Maternal Sleep-Disordered Breathing in Pregnancy Increases Nocturnal Glucose Levels in Women with Gestational Diabetes

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Abstract

Rationale: Maternal sleep-disordered breathing (SDB) in pregnancy is associated with an increased risk of gestational diabetes (GDM). However, it is unknown whether SDB severity is associated with poor glycemic control in GDM. Secondly, it is not clear whether continuous positive airway pressure (CPAP), the mainstay of treatment in the general population, is feasible in pregnant women with GDM.

Objectives: The first two objectives of this thesis were to determine the association between SDB severity and glucose control using continuous glucose monitoring (CGM) over a 72-hour period among women with GDM. Specifically, the relationships between SDB severity and: 1) daytime, nighttime and mean 24-hour glucose levels (Objective 1) and 2) glucose variability (Objective 2) were assessed. Objective 3 determined the objective adherence to CPAP treatment in pregnant women with GDM.

Methods: To achieve objectives 1 and 2, we used a cross-sectional study design including pregnant women with GDM. Participants underwent a one-night, level two home sleep recording and 72-hour CGM. For Objective 1, linear mixed models were used to estimate the association of the apnea-hypopnea index (AHI) with 1) daytime (8am to 9pm), 2) nighttime (11pm-3am; 3am-6am) and 3) mean 24-hour glucose levels. For Objective 2, glucose variability was assessed by the mean amplitude of glucose excursion (MAGE) and the standard deviation of glucose using 24-hour glucose data. For Objective 3, a randomized-controlled study was performed in which pregnant women with GDM were randomized to auto-CPAP (experimental group) or nasal dilator strips (control group) for the remainder of pregnancy. Nightly mean CPAP adherence was objectively measured over the entire treatment period.

Measurements and Main Results: Among 65 participants that were included in the cross-sectional analysis (Objectives 1 and 2), the women were 35±5 (mean±SD) years of age with body mass index (BMI) at enrolment of 33±7 kg/m^2 and 31% were taking insulin and/or metformin for management of their GDM. The mean AHI was 16±11 events/hour. While there were no associations between AHI and daytime or mean 24-hour glucose levels (8am-9pm β: 0.08 mmol/L 95% CI: -0.06, 0.23; 24 hour β: 0.05 mmol/L 95% CI: -0.1, 0.21), increasing AHI (by an increase of 10 events/hour) was associated with elevated nighttime glucose levels, even when adjusted for BMI and medications (11pm-3am β: 0.20 mmol/L (95% CI: 0.04, 0.40)) which, persisted into the morning (8am β:0.26 mmol/L 95% CI: 0.08, 0.4)). For Objective 2, there were no significant associations between SDB and glucose variability. In Objective 3, forty-six participants were diagnosed with SDB. Of those, 22 participants (48%) were randomized to CPAP treatment with the following demographics (mean±SD): 36 ± 5 years of age, BMI of 35 ± 7 kg/m², AHI of 19 ± 9 events/hour and 30 ± 3 weeks gestation at enrolment. Seven participants assigned to CPAP (32%) demonstrated objective adherence of ≥4 hours per night for at least 70% of nights. The average usage for all days during the treatment period was 3 hours and 48 minutes. The average treatment duration period was 37 ± 17 days.

Conclusions: SDB is associated with higher nocturnal and early morning glucose levels in women with GDM, even after adjusting for BMI and medications. While some pregnant participants were adherent to CPAP, more than half of participants with GDM had difficulty tolerating CPAP treatment. Further studies are needed to better understand factors impacting CPAP adherence in the pregnant population.

Résumé

Problématique: L'apnée obstructive du sommeil maternel (AOS) pendant la grossesse est associée à un risque accru de diabète gestationnel (DG). Cependant, il n'est pas connu si la sévérité de l'AOS est un facteur de risque associé à un moins bon contrôle de la glycémie lors de DG. Deuxièmement, on ne sait pas si l'utilisation du traitement habituel par pression positive continue (PPC) pour traiter l'AOS chez des femmes enceintes ayant un DG est faisable.

Objectifs: Les deux premiers objectifs de ce mémoire étaient de déterminer l'association entre la sévérité de l'AOS et le contrôle de la glycémie par la surveillance du glucose en continu (SGC) sur une période de 72 heures chez des femmes ayant du DG. Plus précisément, la relation entre la sévérité de l'AOS et: 1) le niveau moyen de glucose le jour, la nuit et pendant une période de 24h (Objectif 1) et 2) la variabilité moyenne du niveau de glucose (Objectif 2) ont été évaluées. L'objectif 3 a déterminé l'adhésion objective au traitement par PPC chez les femmes enceintes ayant un DG.

Méthode: Pour atteindre les objectifs 1 et 2, une étude transversale a été effectuée chez des femmes enceintes ayant un DG. Un enregistrement de sommeil à domicile de niveau deux a été effectué pour chaque participante ainsi qu'une SGC pendant 72 heures. Pour l'objectif 1, des modèles linéaires mixtes ont été utilisés pour estimer l'association de l'indice d'apnées-hypopnées (IAH) avec les niveaux moyens de glucose pendant: 1) le jour (8 h à 21 h), 2) la nuit (23 h à 3 h; 3 h à 6 h) et 3) une période de 24 heures. Pour l'objectif 2, la variabilité du niveau de glucose a été évaluée par l'amplitude moyenne des excursions glycémiques (AMEG) et l'écart type du glucose en utilisant les données de glucose sur 24 heures. Pour l'objectif 3, une étude randomisée contrôlée a été réalisées lors de laquelle des femmes enceintes ayant un DG ont été randomisées à l'utilisation de PPC auto-pilotée (groupe expérimental) ou de bandelettes nasales (groupe témoin) pour le reste

de leur grossesse. L'adhésion moyenne à la PPC par nuit a été objectivement mesurée pendant toute la période de traitement.

Mesures et principaux résultats : Parmi les 65 participantes qui ont été incluses dans l'analyse transversale (objectifs 1 et 2), les femmes étaient âgées de 35 ± 5 ans (moyenne ± ET) avec un indice de masse corporelle (IMC) de 33 ± 7 kg/m^2 et 31% prenaient de l'insuline et/ou de la metformine pour le contrôle de leur DG. L'IAH moyen était de 16 ± 11 événements / heure. Alors qu'il n'y avait pas d'association entre l'IAH et les niveaux de glucose pendant la journée ou sur 24 heures (8 h à 21 h β: 0.08 mmol/L 95% IC: -0.06, 0.23; 24 heures β: 0.05 mmol/L 95% IC: -0.1, 0.21), l'augmentation de l'IAH (par une augmentation de 10 événements / heure) était associée à des niveaux de glucose nocturnes élevés même après l'ajustement pour l'IMC et la médication (23 h à 3 h β:0.20 mmol/L (95% IC 0.04, 0.40)) qui persistaient jusqu'au matin (8 h β:0.26 mmol/L 95% IC: 0.08, 0.4)). Pour l'objectif 2, il n'avait pas d'associations significatives entre l'AOS et la variabilité du niveau de glucose. Dans l'objectif 3, 46 participantes ont reçu un diagnostique d'AOS. Parmi celles-ci, 22 (48%) ont été randomisées au traitement par PCC avec les données démographiques suivantes (moyenne±ET) : 36 ± 5 ans, IMC lors du recrutement de 35 ± 7 kg/m², IAH de 19 ± 9 événements / heure et 30 ± 3 semaines de gestation au moment du recrutement. Sept participantes assignées au traitement par PPC (32%) ont démontré une adhésion objective de ≥ 4 heures par nuit pour 70% des nuits. L'utilisation moyenne pour tous les jours pendant la période de traitement était de 3 heures et 48 minutes. La durée moyenne du traitement était de 37 ± 17 jours.

