

EDITORIAL

Sleep-disordered breathing in pregnancy and glucose metabolism: is earlier detection better?

Sushmita Pamidi^{1,*}, Rita R. Kalyani^{2,•} and Grace W. Pien³

¹Department of Medicine, Division of Respiratory Medicine, McGill University Health Centre, Montreal, QC, Canada, ²Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD, USA and ³Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

*Corresponding author. Sushmita Pamidi, Department of Medicine, Division of Respiratory Medicine, Sleep Medicine Laboratory, McGill University Health Centre (MUHC), 5252 Boul de Maisonneuve Ouest, Office 3D.65, Montreal, QC H4A 3S5, Canada. Email: sushmita.pamidi@mcgill.ca.

In the past decade, published literature has demonstrated the important relationship of sleep-disordered breathing (SDB) to the development of gestational diabetes mellitus (GDM) in late pregnancy. The prevalence estimates for GDM range between 10% and 25% of pregnancies in different regions worldwide [1]. GDM is defined as diabetes that is diagnosed for the first time during pregnancy, usually in the second or third trimester (24–28 weeks) based on a screening oral glucose tolerance test, in women without known pregestational diabetes. Women with GDM have a greater risk of birth complications, including spontaneous abortion, fetal anomalies, macrosomia, higher rates of cesarian section, and a 10-fold increased risk of developing type 2 diabetes later in life compared to women without GDM. Offspring of mothers with GDM also have an increased risk of developing obesity and type 2 diabetes [2, 3].

Several studies have shown an increased likelihood of GDM [4–8] among women with SDB compared to controls, even after adjusting for obesity. Nevertheless, data establishing how the timing of exposure to SDB influences the risk of developing GDM in late pregnancy is surprisingly sparse. The nuMoM2b study, a prospective cohort study of more than 3700 pregnant women, assessed SDB using home sleep apnea testing (HSAT) and demonstrated significant exposure–response relationships between the apnea–hypopnea index (AHI) and the secondary outcome of GDM development [4]. The odds for GDM in late pregnancy were observed to increase more than 3-fold among women who were found to have SDB during early pregnancy (median time at testing was 12 4/7 weeks of gestation) compared to those without SDB. Assessment of SDB was performed at least 1 week prior to glucose testing, helping to establish the biologic

plausibility of SDB as a risk factor for GDM. SDB was reassessed in mid-pregnancy (~28 2/7 weeks of gestation), however, the temporality of the SDB–GDM relationship in mid-pregnancy is less well established.

Other data include two retrospective studies that used population-based datasets and birth records to examine the relationship between maternal SDB and GDM [9, 10]. These analyses, however, did not distinguish between antenatal and pre-conception obstructive sleep apnea (OSA). Previous studies [4, 6, 9–11] also did not measure insulin resistance among individuals with SDB during early pregnancy. However, worsening severity of SDB detected in mid- to late pregnancy was associated with increased nocturnal and early morning glucose levels in women with GDM [11], adding to the literature on how SDB affects glucose metabolism during pregnancy.

In this issue of the *Journal*, Sanapo and colleagues [12] performed a cross-sectional analysis of data from 2 ongoing studies and reported on the association between SDB in early pregnancy and insulin resistance and fasting glucose levels among 192 overweight or obese women (mean BMI of 35.1 kg/m²) without known pregestational diabetes. Women completed HSAT at a mean of 11.1 gestational weeks. They underwent modified homeostatic model assessment for insulin resistance (HOMA-IR using fasting C-peptide to replace insulin) at ~14–16 weeks of gestation; using this methodology, HOMA-IR was correlated with insulin sensitivity measured by oral glucose tolerance testing in pregnant women enrolled in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [13]. The authors found a linear relationship between respiratory event index (REI) and HOMA-IR after adjustment for demographics,

parity, and gestational age ($\beta = 0.25 \pm 0.025$; $p = .003$) that was attenuated after adjustment for BMI ($\beta = 0.17 \pm 0.026$; $p = .051$). A similar relationship between oxygen desaturation index (ODI) and HOMA-IR remained significant in the fully adjusted model ($\beta = 0.31 \pm 0.024$; $p = .001$). Although the presence of OSA (REI ≥ 5 events/hr) was not significantly associated with pancreatic β -cell function as estimated by the modified HOMA of β -cell function (HOMA-% β using C-peptide), the findings did demonstrate higher fasting glucose and higher fasting C-peptide levels among women with SDB in early pregnancy.

