The dangers of sleep disordered breathing in pregnancy

__Professor Ghada Bourjeily__ and her team from Brown University are focusing their research efforts on understanding the manifestation of sleep disordered breathing (SDB) in pregnancy and the consequent impact on maternal and foetal health.

We spend one third of our life sleeping. As we rest, damaged tissues are repaired and cognitive function and energy levels are restored in preparation for an active day ahead. Sleep deficiency can greatly impact our health, highlighting the importance of good quality sleep. Abnormal breathing patterns during sleep, otherwise known as Sleep Disordered Breathing (SDB), are a common cause of sleep inadequacy. SDB includes a wide spectrum of conditions, from snoring to obstructive sleep apnoea (OSA). OSA occurs when throat muscles relax during sleep, causing the upper airway to collapse. Obstruction reduces airflow for around ten seconds or more, resulting in low levels of blood oxygen saturation (hypoxia). In the long-term, OSA-associated hypoxia can lead to potentially fatal conditions such as hypertension, cardiovascular disease and diabetes mellitus.

PREGNANCY-ASSOCIATED SDB

Interestingly, pregnant women are at a higher risk of developing SDB, due to the physiological changes that occur during pregnancy. For example, plasma volume increases and capillary engorgement causes airway mucosa to thicken, resulting in nasal congestion as the lining of the nose, larynx and trachea swells. This can lead to gestational rhinitis development, which usually improves immediately after delivery. Nasal congestion is a major risk factor for SDB, therefore pregnant women are particularly at risk. Furthermore, during the later stages of pregnancy, the gravid uterus causes the diaphragm to elevate, reducing the functional residual capacity of the lungs by 20%. This may impact oxygen reserve and further contribute to upper airway collapsibility. Snoring is also much more frequent in pregnant (14–45%) compared to non-pregnant women of reproductive age (4%).

Sleep disordered breathing research team. Back row, left to right: Greg Salgueiro, MS, RD, LDN, CIC; Rebecca Lynn; Susan Martin, LDN, IBCLC; Cindy Brosnan, RRT; Patrizia Curran, MD; Christine Allenson, MA, OT, CHES
Front row, left to right: Beth Hott, BA; Tamara Sequeira, RN; Maggie Bublitz, PhD, Ghada Bourjeily, MD, Annaly Aldana, BA, Eva Adodoadji, MD, MPH

The strong association between SDB and pregnancy raises a number of questions: i) does SDB cause detrimental effects in the mother and foetus / newborn? ii) what physiological or biological factors predict the development of SDB in this young population? and iii) what are the mechanisms that result in these adverse effects? Professor Bourjeily and her colleagues have dedicated their research efforts to investigating these interesting questions.

GESTATIONAL HYPERTENSIVE DISORDERS

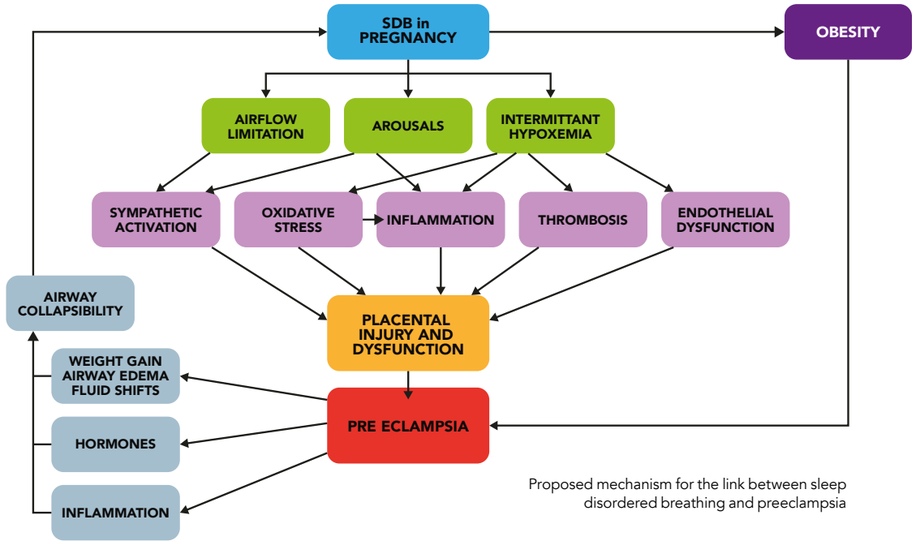
Professor Bourjeily and others have shown that pregnancy-associated SDB (including snoring and OSA) increases the risk of developing gestational hypertensive disorders such as hypertension and pre-eclampsia, even after considering other risk factors such as obesity. Gestational hypertension complicates approximately 6% of all pregnancies and pre-eclampsia is a severe pregnancy disorder, characterised by high blood pressure and either a high level of protein in the urine or other systemic manifestations. The condition may deteriorate further to 'eclampsia' and seizures may occur which may threaten the lives of the mother and child. Pre-eclampsia is also associated with pulmonary oedema, liver abnormalities and renal failure. Though pre-eclampsia is a short-lived condition, it has been suggested to be a precursor of future development of cardiovascular disease.