Conclusion : L'AOS est associée à des niveaux de glucose nocturnes et en matinée plus élevés chez les femmes ayant un DG, même après avoir ajusté pour l'IMC et la médication. Alors que certaines participantes avaient une bonne adhésion au traitement par PPC, plus de la moitié des

participantes ayant un DG avaient de la difficulté à tolérer ce traitement. D'autres études sont nécessaires pour mieux comprendre les facteurs ayant une incidence sur l'adhésion au traitement par PPC chez les femmes enceintes.

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Preface:

This thesis is presented in the traditional format following the guidelines of Library and Archives Canada. The sections of this thesis that are relevant to the analyses relating SDB severity and glucose levels are adapted from an original manuscript entitled 'Maternal Sleep-Disordered Breathing in Pregnancy and Increased Nocturnal Glucose Levels in Women with Gestational Diabetes' (first author: RN), which has been accepted for publication and is in press in the CHEST Journal.

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List of Abbreviations

AASM: American Academy of Sleep Medicine

AHI: apnea-hypopnea index

Auto-CPAP: automatic titrating continuous positive airway pressure

BMI: body mass index

CGM: continuous glucose monitoring

CPAP: continuous positive airway pressure

CSA: central sleep apnea

EEG: electroencephalogram

GDM: gestational diabetes mellitus

HAPO: hyperglycemia and pregnancy outcomes study

HEART2D: hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with type 2 diabetes mellitus

HIF-1: hypoxia-inducible factor

MAD%: mean absolute difference percentage

MAGE: mean amplitude of glucose excursion

MESA: multi-ethnic study of atherosclerosis

NREM: non-rapid eye movement sleep

NREM-AHI: apnea-hypopnea index in non-rapid eye movement sleep

ODI: oxygen desaturation index

OSA: obstructive sleep apnea

PSQI: Pittsburgh sleep quality index

REM-AHI: apnea-hypopnea index in rapid eye movement sleep

RERA: respiratory effort-related arousal

Respiratory arousal index: hypopnea and apnea-related arousals

SDB: sleep-disordered breathing

SAVE: sleep apnea cardiovascular endpoint study

Chapter 1: Introduction

Rationale

Sleep-disordered breathing (SDB) is a common and treatable sleep disorder characterized by intermittent upper airway obstruction during sleep[1]. Clinically, SDB ranges from mild presentations of snoring and upper airway narrowing (i.e. airflow limitation) to frank apneas with complete obstruction of the upper airway. Symptoms of untreated SDB include daytime somnolence, snoring and witnessed apneas[1]. SDB leads to intermittent hypoxia and/or sleep fragmentation. Through these intermediate pathways (intermittent hypoxia and sleep fragmentation), SDB is associated with adverse cardiometabolic sequelae in the general population.

In pregnancy, SDB occurs in 17-45% of women by the third trimester[2] and is substantially more common than in non-pregnant women of similar age (4-9%)[3]. While the mechanisms of SDB during pregnancy are not well understood, weight gain and hormonal factors may play a role[4]. Importantly, weight gain associated with pregnancy may increase the risk of developing SDB, particularly by the third trimester[4]. Gestational weight gain may be associated with increased neck circumference and greater risk of upper airway obstruction[5]. Finally, hormonal factors during pregnancy such as the influence of estrogen and progesterone may also contribute to an increased risk of upper airway congestion and/or upper airway instability[4].

In pregnancy, SDB is associated with maternal complications such as gestational hypertension/preeclampsia and gestational diabetes mellitus (GDM), via hypothesized mechanisms involving increased sympathetic activity and inflammation related to SDB[6-8]. Two meta-analyses estimating the association between maternal SDB and GDM showed similar results with an adjusted odds ratio (OR) of 2-3[6 7]. Both studies are consistent with the nuMoM2b study,

the largest prospective cohort study to date (n~3,100), which objectively assessed for SDB during early and mid-pregnancy. This study found that the adjusted odds ratio between maternal SDB and GDM was 3.47 (95% CI: 1.95, 6.19) when including maternal age, body mass index (BMI) and chronic hypertension as confounders[8]. Despite the accumulating observational evidence demonstrating a strong association between maternal SDB and GDM, randomized controlled trials are necessary to further investigate the causality of this relationship. Importantly, it is also unclear whether women with GDM and untreated SDB have worse glucose control compared to women without SDB.

Hyperglycemia during pregnancy negatively impacts perinatal outcomes[9]. The Hyperglycemia and Pregnancy Outcomes (HAPO) study was a large-scale multinational study that investigated the association between glucose intolerance in pregnancy and perinatal outcomes[10]. Data from this study demonstrated that glucose control between 24 and 28 weeks at gestation, inclusive of glucose values below diagnostic thresholds for GDM, was associated with a continuously increased risk of adverse maternal-fetal and neonatal outcomes (e.g. increased birth weight, fetal hyperinsulinism and neonatal hypoglycemia)[10].

Novel technologies such as continuous glucose monitoring (CGM) allow clinicians and patients with diabetes to better identify, monitor and treat diabetes and abnormal glucose fluctuations that are missed by traditional measurements. For example, Hemoglobin A1C is a crude measurement, reflecting glucose control from the previous two to three months. It also does not provide information on daytime or nighttime glucose variations. CGM is a wearable, subcutaneous sensor that captures on-going measurements of interstitial glucose levels across consecutive days[11] [12]. CGM is becoming increasingly relevant in scientific studies including in pregnancy[13]. CGM also has utility in routine clinical practice for people with diabetes (e.g. in Type 1 Diabetes

populations). The ability to measure glucose in an on-going manner is particularly useful as it enables the analysis of time-dependent changes in glucose.

Glucose variability has also become increasingly important in diabetes care and management and is important with respect to glucose-lowering therapies in the general population[14] [15]. In non-pregnancy, glucose variability is associated with increased adverse outcomes such as microvascular complications and coronary artery disease[16] which restrict oxygen and blood flow to the heart. Additionally, in the general population, SDB was found to be associated with increased glucose variability[17]. However, it is unknown whether SDB is associated with glucose variability in pregnancy.