What are the implications of these findings? Measurements of insulin resistance during early pregnancy are relevant for predicting maternal GDM risk. In a normal pregnancy, insulin resistance progressively increases during pregnancy until term to facilitate glucose transport across the placenta for fetal growth. Women with higher degrees of insulin resistance are at risk of developing GDM. During first-trimester glucose screening, impaired fasting glucose levels and/or an A1C level slightly above normal may indicate a higher risk for GDM and need for insulin during pregnancy [2]. Furthermore, results from the HAPO study have demonstrated that even mildly elevated glucose levels may be harmful for maternal-fetal health [14]. Thus, identifying risk factors for abnormal glucose metabolism during early pregnancy is an important clinical and research goal [15] that may yield novel treatments. The findings of the Sanapo study are relevant in that SDB in early pregnancy is associated with insulin resistance biomarkers that are likely to signify an elevated risk of developing GDM later in pregnancy.

In the Sanapo study, women with OSA (vs. no OSA) were older, more obese, and had a higher likelihood of being multipara [12], similar to prior studies [4, 16, 17]. It is possible that some women in the Sanapo study had SDB prior to conception. However, without robust data on pre-conception SDB, it is impossible to examine whether antenatal SDB differentially impacts glucose metabolism and risk of GDM, in comparison to pre-conception SDB. While the ODI (mean 16 ± 12 events/hr) had a stronger association with HOMA-IR compared to REI (mean 7.7 ± 6.8 events/hr; $p = .001$ vs. $p = .051$, respectively), the desaturations were not all associated with respiratory events, and therefore the relevance of these findings need further exploration. Furthermore, several studies indicate that SDB in pregnancy is characterized predominantly by milder respiratory events, such as hypopneas with arousals and flow limitation, rather than by apneas and hypopneas with desaturation [4, 5, 11, 16–20]. Thus, the overall prevalence and clinical significance of respiratory events with desaturation in pregnancy are not yet well understood. Since limited HSAT rather than full polysomnography was used in the Sanapo study [12], it is unknown if REM-related SDB may have driven some of the relationships between SDB and metabolic dysfunction, as has been shown in prior studies [6, 11]. Furthermore, this was a cross-sectional study in which only fasting measures of glucose and C-peptide were available to assess insulin resistance and beta cell function. Women with normal or low BMI were also not included in this study.

To date, despite the management of GDM with lifestyle behavior change and/or antihyperglycemic drug therapy as needed [2], the prevalence of GDM has been increasing steadily over the past several years [21, 22]. Thus, additional novel interventions are needed to optimize the prevention of GDM. While preliminary data from interventional studies have shown improvement in nocturnal glucose levels [23] and insulin secretion among

women with GDM adherent to continuous positive airway pressure (CPAP) [24], larger studies are needed. This new work from Sanapo and colleagues a compelling rationale for future interventional studies that target the treatment of SDB earlier on in the pregnancy to improve glucose metabolism during early gestation and potentially prevent the development of GDM later in pregnancy. In turn, such interventions may decrease the cascade of future cardiometabolic risk for both mother and child. However, screening, diagnosing, and treating SDB during the limited duration of pregnancy pose substantial practical challenges for the treating physician. Future studies on pragmatic care pathways and optimizing CPAP adherence will be ultimately needed to translate research findings into clinical practice.

Disclosure Statement

The authors do not have any disclosures.