So, how does SDB cause pre-eclampsia? One of the possible mechanisms could be placental hypoxia. In a study, performed by Professor Bourjeily and her team, a quantitative analysis of immunohistochemical markers of hypoxia were compared between the placentas of pregnant women with OSA/snoring and non-snoring controls. Expression of the hypoxia marker carbonic anhydrase was more prevalent in OSA placentas (91.3%) compared to the controls (57.5%). In addition, the team has demonstrated that placenta secreted blood markers are altered in women with OSA compared to controls. Professor Bourjeily hypothesises that placental hypoxia that may occur as a consequence of SDB could trigger a cascade of events that lead to pre-eclampsia. The hypoxic placenta secretes a variety of different soluble molecules into the bloodstream that impacts maternal endothelial function. In fact, endothelial abnormalities have been demonstrated in patients with OSA, regardless of the severity level. Endothelial dysfunction is characterised by an imbalance of hormones that control blood pressure. Consequently, hypertension can develop which, if not monitored, can lead to heart disease.

Furthermore, inflammation could be the missing link between SDB and hypertensive disorders. Sleep disturbance is associated with high levels of interleukin-6 in the later stages of pregnancy. This inflammation marker is strongly associated with pre-eclampsia. Nevertheless, much more research is needed to fully understand this relationship.

GESTATIONAL DIABETES

In a study conducted on 1000 patients, Professor Bourjeily also demonstrated that there is a significant association between gestational diabetes and third trimester SDB (which includes snoring, gasping and apnoeas) regardless of other factors such as BMI and smoking. In addition, in a large population-based sample that included over 1.5 million women, a diagnosis of OSA was associated with an increased risk for gestational diabetes, after adjusting for multiple risk factors.



Proposed mechanism for the link between sleep disordered breathing and preeclampsia

Gestational diabetes affects 2–10% of pregnancies and is characterised by glucose intolerance. Serious pregnancy complications can result from gestational diabetes, including pre-eclampsia, increased risk of caesarean delivery and preterm labour. In addition, gestational diabetes is strongly associated with future development of type II diabetes, a highly morbid condition.

Excessively high blood glucose levels, as a result of SDB, may be related to a range of interlinking factors. For example, airflow limitation and hypoxia can result in increased sympathetic activation (part of the nervous system involved in the 'fight or flight response'), which can i) inhibit insulin secretion from the pancreas, ii) exacerbate insulin resistance (cells cannot respond to insulin signals which trigger glucose uptake from the blood) or iii) stimulate glucose release from liver cells into the bloodstream. Additionally, oxidative stress can damage pancreatic beta cells, where insulin is produced, resulting in a reduction in insulin secretion.

Dr Bourjeily is currently investigating additional pathways that may link SDB and gestational diabetes.

FOETAL RISK AND DELIVERY

Results from studies focusing on the consequences of SDB on foetal outcomes are conflicting. SDB (both snoring and OSA) appears to be associated with preterm birth (birth occurring before 37 weeks gestation) in multiple studies, including Dr Bourjeily's. The risk of growth restriction and small for gestational age remains controversial. Dr Bourjeily is currently investigating the risk of growth restriction and other neonatal outcomes in a large population-based dataset that linked maternal and neonatal records. Other potential adverse foetal impacts include reduced heart and growth rate. Despite these inconsistent findings, the majority of studies provide supportive evidence that suggests that women who snore, have short sleep duration and OSA are at a higher risk of caesarean delivery, compared to controls.

FUTURE STUDIES

The work of Professor Bourjeily and her colleagues has greatly advanced our knowledge regarding the effects of pregnancy-induced SDB. However, more research is needed to fully understand mechanisms behind the association. The team are now focussing their research efforts on exploring why SDB prevalence more than doubles in later stages of pregnancy compared to earlier stages. By determining the physiological factors that predict the onset of SDB in late pregnancy, the team are aiming to create a model, alongside simple testing, that can be used as a preventative tool, to identify SDB development. The patient can then be treated before the SDB becomes more severe. As SDB is a relatively easy condition to treat with ways that are not thought to negatively impact the foetus, investigating this condition that may impact up to a third of all pregnant women should be a priority.