Another major understudied aspect of SDB in pregnancy is the adherence to continuous positive airway pressure (CPAP) treatment. CPAP adherence may be objectively assessed via download from the modem or memory chip and provides information on hours of daily usage, efficacy and mask leak. However, CPAP adherence has not been well described in pregnancy. In the general population, adherence rates range between 30 – 60% when using a conventional cut-off of acceptable adherence as >4h/night for at least 70% of nights[18]. Despite low adherence in the general population, it is possible that pregnant women may exhibit higher adherence to CPAP treatment during pregnancy given the potential benefits for both maternal and fetal health. Therefore, sleep practitioners may view pregnant women as a highly motivated group to adhere to this treatment. However, this anticipated motivation may be offset by difficulty tolerating CPAP treatment caused by other sleep-disruptive factors during pregnancy. Until now, CPAP adherence, measured by hourly objective daily usage in pregnant women with SDB has not been rigorously studied or reported in the literature.

Hypotheses

There were two major hypotheses of our study. First, we hypothesized that in pregnant women with GDM, SDB severity is associated with worse glucose control and increased glucose variability. Our second hypothesis was that CPAP is a feasible treatment option for pregnant women with GDM who have SDB.

Objectives

Based on these hypotheses, this thesis encompasses three objectives. The first is to determine whether SDB severity is associated with greater glucose levels (daytime, nighttime and mean 24-hour) in pregnant women with GDM using CGM. The second objective is to estimate whether SDB severity is associated with greater glucose variability in pregnant women with GDM. Both of these objectives were performed as part of a cross-sectional analysis of baseline data. The third, and final, objective was to determine whether pregnant women with both GDM and SDB are adherent to CPAP and whether CPAP is a feasible treatment option in pregnancy.

Chapter 2: Background and Literature Review

Sleep-Disordered Breathing (SDB): Diagnosis and Scoring Criteria

In the literature, SDB includes two types of respiratory breathing pauses: central sleep apnea (CSA) and, more commonly, obstructive sleep apnea (OSA). Typical obstructive events include recurrent episodes of partial airway obstruction (hypopneas) and/or the complete obstruction of the upper airway (apneas). For the purposes of this thesis, SDB refers to upper airway obstruction during sleep, characterized by intermittent hypoxia, sleep fragmentation or both. Generally, SDB may be clinically recognized by presenting symptoms of snoring and/or excessive daytime sleepiness. In the general population, risk factors of SDB include age, male sex, elevated BMI and African American ethnicity[19-26].

The presence of SDB may be diagnosed by four main levels of sleep studies: 1) Level I studies are the more common, gold standard, diagnostic polysomnography conducted in a hospital or sleep lab which, record a minimum of seven channels: electroencephalogram (EEG), electrooculogram (eye movements), electromyogram (limb movements), electrocardiogram (heart rate and rhythm), body position and respiratory channels including airflow (as reduction and duration of nasal pressure is important for measuring hypopneas[27]), respiratory effort and oxygen saturation[28-30]. 2) Level II studies, or unattended at-home polysomnography, are more commonly used for research purposes only[29]. Although Level II studies are often completed at-home, they are usually of similar quality to Level I studies as they record the same signals. The fundamental difference is that there is no technician present in this type of study[29 31-33]. Accumulating data suggests an increase in technical failure rates with at-home polysomnography studies compared to in-lab polysomnography[34 35]. Failure rates for at-home studies have been reported to be higher (4.7%[34] to 5.3%[35]) than in-lab polysomnography failure rates (1.5-3.1%)[34 35]. 3) Level III studies

are also completed at home, but capture fewer signals than level I and II studies. This type of study measures limited cardiopulmonary parameters: two respiratory variables (i.e. respiratory effort and airflow), oxygen saturation and a cardiac variable (i.e. heart rate or electrocardiogram)[1 28]. 4) Level IV studies include devices that measure only one or two parameters, usually oxygen saturation and heart rate, and occasionally only airflow[28].

Polysomnography provides important respiratory metrics[28 29 36]. The apnea-hypopnea index (AHI) captures the average number of apnea and hypopnea episodes per hour across the entire duration of sleep[37]. Apneas are defined as a complete airflow cessation (at least a 90% reduction in airflow) for at least 10 seconds[38]. According to the American Academy of Sleep Medicine (AASM) manual, hypopneas are defined in two ways: 1) A >30% airflow reduction for at least 10 seconds accompanied with >3% oxygen desaturation or an arousal (Recommended definition)[38] or 2) events lasting for at least 10 seconds and accompanied by at least 30% airflow reduction and a minimum of 4% oxygen desaturation (Acceptable definition)[38]. Respiratory effort-related arousals (RERAs) are a type of event that does not meet the criteria of a hypopnea or an apnea. RERAs are defined by airway obstruction/reduced airflow, associated with increased respiratory effort that resolves with an arousal[38]. REM-related AHI (REM-AHI) reflects the AHI during REM sleep specifically. SDB events during the REM period are longer in duration (by 30 seconds), associated with greater oxygen desaturation and occur more frequently compared to events in non-REM sleep[39-41]. The oxygen desaturation index (ODI) captures the average number of arterial oxygen desaturation events, of at least 3%, per hour across the sleep period[42].

Depending on the scoring criteria and type of study used, the frequency of apneas and hypopneas can vary. For example, the Chicago scoring criteria[27 43] is a more sensitive scoring criteria compared to the AASM criteria[42]. Compared to the recommended AASM hypopnea

definition given above, the Chicago Scoring Criteria defines hypopneas as an event with a 50% or greater decrease in airflow or a lesser, discernable airflow reduction associated with a 3% or greater oxygen desaturation or arousal[43]. The fundamental difference with the AASM definitions is that the Chicago Scoring Criteria captures hypopneas with >50% airflow reduction without >3% oxygen desaturation or the presence of an arousal. The findings of a retrospective polysomnography study investigating the impact of scoring criteria on final AHI values showed that the median AHI per AASM protocol was 30% of the median AHI when using the Chicago scoring criteria[27]. This study highlighted that differences in hypopnea definitions, based on the scoring criteria being used, are associated with notable differences in AHI values. Lack of ability to capture arousals by Level III and IV studies in addition to sensor dislodgement and poor quality signals may contribute to underestimated AHI values[1]. Further, the lack of EEG recordings in these studies[29 39] prevent sleep specialists from discerning events in REM sleep compared to non-REM sleep rendering them unable to compute REM-AHI. AHI with arousals (part of the Recommended definition of hypopnea) has a stronger association with low arousal threshold and may be important for future studies assessing the effect of SDB on outcomes[44].

SDB in the General Population and Cardiovascular Outcomes

In the general population, SDB may lead to increased cardiovascular disease such as hypertension[45-48]. Risk factors for SDB (e.g. obesity and male sex) are also risk factors for cardiovascular disease and hypertension[23]. Studies have shown that SDB is associated with the development of adverse cardiovascular outcomes independent of well-documented confounders, such as BMI[49-51].

