby: a prospective preconception cohort study. Am J Hypertens. 2017;30(4):382–388. [PubMed: 28057630]

16. Haug EB, Horn J, Fraser A, et al. Pre-pregnancy blood pressure and offspring sex in the hunt study, Norway. Am J Hypertens. 2017;30(9):e7–e8. [PubMed: 28633300]

17. Enninga EA, Nevala WK, Creedon DJ, Markovic SN, Holtan SG. Fetal sex-based differences in maternal hormones, angiogenic factors, and immune mediators during pregnancy and the post-partum period. Am J Reprod Immunol. 2015;73(3):251–262. [PubMed: 25091957]

18. Kim-Fine S, Regnault TR, Lee JS, et al. Male gender promotes an increased inflammatory response to lipopolysaccharide in umbilical vein blood. J Matern Fetal Neonatal Med. 2012;25(11): 2470–2474. [PubMed: 22506729]

19. Khalyfa A, Cortese R, Qiao Z, et al. Late gestational intermittent hypoxia induces metabolic and epigenetic changes in male adult offspring mice. J Physiol. 2017;595(8):2551–2568. [PubMed: 28090638]

20. Cortese R, Khalyfa A, Bao R, Andrade J, Gozal D. Epigenomic profiling in visceral white adipose tissue of offspring of mice exposed to late gestational sleep fragmentation. Int J Obes (Lond). 2015;39(7):1135–1142. [PubMed: 25801690]

21. Cowans NJ, Stamatopoulou A, Maiz N, Spencer K, Nicolaides KH. The impact of fetal gender on first trimester nuchal translucency and maternal serum free beta-hCG and PAPP-A MoM in normal and trisomy 21 pregnancies. Prenat Diagn. 2009;29(6): 578–581. [PubMed: 19288535]

22. Illescas T, Fernandez C, Ortega D, de la Puente M, Coronado P, Montalvo J. Influence of gravidity and foetal gender on the value of screening variables in the first trimester of pregnancy. Eur J Obstet Gynecol Reprod Biol. 2013;167(1):14–17. [PubMed: 23178003]

23. Spencer K, Ong CY, Liao AW, Papademetriou D, Nicolaides KH. The influence of fetal sex in screening for trisomy 21 by fetal nuchal translucency, maternal serum free beta-hCG and PAPP-A at 10–14 weeks of gestation. Prenat Diagn. 2000;20(8):673–675. [PubMed: 10951481]

24. Jarvela IY, Zackova T, Laitinen P, Ryynanen M, Tekay A. Effect of parity and fetal sex on placental and luteal hormones during early first trimester. Prenat Diagn. 2012;32(2):160–167. [PubMed: 22418960]

25. Toriola AT, Vaarasmaki M, Lehtinen M, et al. Determinants of maternal sex steroids during the first half of pregnancy. Obstet Gynecol. 2011;118(5):1029–1036. [PubMed: 22015870]

26. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86(3):1175–1180. [PubMed: 11238505]

27. Christine Knickmeyer R, Baron-Cohen S. Fetal testosterone and sex differences. Early Hum Dev. 2006;82(12):755–760. [PubMed: 17084045]

28. Veiga-Lopez A, Steckler TL, Abbott DH, et al. Developmental programming: impact of excess prenatal testosterone on intrauterine fetal endocrine milieu and growth in sheep. Biol Reprod. 2011;84(1):87–96. [PubMed: 20739662]

29. Carlsen SM, Jacobsen G, Romundstad P. Maternal testosterone levels during pregnancy are associated with offspring size at birth. Eur J Endocrinol. 2006;155(2):365–370. [PubMed: 16868152]

30. Gitau R, Adams D, Fisk NM, Glover V. Fetal plasma testosterone correlates positively with cortisol. Arch Dis Child Fetal Neonatal Ed. 2005;90(2):F166–169. [PubMed: 15724043]

31. Rodeck CH, Gill D, Rosenberg DA, Collins WP. Testosterone levels in midtrimester maternal and fetal plasma and amniotic fluid. Prenat Diagn. 1985;5(3):175–181. [PubMed: 4022941]