Professor Bourjeily and others have shown that pregnancy-associated SDB (including snoring and OSA) increases the risk of developing gestational hypertensive disorders such as hypertension and pre-eclampsia

Behind the Bench

Professor Ghada Bourjeily

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Research Objectives

Prof Bourjeily's work studies the links between sleep disordered breathing, pregnancy and perinatal outcomes. She looks at both the effect on pregnancy outcomes and the potential for long-term implications for these women.

Funding

NIH, Chest Foundation

Collaborators

- Geralyn Messerlian, PhD Professor of Pathology, Brown University
- Maggie Bublitz, PhD, Assistant Professor of Psychiatry and Human Behavior and Medicine, Brown University
- Fusun Gundogan, MD, Associate Professor of Pathology, Brown University
- The obstetric medicine team at Lifespan under the directorship of Dr Lucia Larson, Associate Professor of Medicine, Brown University, division director of Obstetric Medicine, and Peg Miller, Associate Professor of Medicine, Brown University and Chief of Women's Services at Lifespan
- Marshall Carpenter, MD, Maternal Fetal Medicine, and the obstetric team of providers who help facilitate patient recruitment

Bio

Ghada Bourjeily is associate professor of medicine at the Warren Alpert Medical School of Brown University in the divisions of pulmonary, critical care and sleep medicine, and obstetric medicine. She is the director of women's research at the women's medicine collaborative at the Miriam Hospital and director of the pulmonary disease in pregnancy program.

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Q&A

Why is sleep disordered breathing so prevalent in pregnant women?

SDB is more prevalent in pregnant women compared to non-pregnant young women likely because so many physiological changes occur in pregnancy that may impact the upper airway, the lungs and the heart. The upper airway, including the nose and the laryngeal area, appears to be more oedematous (swollen) in pregnancy and this may significantly contribute. Resting lung volumes also change in pregnancy, potentially impacting the upper airway. Pregnancy hormones may also play a role in the development or the worsening of this condition in pregnancy. We do not understand yet which of these changes has the biggest impact on its development but are hoping to get more answers in the near future.

SDB is related to gestational diabetes and hypertensive disorders. Are there any other conditions that could actually be caused by SDB?

Though it makes biological sense that gestational hypertension and gestational diabetes could be caused by sleep disordered breathing, research to date does not confirm causality. Hence, we talk about associations. Future studies that look at the impact of therapy on these outcomes or establishing a temporal relationship between these conditions can help us establish causality further. In a recent study we have shown that SDB has been associated with other severe maternal illness such as pulmonary oedema, congestive heart failure, risk of admission to the intensive care unit, as well as an increased risk of a hysterectomy. There also appears to be an elevated risk of requiring a Caesarean delivery once diagnosed with SDB.

How does pregnancy-induced SDB affect foetal health?

The foetus and the placenta may be target organs in the case of SDB, just like the heart and the kidney may be impacted by SDB. To date, there has been quite a few data linking SDB to preterm birth with a recent study showing an increased risk of both induced and spontaneous preterm birth. Data are inconsistent in showing evidence of growth restriction. What is lacking in the literature is an understanding of the timing of development of SDB and how SDB pre-dating pregnancy would differently impact foetal growth. For instance, is it possible that long standing SDB may cause some protective mechanisms to take effect further protecting the foetus compared to SDB that develops in pregnancy? These are questions we do not have answers to at this time.

Are women affected by the impacts of pregnancy-induced SDB, following birth?

This is an area where the research is still lacking. In an indirect way, we could say that if SDB is increasing the risk of pre-eclampsia for instance, and pre-eclampsia is associated with short term risk factors and long term adverse cardiovascular risk factors, SDB may be increasing the risk of future cardiovascular disease. However, we (the collective we) have not yet studied how or whether SDB could impact (mediate or catalyse) the link between pre-eclampsia and cardiovascular disease, or the link between gestational diabetes and type II diabetes for instance.

What further research will you be conducting?

We would like to focus our future research on better understanding mechanisms of these associations as those may be quite different in the pregnant population due to the duration of the exposure, the accelerated outcomes, the hormonal milieu and other factors associated with pregnancy. We also would like to identify therapeutic targets and understand barriers to therapy in women who may be minimally symptomatic.