The underlying mechanisms associated with intermittent hypoxia and sleep fragmentation, which may be associated with adverse cardiovascular outcomes, include increases in sympathetic

activity, inflammation and oxidative stress[48 52]. SDB-induced hypoxia is hypothesized to activate an inflammatory response thereby releasing inflammatory mediators (e.g. C-reactive protein and interleukin 6) that contribute to the pathophysiology of coronary heart disease[53]. On a cellular level, the release of inflammatory mediators from blood vessels, monocyte activation and impaired defense mechanisms against thrombosis may lead to plaque rupture and endothelial injury[48].

Similar mechanisms are hypothesized to underlie the relationship between SDB and hypertension. Independent of daytime hypertension, SDB itself is associated with recurring surges in nocturnal blood pressure[54]. Increases in sympathetic activity caused by SDB is believed to lead to hypertension, endothelial dysfunction and increased plasma endothelin-1 levels, a vasoconstrictor peptide[48]. One seminal study by Somers et al., showed that recurrent and intermittent hypoxia events along with changes in intrathoracic pressure are associated with altered hemodynamics [55]. In this study, the investigators recorded blood pressure, heart rate, sympathetic nerve activity and polysomnography during wakefulness and sleep. Sympathetic activity was captured with the use of microneurography, a direct multiunit intraneural recording of sympathetic output to muscle blood vessels[55]. The results of the study showed that participants with SDB exhibited increased levels of sympathetic activity, blood pressure and heart rate during sleep that persisted into wakefulness compared to control participants matched based on demographic characteristics[55]. The results of this study were also consistent with other studies showing that SDB is associated with increased sympathetic activity[56-59].

The investigators of a large population-based study, the Multi-Ethnic Study of Atherosclerosis (MESA), assessed the relationship between SDB severity indices and systolic and diastolic blood pressure[60]. The authors found that higher AHI, accompanied with >4% oxygen desaturation, was associated with elevated systolic and diastolic blood pressure[60]. This is

consistent with a recent meta-analysis of seven studies and 1,562 participants showing that the prevalence of SDB was associated with increased risk of non-dipping activity in nocturnal blood pressure (OR = 1.47 95% CI: 1.07, 1.89; p-value <0.01)[61]. Further to this, the investigators of a ten year observational study estimated the association of SDB as a risk factor for cardiovascular events[45]. The authors compared the risk of adverse cardiovascular outcomes between four groups of men: 1) snoring men without SDB 2) men with untreated SDB 3) men with SDB treated with CPAP and 4) healthy men from the general population. The investigators found that those with severe, untreated SDB experienced more fatal (1.06/100 person-years, p-value <0.01) and non-fatal (2.13/100 person-years, p-value <0.01) cardiovascular events than the three other groups[45]. Similarly, severe, untreated SDB was associated with a significant increase in risk of fatal (OR: 2.87 95% CI: 1.17, 7.51) and non-fatal (OR: 3.17 95% CI: 1.12, 7.51) cardiovascular events after adjusting for age, BMI, existing cardiovascular disease, medical comorbidities, smoking status, alcohol use and diabetes medication[45]. Likewise, a cross-sectional analysis of the Wisconsin Sleep Cohort assessing SDB and the occurrence of stroke in the cohort showed that participants with an AHI ≥ 20 had increased odds for stroke (OR: 4.33 95% CI: 1.32, 14.24) compared to those without SDB after adjusting for age, sex, BMI, cigarette use and alcohol use[61 62]. Other prospective, observational studies have shown similar reproducible associations between SDB and cardiovascular/stroke risk[62 63].

Recent studies also show that REM-related SDB is associated with poor cardiovascular outcomes[64 65]. In REM-related SDB, the adjusted hazard ratio for poor cardiovascular outcomes in severe SDB was 1.35 (95% CI: 0.98, 1.85), increasing to 2.56 (95% CI: 1.46, 4.47) in participants with pre-existing cardiovascular disease[64]. The composite cardiovascular end points assessed in this study included myocardial infarction, coronary artery revascularization, congestive heart

failure and stroke[64]. This study highlighted the association between REM-predominant SDB and higher incidence of worsened cardiovascular outcomes when combined with pre-existing cardiovascular disease[64]. Another recent study revealed that the transition of SDB from REM sleep into non-REM sleep is associated with an increased incidence of cardiovascular events with existing REM-related SDB at baseline[65].

Although the above-mentioned observational studies support the association between SDB and cardiovascular outcomes, findings from the interventional literature are conflicting to such studies. In the Sleep Apnea Cardiovascular Endpoints (SAVE) study, participants aged 45 to 75 years with moderate to severe SDB and coronary or cerebrovascular disease, did not experience significant impact on neither individual nor cardiovascular endpoints (hospitalization for cardiovascular reasons, myocardial infarction, stroke or death due to cardiovascular reasons) with CPAP treatment compared to the standard care group (HR: 1.10 95% CI: 0.91, 1.32)[66]. This data is consistent with findings of the SERVE-HF trial, another interventional study investigating the association of a servo-ventilation device in participants with low left ventricular ejection fraction (45% or less) and SDB (predominantly CSA)[67]. The primary endpoint of this study was a time-to-event analysis of death, lifesaving cardiovascular intervention and other cardiovascular endpoints. Participants receiving the ventilation intervention did not show significantly differing incidence of the primary end point (54%) compared to the control group (51%) (HR: 1.13 95% CI: 0.97, 1.31)[67]. It is important to note that the lack of differences between intervention and control groups in these studies may be due to low CPAP adherence. In the SAVE study, participants receiving CPAP exhibited an average adherence of 3.3 ± 2.3 hours/night[66].

SDB in the General Population and Glucose Metabolism

SDB has been found to be associated with impaired glucose regulation resulting in insulin resistance, decreased insulin sensitivity and glucose intolerance in clinical studies assessing healthy participants, prediabetic participants and participants with type 2 diabetes[68-70]. In a review and meta-analysis quantifying the risk of sleep disturbances relative to traditional risk factors in the development of diabetes, Anothaisintawee et al. investigated eight studies (n = 63,647)[71]. In this meta-analysis, the unadjusted pooled relative risk ratio of SDB in the development of diabetes was 2.02 (95% CI: 1.57, 2.61). After adjusting for age, sex and BMI, the adjusted odds ratio was ~1.5 (95% CI: 1.27, 1.75)[71]. A prospective analysis combining non-diabetic participants from the Atherosclerosis Risk in Communities and Sleep Heart Health studies showed a dose response between SDB severity and incident diabetes[72]. Participants with severe SDB were at a 2.75 (95% CI: 1.81, 4.19) times higher risk of incident diabetes compared to participants without SDB after adjusting for BMI and waist circumference[72].