32. van de Beek C, Thijssen JH, Cohen-Kettenis PT, van Goozen SH, Buitelaar JK. Relationships between sex hormones assessed in amniotic fluid, and maternal and umbilical cord serum: what is the best source of information to investigate the effects of fetal hormonal exposure? Horm Behav. 2004;46(5):663–669. [PubMed: 15555509]

33. Hagemenas FC, Kittinger GW. The influence of fetal sex on plasma progesterone levels. Endocrinology. 1972;91(1):253–256. [PubMed: 4623633]

34. Driver HS, McLean H, Kumar DV, Farr N, Day AG, Fitzpatrick MF. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. Sleep. 2005;28(4):449–456. [PubMed: 16171289]

35. DiPietro JA, Costigan KA, Shupe AK, Pressman EK, Johnson TR. Fetal neurobehavioral development: associations with socioeconomic class and fetal sex. Dev Psychobiol. 1998;33(1):79–91. [PubMed: 9664173]

36. Ray JG, Huang T, Meschino WS, Cohen E, Park AL. Prenatal biochemical screening and long term risk of maternal cardiovascular disease: population based cohort study. Bmj. 2018;362:k2739. [PubMed: 29997198]

37. Spencer K, Yu CK, Cowans NJ, Otigbah C, Nicolaides KH. Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery doppler. Prenat Diagn. 2005;25(10):949–953. [PubMed: 16086443]

38. Bourjeily G, Curran P, Butterfield K, Maredia H, Carpenter M, Lambert-Messerlian G. Placenta-secreted circulating markers in pregnant women with obstructive sleep apnea. J Perinat Med. 2015;43(1):81–87. [PubMed: 24846956]

39. Louis JM, Koch MA, Reddy UM, et al. Predictors of sleep-disordered breathing in pregnancy. Am J Obstet Gynecol. 2018; 218(5):521. e521–521, e512. [PubMed: 29523262]

40. Wilson DL, Walker SP, Fung AM, O'Donoghue F, Barnes M, Howard M. Can we predict sleep-disordered breathing in pregnancy? The clinical utility of symptoms. J Sleep Res. 2013;22(6): 670–678. [PubMed: 23745721]

41. Facco FL, Ouyang DW, Zee PC, Grobman WA. Development of a pregnancy-specific screening tool for sleep apnea. J Clin Sleep Med. 2012;8(4):389–394. [PubMed: 22893769]

42. Balserak BI, Zhu B, Grandner MA, Jackson N, Pien GW. Obstructive sleep apnea in pregnancy: performance of a rapid screening tool. Sleep Breath. 2019;23(2):425–432. [PubMed: 30232680]

43. Bourjeily G, Raker CA, Chalhoub M, Miller MA. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. Eur Respir J. 2010;36(4):849–855. [PubMed: 20525714]

44. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159–167. [PubMed: 16175681]

45. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144(7):768–773. [PubMed: 7148898]

46. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32(Suppl 1):S62–S67. [PubMed: 19118289]

47. Malhame I, Bublitz MH, Bourjeily G. The challenge of screening for obstructive sleep apnea in pregnancy. Ann Am Thorac Soc. 2019;16(10):1242–1244. [PubMed: 31573345]

48. Reik W, Lewis A. Co-evolution of X-chromosome inactivation and imprinting in mammals. Nat Rev Genet. 2005;6(5):403–410. [PubMed: 15818385]

49. Murphy VE, Gibson PG, Giles WB, et al. Maternal asthma is associated with reduced female fetal growth. Am J Respir Crit Care Med. 2003;168(11):1317–1323. [PubMed: 14500261]

