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Can Diagnostic Specificity and Phenotyping Aid in Evaluating Cardiometabolic Risk of Maternal Sleep-disordered Breathing?

Sleep-disordered breathing (SDB) is a common disorder in pregnancy but its prevalence varies with the degree of risk in the population, methodology, and definition (1, 2). Further, associations between SDB in pregnancy and adverse outcomes are well documented. Large population-based studies have demonstrated an association with hypertensive disorders of pregnancy, gestational diabetes, and severe maternal morbidity (3, 4). Moreover, the prospective nuMoM2B (Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-Be) study confirmed the links between SDB and preeclampsia and gestational diabetes (1). Indeed, after correcting for maternal age, body mass index, chronic hypertension, and gestational weight gain, SDB in early- and mid-pregnancy was associated with a twofold increase in the risk of preeclampsia and a nearly threefold increase in the risk of gestational diabetes (1). These adverse outcomes are important causes or key contributors to severe maternal morbidity and maternal mortality, are the source of an important societal and financial burden, and have been linked to long-term adverse outcomes for mother and offspring.

Mouse models of preeclampsia show subsequent cardiac abnormalities, including higher fibrin deposit counts in cardiomyocytes as well as functional abnormalities as measured by ultrasonography before and after dobutamine stress tests (5). Women with a history of preeclampsia have higher myocardial mass and thicker left ventricular walls at 12-year follow-up, abnormalities that correlate with pregnancy antiangiogenic profiles (6). A recent meta-analysis confirmed (7) that women with preeclampsia have a higher risk of major cardiac events and cardiovascular disease. Population-based studies demonstrate that in middle-aged women undergoing coronary revascularization, a single episode of maternal placental syndrome doubles the risk of death, whereas recurrent maternal placental syndrome quadruples that risk (8). Similarly, gestational diabetes is an established risk factor for the development of type II diabetes (9) and cardiovascular disease in women (10). Despite the contribution of SDB to adverse cardiovascular outcomes in the general population and its link to preeclampsia and gestational diabetes, little is known about the cardiovascular and metabolic risks of maternal SDB after delivery.

In this issue of the *Journal*, Facco and colleagues (pp. 1202–1213) note the nuMoM2B Heart Health study followed a subset of the cohort ($n = 1{,}964$) who had a level III home sleep test either in early or late gestation (or both) of their first pregnancy and assessed for new-onset hypertension and metabolic syndrome 2–7 years after the index pregnancy (11). The study used two definitions for SDB: apnea–hypopnea index (AHI) of $\geqslant$5 events/h (3% desaturation rule for hypopnea), and oxygen desaturation index (ODI) of $\geqslant$5 events/h. The primary analyses used dichotomous AHI and ODI definitions from the early- or mid-pregnancy assessments to examine the risk of incident hypertension and metabolic syndrome (three or more of the following: elevated waist circumference, triglycerides, glucose, and/or blood pressure and/or reduced high-density lipoprotein concentrations) after a median of ~3 years. The secondary analyses examined cross-sectional associations between AHI and ODI at the 2- to 7-year follow-up and the same cardiometabolic outcomes. The investigators also assessed the trajectory of SDB status between pregnancy and follow-up and its link to these outcomes. There was no significant association between SDB in pregnancy and incident hypertension when SDB was defined by AHI criteria, but when SDB was defined

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by ODI, there was a twofold increased adjusted risk for hypertension. The adjusted risk for metabolic syndrome was elevated regardless of SDB definition. Interestingly, mediation analyses showed that ODI of at least 5 in pregnancy had a significant controlled direct effect on metabolic syndrome risk unrelated to the impact of hypertensive disorders of pregnancy and gestational diabetes.

The tremendous efforts put forth by the nuMom2b investigators to recruit this large sample of pregnant women, obtain objective measures of SDB at multiple time points, and follow the participants longitudinally have already produced important new knowledge about sleep in healthy primiparous women. Though prior studies have demonstrated that nearly 50% of women with SDB diagnosed in pregnancy continue to have the disorder postpartum (12), this study sheds further light on the natural history of SDB in the perinatal period by showing that about 5–6% of women develop SDB within a few years of delivery.

This study again demonstrates the limitations of the conventional measure of AHI as a predictor of adverse cardiovascular and metabolic outcomes, particularly in the pregnant population. In this cohort, the ODI was a better predictor of hypertension and metabolic syndrome at ~3 years postpartum, despite strong correlations among ODI, AHI, and body mass index. These data suggest that respiratory events that do not meet flow reduction criteria for hypopneas may contribute to cardiovascular and metabolic risk in expectant mothers. The authors and others have argued that pregnant women have frequent airflow limitations that do not meet the criteria for apneas or hypopneas, and that the magnitude of SDB exposure may be underestimated in this population (13, 14). Recent attention to different SDB phenotypes (15) and data establishing links between the timing of SDB onset during pregnancy and other outcomes that could increase cardiometabolic risk (e.g., depression [16]) highlight the complexity of identifying a definitive predictor of untoward outcomes related to SDB. Therefore, we would not advocate that clinicians or researchers rely only on ODI to assess SDB in perinatal women at this stage of the science. Indeed, sleep fragmentation, duration, and timing likely also play a role in untoward outcomes (17).