The underlying mechanisms for the relationship between SDB and poor glucose control are not fully understood, but it is plausible that sleep disruption and intermittent hypoxia may contribute to metabolic dysfunction including decreased insulin sensitivity [73]. Studies conducted in animal models and cell cultures have shown that intermittent hypoxia activates the transcription of hypoxia-inducible factor[74-76]. Hypoxia-inducible factor (HIF-1) is partly involved in regulating oxygen homeostasis and other physiological processes such as glucose and lipid metabolism[74 77-80]. The activation of HIF-1 upregulates sterol proteins[74] responsible for raising serum and fatty acid concentrations in the liver, thereby increasing insulin resistance[81 82]. Increased free fatty acids prevent insulin-induced glucose uptake, prevent glycogen synthesis and inhibit the insulin-mediated suppression of glycogenolysis further promoting insulin resistance[83]. Intermittent

hypoxia is also responsible for increases in NF kappaB, a nuclear transcription factor[84-86] that contributes to the inflammatory response[87 88]. Pro-inflammatory signaling pathways and pro-inflammatory cytokines such as restin, leptin and adiponectin prevent insulin signal transduction and can lead to insulin resistance in the liver, skeletal muscles and adipose tissue[89].

In experimental and observational studies done in healthy participants, SDB has been shown to be associated with decreased insulin sensitivity and impaired glucose control[90 91]. In one cohort of healthy, lean men diagnosed with SDB and without any comorbidities, SDB (vs. controls) was associated with greater insulin resistance and increased insulin secretion[90]. In another cohort of healthy participants, exposure to 5 hours of intermittent hypoxia was associated with decreased insulin sensitivity and glucose effectiveness compared to normoxic conditions[91]. Another experimental study evaluated the effect of sleep fragmentation through the use of auditory and mechanical stimuli across all sleep stages in healthy participants[68]. Similarly to the intermittent hypoxia study previously mentioned, after two nights of sleep fragmentation, participants in this experimental study demonstrated decreased insulin sensitivity and glucose effectiveness[68]. This study also showed that participants had elevated cortisol levels at night and sympathetic activation with carry-over implications into the morning[68]. The authors further suggested that increases in sympathetic and adrenocortical activity may contribute to the impaired metabolic effects caused by sleep fragmentation in SDB[68]. Finally, in healthy and lean individuals subjected to suppression of deep non-REM, slow wave sleep, there was a 25% decrease in insulin sensitivity after three nights of exposure[69]. Based on these experimental studies, there is accumulating evidence to suggest that sleep fragmentation and intermittent hypoxia are associated with disruptions in glucose metabolism.

While the observational and experimental data above is compelling, it is not conclusive of a causal relationship between SDB and abnormal glucose metabolism. In one randomized crossover study of SDB treatment, participants with moderate to severe SDB acclimated to CPAP were subjected to polysomnography with CPAP at baseline and again after CPAP withdrawal with a one to four week washout[59]. The authors found that a two-night treatment withdrawal, as a surrogate of untreated SDB, was associated with increased nocturnal free fatty acids, glucose and cortisol all of which were proportional to the frequency of respiratory events and sleep fragmentation which activated sympathetic activity[59]. Additionally, in a double-blind crossover design of healthy men, the authors reported differing norepinephrine levels based on oxygen conditions[92]. Intermittent hypoxia was associated with an elevated release of epinephrine in plasma when compared to levels during normal oxygen conditions[92]. The authors hypothesized such increased epinephrine release may be a mediator for glucose intolerance in the presence of hypoxia[92].

In two clinical studies investigating the association of SDB treatment on metabolic outcomes[93 94], the authors found that Hemoglobin A1C levels were significantly reduced after treatment[93]. Likewise, treatment was associated with reduced fasting glucose, mean 24-hour glucose and norepinephrine levels[94]. These studies suggest that SDB may have pathophysiological implications in impaired glucose control. These studies are also consistent with a proof-of-concept, randomized-controlled trial that investigated the association of SDB treatment on glucose metabolism in a prediabetes population. The authors found that the placebo group exhibited significantly higher glucose levels and reduced insulin sensitivity when compared to the treatment group after a post-treatment oral glucose tolerance test[70]. Similar findings were shown in studies enrolling participants with type 2 diabetes [93-95].

SDB in REM sleep may play an important role in glucose metabolism. In normal individuals, glucose concentration and blood glucose have been shown to decrease during REM sleep[96]. In one study of healthy individuals without SDB and with normal glucose tolerance, interstitial glucose levels fell during sleep, particularly during the REM period[96 97]. REM-related SDB refers to the period in which apneas and hypopneas occur mostly during REM sleep. Quantitatively, REM-related SDB is defined as REM-AHI >5 and non-REM AHI <5 with REM sleep lasting for at least 30 minutes[98]. A large clinical, cross-sectional study found that REM-related SDB prevalence raged from ~14 to ~37% in their sample depending on the REM-SDB definition used[99]. SDB in REM sleep is likely a contributing factor to impaired glucose control[39]. The sympathetic effect that occurs during SDB is reported to be even more profound during REM sleep[55]. SDB in REM sleep has been shown to reverse the dipping effect, analogous to blood pressure, of interstitial glucose concentration[96]. In the Sleep Heart Health Study, the investigators aimed to estimate the association between REM-related SDB, glucose metabolism and insulin profiles[100]. Here, REM-AHI was associated with insulin resistance, but not with fasting glucose or glucose intolerance after adjusting for age, sex, race, adiposity, non-REM AHI and self-reported sleep duration. In another study prospectively quantifying the association of SDB in REM on Hemoglobin A1C, REM-AHI was independently associated with increased Hemoglobin A1C[39].

Sex-Related Differences in SDB

There are three conventional categories of SDB severity with varying prevalence: 1) mild SDB (AHI ≥ 5) 2) moderate SDB (15 ≤ AHI < 30) and 3) severe SDB (AHI ≥ 30)[37]. The prevalence of moderate to severe SDB is dependent on BMI, age and sex; however, in the general population the range is between 3 and ~50%[28 101 102]. In Canada, the prevalence of SDB is approximately 3% (rising to 5% in adults 45 years of age and older) [103]. Additionally, 26% of Canadian adults reported

symptoms and risk factors associated with a high risk of developing SDB[28]. Of the 3.4% of Canadians with SDB, it is more common in Canadian men (65%) than women (35%)[103]. More globally, a recent study has shown that the prevalence of any degree of SDB, particularly in women, has increased from ~15% in 1994 to ~20% in 2010[101]. The prevalence of moderate to severe SDB is 9% in women aged 30-49 years, 13.5% in women who are obese and 4% among non-obese women[101]. In men, the prevalence has increased from 25% to ~35% between the late 1980s/1990s to the early 2000s[101]. Following the same subgroups, the prevalence of moderate to severe SDB is 10% in men between 30 and 49 years of age, 45% in men of the same age range who are obese and 18% among non-obese men[101]. One important consideration that impacts prevalence is the possible underdiagnosis of SDB[104]. The findings from one cohort study showed that 1.6% of participants were diagnosed for SDB, 0.6% were diagnosed and treated for SDB; however, SDB was prevalent in 4.1% of participants based on patient-reports of snoring and sleepiness[104]. Another factor of prevalence is evidence of clinical, population-based and interventional studies having samples largely composed of males[41 55 59 90 96 105 106].