50. Anderson UD, Olsson MG, Kristensen KH, Akerstrom B, Hansson SR. Review: biochemical markers to predict preeclampsia. Placenta. 2012;33(Suppl):S42–S47. [PubMed: 22197626]
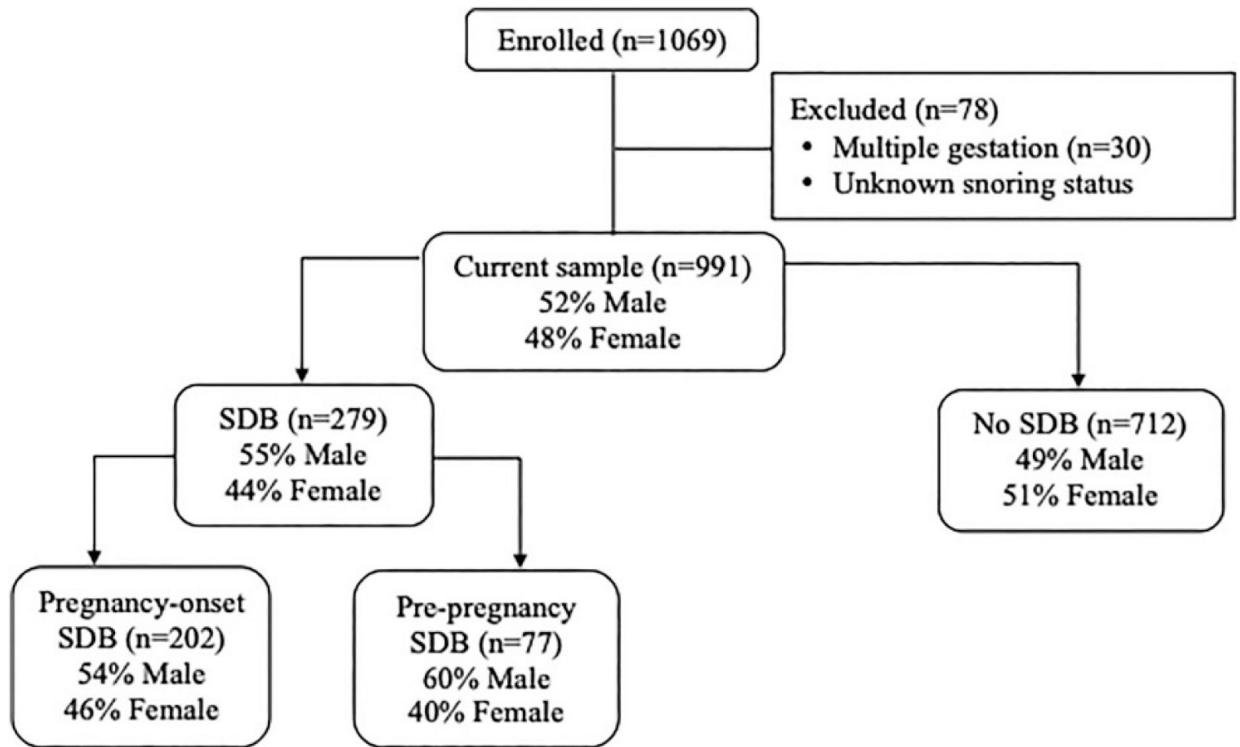
Figure 1.
Flow diagram of participants included for analyses and sex of infants.

Table 1.

Study Demographics.

	Total Sample N = 991	SDB (loud habitual snoring) N = 279	No SDB (no loud snoring) N = 712
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age	29 (10)	31 (15)	29 (6)
Race (% White)	70%	73%	69%
Ethnicity (% Hispanic)	15%	12%	16%
BMI at hospital admission	32 (6)	34 (7)	31 (6)
Fetal sex (% male)	52%	56%	49%

Abbreviations: BMI, body mass index; SDB, sleep disordered breathing.

Table 2.

Fetal Sex as a Moderator of Association Between SDB and Adverse Outcomes.[a]

	β	*P* value	OR (95% CI)
Preterm birth (<37 weeks)	−.10	.62	0.90 (0.60–1.35)
Low birth weight (<2500 grams)	.94	.12	2.55 (0.77–8.38)
Hypertensive disorders of pregnancy	.41	.02	1.51 (1.08–2.11)
Gestational diabetes	.34	.08	1.41 (0.96–2.07)

[a]All analyses adjusted for maternal age and body mass index at the time of hospital admission. Hypertensive disorders of pregnancy included diagnoses of preeclampsia and/or pregnancy-induced hypertension.