References

1. Guariguata L, et al. Global estimates of the prevalence of hyperglycaemia in pregnancy. *Diabetes Res Clin Pract.* 2014;103(2):176–185. doi:10.1016/j.diabres.2013.11.003
2. American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: standards of medical care in diabetes—2022. *Diabetes Care.* 2022;45(Supplement 1):S232–S243.
3. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes Res Clin Pract.* 2014;103(3):341–363.
4. Facco FL, et al. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. *Obstet Gynecol.* 2017;129(1):31–41. doi:10.1097/AOG.0000000000001805
5. Reutrakul S, et al. Interactions between pregnancy, obstructive sleep apnea, and gestational diabetes mellitus. *J Clin Endocrinol Metab.* 2013;98(10):4195–4202. doi:10.1210/jc.2013-2348
6. Izci Balserak B, et al. Obstructive sleep apnea is associated with newly diagnosed gestational diabetes mellitus. *Ann Am Thorac Soc.* 2020;17(6):754–761. doi:10.1513/AnnalsATS.201906-473OC
7. Pamidi S, et al. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2014;210(1):52.e1–52.e14.
8. Luque-Fernandez MA, et al. Sleep-disordered breathing and gestational diabetes mellitus: a meta-analysis of 9,795 participants enrolled in epidemiological observational studies. *Diabetes Care.* 2013;36(10):3353–3360. doi:10.2337/dc13-0778
9. Chen YH, et al. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. *Am J Obstet Gynecol.* 2012;206(2):136.e1–136.e5.
10. Bin YS, et al. Population-based study of sleep apnea in pregnancy and maternal and infant outcomes. *J Clin Sleep Med.* 2016;12(6):871–877. doi:10.5664/jcsm.5890
11. Newbold R, et al. Maternal sleep-disordered breathing in pregnancy and increased nocturnal glucose levels in women with gestational diabetes mellitus. *Chest.* 2021;159(1):356–365. doi:10.1016/j.chest.2020.07.014
12. Sanapo L, et al. Association between sleep disordered breathing in early pregnancy and glucose metabolism. *Sleep.* 2022;45(4):1–9.

13. Radaelli T, et al. Estimates of insulin sensitivity using glucose and C-peptide from the hyperglycemia and adverse pregnancy outcome glucose tolerance test. *Diabetes Care*. 2010;**33**(3):490–494. doi:[10.2337/dc09-1463](https://doi.org/10.2337/dc09-1463)
14. Metzger BE, et al. Hyperglycemia and adverse pregnancy outcomes. *Clin Chem*. 2019;**65**(7):937–938. doi:[10.1373/clinchem.2019.303990](https://doi.org/10.1373/clinchem.2019.303990)
15. Huhn EA, et al. Controversies in screening and diagnostic criteria for gestational diabetes in early and late pregnancy. *Front Endocrinol (Lausanne)*. 2018;**9**:696. doi:[10.3389/fendo.2018.00696](https://doi.org/10.3389/fendo.2018.00696)
16. Pamidi S, 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. doi:[10.1136/thoraxjnl-2015-208038](https://doi.org/10.1136/thoraxjnl-2015-208038)
17. Pien GW, et al. Risk factors for sleep-disordered breathing in pregnancy. *Thorax*. 2014;**69**(4):371–377. doi:[10.1136/thoraxjnl-2012-202718](https://doi.org/10.1136/thoraxjnl-2012-202718)
18. Edwards N, et al. Sleep disordered breathing and pregnancy. *Thorax*. 2002;**57**(6):555–558.
19. Connolly G, et al. Inspiratory flow limitation during sleep in pre-eclampsia: comparison with normal pregnant and nonpregnant women. *Eur Respir J*. 2001;**18**(4):672–676. doi:[10.1183/09031936.01.00053501](https://doi.org/10.1183/09031936.01.00053501)
20. Bourjeily G, et al. Airflow limitations in pregnant women suspected of sleep-disordered breathing. *Sleep Med*. 2014;**15**(5):550–555. doi:[10.1016/j.sleep.2014.01.004](https://doi.org/10.1016/j.sleep.2014.01.004)
21. Deputy NP, et al. Prevalence and changes in preexisting diabetes and gestational diabetes among women who had a live birth—United States, 2012–2016. *MMWR Morb Mortal Wkly Rep*. 2018;**67**(43):1201–1207. doi:[10.15585/mmwr.mm6743a2](https://doi.org/10.15585/mmwr.mm6743a2)
22. Getahun D, et al. Gestational diabetes in the United States: temporal trends 1989 through 2004. *Am J Obstet Gynecol*. 2008;**198**(5):525.e1–525.e5.
23. Duong A, et al. CPAP treatment reduces nocturnal glucose levels in gestational diabetes: a pilot randomized-controlled trial (RCT). Presented at: American Thoracic Society 2020—A97. SRN: New Insights into the Cardiometabolic Consequences of Insufficient Sleep.
24. Chirakalwasan N, et al. Continuous positive airway pressure therapy in gestational diabetes with obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med*. 2018;**14**(3):327–336. doi:[10.5664/jcsm.6972](https://doi.org/10.5664/jcsm.6972)