Several studies suggest that women present with SDB in clinically different ways than men[107-111]. In terms of reporting SDB symptoms, women are less likely to acknowledge symptoms of snoring due to negative social perceptions associated with snoring[24 108]. This may contribute to underdiagnosis in this population[107]. Additionally, SDB in women may also be underdiagnosed due to underreporting of snoring by bed partners[112]. In one clinical study, women who snored were more likely to have excessive daytime sleepiness compared to men who snored[108]. On the other hand, in the Sleep Heart Health Study, which consisted of a community-based sample, the investigators showed that women were less likely to have an Epworth Sleepiness Scale > 10 (scores above 10 are considered abnormal) when compared to men[113]. In the clinical study, women from

the general population were between 20 and 69 years whereas the Sleep Heart Health Study consisted of women 40 years and older with SDB. It is also worth mentioning that the inconsistent evidence based on these two studies may suggest that current assessments of sleepiness, such as the use of the Epworth Sleepiness Scale[114], may not be an ideal measurement of sleepiness in women[113].

AHI values have also been reported to be lower in women, even when underlying risk factors (e.g. age and BMI) were not significantly different between men and women[109]. This could be due, in part, to the differences in the physiological and structural composition of the upper airway in women with no significant gender related differences in baseline characteristics[110]. For example, adiposity distribution differs between men and women, with men having more visceral adiposity composition while women tend to have more subcutaneous composition[115]. One study showed that women may have a less collapsible airway than men thereby reducing pharyngeal resistance[110].

SDB in Pregnant Women

Women may experience increased sleep disturbances due to the physical changes that occur with pregnancy[116]. Sleep architecture and sleep patterns have been reported to change as early as the first trimester due to increased urinary frequency as dilation of the pelvis and ureters promote nocturia[117 118]. In addition to this, weight gain associated with pregnancy may narrow the upper airway and increase airway resistance, leading to an increased risk of SDB[118]. More specifically, gestational weight gain may be associated with increased neck circumference as fat deposits begin to accumulate around the upper airway thereby reducing oxygen flow and obstructing breathing[5]. Furthermore, reductions in functional residual capacity as pregnancy progresses, particularly in recumbency, may be associated with reductions in upper airway calibre

due to lung volume-dependent effects, predisposing to upper airway collapse[119]. In one prospective cohort study, the authors aimed to estimate whether pregnancy was associated with upper airway narrowing[118]. In this study, the authors used the acoustic reflection technique as a means of measuring the upper airway[120-122]. In their cohort of third trimester pregnant women (n=100), the authors found that pregnant women had significantly smaller upper airways and lower mean pharyngeal areas compared to non-pregnant women as controls[118].

By the third trimester, women also experience physiological changes such as increases in blood volume and renal blood flow. Further to this, another physiological consideration of SDB risk in pregnancy is the fluctuation of esophageal pressure which increases gastrointestinal symptoms of reflux disease. The presence of gastric reflux disease in pregnancy[116 123 124] may disrupt sleep and contribute to sleep fragmentation, further contributing to decreased airway stability and greater risk for SDB events[125].

Hormonal changes that occur during the gestation period may also promote SDB in pregnancy. Examples of such changes include the effect of estrogen which narrows the upper airway resulting in upper airway congestion, increased airway edema and increased snoring[126-128]. Progesterone may also promote SDB in pregnancy; however, the evidence is inconsistent. In one study, it was hypothesized that progesterone drives increases in respiratory drives and ventilation, which may increase upper airway collapsibility[129]. However, another study showed data contrary to this as these findings suggested that progesterone may be protective against SDB by enhancing upper airway dilation during sleep[130]. In non-pregnancy, overnight rostral fluid shifting[131-133] and fluid retention causing edema[134 135] have been suggested as possible contributing factors of SDB. Although these mechanisms may likely extend into the mechanisms of SDB in pregnancy, studies to better understand such mechanisms have not yet been done.

Although underdiagnosed, SDB is common in pregnancy. As pregnancy progresses, SDB symptoms become more apparent particularly during the third trimester with overall snoring prevalence rising to 30% by the end of pregnancy compared to 7.1% of participants reporting habitual snoring at study entry during the first trimester[5]. In one representative study using full polysomnography, the authors showed that the percentage of participants with SDB increased from 10 to 25% from the first to the third trimester[2]. A systematic review of full polysomnography found that the prevalence of SDB by the third trimester was 17-45% depending on BMI, age at gestation, SDB symptoms, underlying risk factors, sleep study level and associated scoring criteria[117]. Although snoring is a common symptom of SDB and is a common occurrence in pregnant women[136], other symptoms such as gasping, choking, breathing difficulties and apneas have a greater specificity for SDB than snoring alone[137 138]. However, it should be noted that it is unclear what threshold of AHI is used to define significant SDB in pregnancy (i.e. at which threshold it becomes clinically important to manage and treat to prevent adverse outcomes).

Different scoring criteria, type of study and AHI cut-offs have been reported to affect SDB prevalence in pregnancy. SDB in pregnancy is characterized by milder degrees of obstruction. In one cohort study, there was a greater frequency of hypopneas with arousals (mean of 7.3 events/hour) compared to AHI (mean of 1.8 events/hour) and hypopneas with 3% desaturation (mean of 1.89 events/hour)[2]. Using in-lab polysomnography and the Chicago Scoring Criteria, the prevalence of SDB increased from 11% in the first trimester to 27% in the third trimester[2]. In contrast, when using a Level III study with events scored per AASM protocol, the prevalence of SDB in pregnancy was found to be 4% in early pregnancy and 8% in mid pregnancy[8]. Prevalence of SDB in pregnancy therefore varies based on the study, scoring criteria and cut-offs used.

SDB and Adverse Outcomes in Pregnancy

There is emerging interest in investigating the association of SDB, and SDB symptoms, on adverse pregnancy outcomes. SDB may be a risk factor for gestational hypertension, preeclampsia and poor cardiovascular outcomes. An increase in sympathetic activity due to SDB in pregnancy has been associated with overall worse control of chronic maternal blood pressure[139]. As in the general population, SDB-related increases in inflammation, oxidative stress and sympathetic activity are believed to lead to endothelial dysfunction[140]. Observational studies have estimated that the adjusted odds ratio between SDB and gestational hypertension and preeclampsia ranges between 1.5 and 2.5 when accounting for relevant confounders such as BMI; the estimated odds ratio being ~3.5 in nuMoM2b study, the largest prospective cohort to date[8 136 141-143]. In a cohort study that compared pregnant obese women with normal weight controls, women with SDB were more likely to experience maternal hypertension and pre-eclampsia[144]. SDB symptoms in pregnancy are also associated with reduced maternal cardiac output to the growing fetus[139]. A large, national database study found that SDB in pregnancy was also associated with increased odds of cardiomyopathy (aOR: 9 95% CI: 7.47, 10.87), congestive heart failure (aOR: 8.94 95% CI: 7.45, 10.73), pulmonary embolism (aOR: 4.5 95% CI: 2.3, 8.9) and a five-fold increase of in-hospital death all of which were exacerbated by obesity[145].