The nuMoM2B participants should continue to be assessed at regular intervals to further examine long-term outcomes in this well-characterized sample. In addition, assembling a new, larger cohort of women and their infants would *1*) allow replication of key findings from nuMoM2B; *2*) take advantage of new technologies and study methods to evaluate sleep and circadian measures that likely contribute to poor outcomes for pregnant people and their offspring (e.g., sleep fragmentation, light exposure, napping, and biomarkers); and *3*) incorporate "lessons learned" from nuMoM2B. A larger sample would allow for examination of factors like fertility, parity, and medication use, which would not only increase generalizability but also allow for more rigorous statistical approaches (e.g., sophisticated mediation modeling, adjustment for multiple statistical tests). For instance, the role that susceptibility to cardiometabolic derangements before or in the early stages of pregnancy plays in the associations between SDB and these outcomes cannot be examined in the nuMoM2B cohort. It is possible that pregnant women with SDB have an inherent risk for cardiometabolic disorders that are associated with SDB rather than caused by SDB. Our recent data, for instance, have demonstrated that women with objective SDB in early pregnancy already have a higher degree of insulin resistance even after adjusting for multiple confounders (18). Thus, women with SDB in early pregnancy (when SDB likely predated pregnancy, as physiologic changes that predispose to the development of SDB in early pregnancy are minimal) have a phenotype that predisposes them to adverse perinatal outcomes. Whether that remains true for long-term outcomes remains to be determined. In addition, as the authors acknowledge, the latest study included numerous analyses but did not adjust for multiple comparisons, raising the possibility of spurious findings. A larger sample would also provide the opportunity to control for prior and subsequent pregnancies rather than attribute negative outcomes to the index pregnancy alone and not to preexisting risk, subsequent pregnancies, or their associated sleep or cardiometabolic exposures.

In conclusion, this study refines our understanding of the short- and long-term comorbidities associated with maternal SDB; however, more knowledge is needed to develop and test targeted interventions to mitigate the negative effects of disordered sleep during pregnancy. ■

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Treatments of Multidrug-Resistant Tuberculosis: Light at the End of the Tunnel

Tuberculosis is the leading cause of bacterial infectious diseases death worldwide (1). Over the past decade, the number of patients identified with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant tuberculosis (MDR-TB; RR-TB plus isoniazid-resistant tuberculosis) has increased by approximately 20% annually (2). MDR/RR-TB is related to long treatment duration, incurs high treatment costs, and generally leads to poor treatment outcomes (3).

After decades of neglect, the field of antituberculosis drug development is fortunately now observing explosive growth. A substantial number of novel compounds are entering the clinical stages of drug development, and repurposed drugs are being clinically evaluated for efficacy, safety, and tolerability in the treatment of MDR/RR-TB.

Repurposing of antibiotics that were developed for indications other than tuberculosis is an inexpensive strategy to bridge the time until novel drugs become available. This approach worked with moxifloxacin, linezolid, and clofazimine successfully, three of the five best available drugs for the treatment of MDR/RR-TB. β-lactams are another class of antibiotics under evaluation for this purpose. In this issue of the *Journal*, De Jager and colleagues (pp. 1228–1235) report on the early bactericidal activity of different concentrations of meropenem plus clavulanate (4). Unfortunately, the effect was only modest, and the treatment was poorly tolerated. Moreover, the intravenous route of administration of meropenem is operationally not feasible in most countries where MDR/RR-TB is prevalent.

The first clinical trial for a regimen to treat MDR-TB based on a novel antituberculosis medicine was initiated in 2007 (5), and we now find ourselves in the enviable position of having a World Health Organization–endorsed 9-month oral regimen for MDR-TB and a 6-month oral regimen for extensively drug-resistant TB (6) (i.e., at the time of World Health Organization endorsement defined as MDR-TB plus resistance to a fluoroquinolone and/or amikacin, capreomycin, or kanamycin; since then, extensively drug-resistant TB has been redefined as MDR-TB plus resistance to any fluoroquinolone plus bedaquiline and/or linezolid) (7) with 3 new regimens recently reported, plus 10 regimens currently under study (Table 1). Despite this, for many regions, including Europe, the majority of patients with MDR/RR-TB still require an individualized

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