Delivery complications and poor fetal outcomes have also been found to be associated with SDB in pregnancy. In one cohort study comparing pregnant obese women with normal-weight controls, women with SDB were more likely to experience preterm delivery[139]. Another study considering healthy, non-obese women with objectively measured SDB in the third trimester, showed that obstructive hypopneas were associated with delivery of small for gestational age infants[146]. Other studies have also shown that SDB symptoms are associated with higher rates of

unplanned Caesarean sections[141], poor obstetrical outcomes and preterm delivery[144]. These findings are consistent with studies done in animal models which showed that SDB, characterized by intermittent hypoxia or sleep fragmentation, was associated with reduced fetal growth [147] and offspring ventilatory effects[147].

Gestational Diabetes (GDM)

Pregnancy is a state of progressive insulin resistance with potential for increased susceptibility to SDB[148] and worsened glucose outcomes[149] such as gestational diabetes. Gestational diabetes is considered as glucose intolerance that arises during pregnancy between 24-28 weeks gestational age[150]. Diagnosis is based on an oral glucose tolerance test which identifies abnormal fasting glucose levels. Some endocrinology and gestational diabetes clinics follow the World Health Organization 2013 guidelines for this test to confirm diagnosis: 1) an abnormal 50g screening test with level > 11.1 mmol/L or 2) an abnormal fasting 1-hour value (10 mmol/L or greater) or abnormal 2-hour value (8.5 mmol/L or greater)[151 152] with the HAPO study largely guiding GDM cut-offs and practice guidelines[153]. Despite the existing guidelines on lifestyle and behavioural management, GDM is common and is becoming increasingly prevalent as shown in an American population-based study where GDM prevalence doubled between 1994 and 2002[154]. The current prevalence of GDM ranges between 8-16%[155 156] depending on the study population. This increasing prevalence is mostly due to underlying factors such as the global increase in obesity, differences in ethnicity, existing comorbidities and the diagnostic criteria used.

Similarly to SDB in pregnancy, hyperglycemia during pregnancy is associated with an increased risk of adverse perinatal outcomes including preeclampsia, mortality, increased rates of caesarean deliveries, macrosomia and delivery complications[157]. A large, multinational study (HAPO) showed significant continuous relationships between maternal glucose levels that were

below the conventional diagnostic threshold of diabetes and increased birth weight, delivery by caesarian section and neonatal hypoglycemia[158]. Moreover, a HAPO follow-up study demonstrated increased risk of insulin resistance and impaired glucose tolerance among children exposed to maternal hyperglycemia during pregnancy[159]. These studies highlight that even mildly elevated glucose levels may be harmful for the mother and fetus. Identifying modifiable risk factors for hyperglycemia in pregnancy is therefore important in order to ultimately improve perinatal health outcomes and future child health and development.

Risk factors of GDM include certain high-risk ethnicities, obesity, GDM during a previous pregnancy, age and a family history of type 2 diabetes[160]. SDB is hypothesized to disrupt glucose tolerance and impair insulin sensitivity in pregnancy as observed in the general population[7]. Therefore, SDB may also serve as an additional novel, reversible risk factor for GDM. Two recent meta-analyses showed that the adjusted odds ratio for the association between maternal SDB and GDM ranged between 2.1 (95% CI: 1.38, 3.23)[6] and 3.1 (95% CI: 1.89, 4.96)[7] after adjusting for BMI. These results are consistent with nuMoM2b, the largest prospective cohort to date on SDB and pregnancy outcomes, which showed that the adjusted odds ratio between maternal SDB and GDM was ~3.5 (95% CI: 1.95, 6.19) after adjustment for age, BMI, gestational weight gain and other confounders[8].

As in the general population, obesity also serves as an important risk factor for both SDB and GDM with BMI-stratified analysis suggesting that pregnant women who are obese may have a stronger association between SDB and GDM[7]. Despite this, BMI-adjusted analyses suggest that the association between SDB and GDM is not largely driven by BMI[6-8]. While independent associations have been observed, there are limitations with existing observational studies estimating the relationship between SDB and GDM in pregnancy. Residual confounding by

obesity cannot be completely excluded since BMI is a suboptimal measure of overall obesity[161] [162]. Furthermore, causal relationships cannot be estimated from observational data.

In the only interventional study to date including obese women with both SDB and GDM, the authors aimed to estimate the association of SDB treatment on glycemic control in women with GDM[163]. The primary objective of this study was to assess the association of SDB on glucose metabolism based on an oral meal tolerance test at baseline and two weeks after treatment. The authors did not find significant outcome differences in glucose metabolism between the CPAP and the wait-listed control group at either of the two timepoints[163]. In reporting their secondary outcomes, they showed that CPAP treatment was associated with greater insulin secretion and improved maternal-fetal outcomes such as fewer preterm delivery events, caesarean sections and neonatal intensive care unit admissions[163]. However, in addition to the small sample size (n=18), there were limitations to this study. The authors used subjective questionnaires (the Berlin Questionnaire and Epworth Sleepiness Scale)[164-166] and a portable level III sleep recording device rather than full polysomnography to diagnose SDB. Secondly, CPAP adherence was low with 3.4 hours of nightly usage and the treatment period was only 2 weeks in duration. Further studies are therefore warranted to determine the effects of SDB treatment on glucose control and maternal-fetal outcomes.

Measurements of Glucose Control

Hemoglobin A1C measures the percentage of hemoglobin that is bound by glucose. It has been found to be well correlated with blood glucose concentration[167] and mean glucose levels over time [168]. A prospective study showed strong associations between Hemoglobin A1C and vascular outcomes in participants living with type 2 diabetes in the United Kingdom[169]. Achieving optimal glucose control was associated with decreased risk of diabetes-related outcomes and microvascular

complications in non-pregnant individuals with type 2 diabetes[169]. Today, conventional measurements of glucose control, including Hemoglobin A1C and postprandial glucose measurement, are used to guide clinical-decision making processes in the general population[170] to reduce micro and macrovascular complications[171] and may be useful in predicting diabetes risk[172] and adverse cardiovascular outcomes[173].

In pregnancy, Hemoglobin A1C is a suboptimal measurement of glucose control. Hemoglobin A1C reflects blood glucose only for the previous 60 – 90 days[174] and may not accurately represent glycemic control (i.e. may overestimate or underestimate glucose concentrations) in the presence of anemia, which may interfere with the lifespan of erythrocytes[175]. The utility of Hemoglobin A1C in pregnancy is further limited due to increased erythrocyte turnover, and the inability to detect short-term changes in glucose control[176] which may reflect clinically important hyperglycemia in pregnancy.

There is emerging interest in using CGM[13 93 177-179] as a more comprehensive measure of glucose control over a 24-hour time period. CGM reports glucose levels based on glucose concentrations present in subcutaneous, interstitial fluid[180]. A wearable, glucose oxidase-based sensor is inserted under the skin. The sensor undergoes a reaction of electron transfer, creating a current that is proportional to the interstitial glucose concentration allowing for comprehensive detection of blood glucose fluctuations[180]. Interstitial glucose levels have been found to be comparable to venous blood glucose measurements[181 182]. CGM becomes clinically useful as shown in one study examining 24-hour profiles of glucose taken every 15 to 30 minutes. This study showed variations in plasma glucose levels throughout the day without significant changes in insulin[94]. When considering its utility in SDB and glucose impairment specifically, CGM allows diabetes care teams the ability to examine the effect of CPAP in improving glucose metabolism

and control[93]. CGM has been validated in normoglycemic individuals[11], in adults with type 1 or type 2 diabetes[181] and has been shown to be safe and well-tolerated in pregnant women who had type 1 diabetes[13] or who were healthy during pregnancy[179]. CGM has the advantage of providing real-time data and enables the assessment of temporal changes in glucose.

Glucose variability, which can be obtained from CGM, is a measure of deviation from physiological steady states[183] and captures fluctuations in glucose levels such as increases in postprandial glucose and hypoglycemic excursions which are typically associated with cardiovascular outcomes in type 2 diabetes[184 16]. Glucose variability is generally greater in type 2 diabetes and in individuals with poor glucose control[184]. However, in one study done with three categories of glucose control (normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetic participants), the authors showed that healthy, normo-glycemic individuals also exhibited some level of glucose variability[185].

It has been hypothesized that glucose fluctuations, inclusive of spikes in postprandial glucose, may negatively influence diabetes risk and micro and macrovascular outcomes in the type 2 diabetes population[184]. Evidence of the pathophysiology of increased glucose variability and poor outcomes is still not entirely clear but a number of mechanisms have been proposed: 1) increased oxidative stress, 2) the atherogenic action of postprandial glucose leading to an increase in serum lipids[184 186] and 3) endothelial dysfunction caused by fluctuations[187] which may lead to decreased vasodilation, thereby potentially increasing cardiovascular risk[188]. Increased glucose fluctuations have a greater impact on oxidative stress compared to chronically sustained hyperglycemia[189]. Intermittent exposure to hyperglycemia, rather than constant exposure, has been found to be associated with oxidative stress-induced apoptosis of endothelial cells[190]. Glucose variability may induce oxidative stress and cellular dysfunction due to an overproduction of

superoxide which trigger a deleterious cascade[191 192]. Rising concentrations of intracellular reactive oxygen species cause, and impair, angiogenesis due to ischemia and trigger inflammatory pathways which alters epigenetic makeup due to its maintenance and expression of proinflammatory genes[191 192]. Further research is needed to further establish mechanisms and clinical outcomes associated with glucose variability and flucatuations[193].

Glucose variability is becoming an increasingly relevant index that may be associated with cardiovascular outcomes in the general population[14 184 194-197]. In a review of 18 studies estimating glucose variability and diabetic outcomes in participants with type 1 or type 2 diabetes, characterization of glucose variability was associated with microvascular complications in type 1 diabetes[14]. In type 2 diabetes, glucose variability was associated with diabetic retinopathy development, macrovascular complications and mortality[14]. One observational study considered in this review was the Verona Diabetes Study[196]. In this study, the authors evaluated the association between fasting plasma glucose variability and mortality in older adults with type 2 diabetes[196]. After a ten year follow up, the authors found that glucose variability was an independent predictor of overall mortality (39.7/1,000 person-years), as well as cardiovascular and cancer mortality[196]. Contrary to this, another observational study that conducted a reanalysis of the data from the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (HEART2D) found that lower glucose variability was not associated with reduced cardiovascular outcomes[194]. Given the conflicting evidence, further research is likely warranted to investigate the relationship between glucose variability and clinical outcomes in various populations.

There are different methods used to quantify glucose variability. A previously used measurement was the M-value introduced by Schlichtkrull which, considered the mean of the log

transformation of blood glucose deviations from a specified reference value. This value had an amplitude correction factor and made special considerations for hypoglycemia more than hyperglycemia[183 198]. However, a major limitation of the M-value was that it incorporated mean glycemia and did not consider glucose variability alone, highlighting a need for more specific and reflective glucose variability metrics. Other useful methods include the standard deviation, coefficient of variation and graphical representations[199].

The Mean Amplitude of Glucose Excursion (MAGE) is an adaptation of the M-Value. In one prospective study of non-diabetic participants by the American Heart Association, MAGE was estimated to be strongly associated with cardiovascular events in participants with coronary artery disease[200]. This is consistent with other studies that estimate an association between MAGE and increased incidence of secondary cardiac events in the general population[201-203]. The standard deviation of glucose is another common metric of glucose variability given its ease of calculation[183] and may be computed in different ways such as calculating the total standard deviation, intraday standard deviation and inter day standard deviation[199]. There are a number of studies that have investigated glucose variability in pregnant women with diabetes; however, it is unclear whether glucose variability may[204] or may not[205] be associated with delivery of large for gestational age infants in women with gestational diabetes and/or type 2 diabetes.

Treatment of SDB

Although there are different treatment options available for SDB resolution, CPAP is the gold standard of treatment[206 207]. CPAP has been found to improve overall quality of life and reduce AHI and sleepiness in the general population[66 206 208-212]. CPAP includes a nasal-oral face mask or nasal mask connected to a blower unit that supplies an ongoing pressure of air. It functions to prevent upper airway collapsibility by gently forcing the airway open. Although it is largely

beneficial in remedying SDB, resolution of the disorder is heavily dependent on participants meeting the published accepted adherence guidelines for adequate use. Adequate adherence is defined by at least four hours of use per night, on average, for at least 70% of nights[213-216]. In one study that reviewed trends of CPAP adherence rates across the previous 20 years in the general population (specifically adults with SDB), the authors showed that adherence is generally low with the range being between 30 – 60%[18].

The mechanism of action of CPAP is to open the airway through a stream of constant, pressurized air, thereby preventing upper airway collapse. Positive airway pressure may be delivered through an auto-titrating CPAP (auto-CPAP) device or a fixed CPAP device[217]. Fixed CPAP devices emit a constant pressure throughout the entire sleep period[217]. The auto-CPAP device varies the emitting pressure based on changes in airflow resistance[217]. Such resistance in airflow may be caused by various factors including posture, sleep stage and the degree of nasal congestion[217]. A major benefit of auto-CPAP therapy is the ability to prescribe PAP without requiring an in-laboratory titration to determine the optimal pressure[218]. Studies have demonstrated that there are no significant differences in adherence and sleepiness measures between auto- and fixed CPAP[218 219].

Generally, CPAP has been associated with improved clinical outcomes in the context of adequate adherence[217]. Early studies investigating CPAP adherence in the general population relied on subjective, participant-reported outcomes such as verbal confirmation and the use of diaries[220 221]. Investigators have demonstrated that one major limitation of subjective measurements is a lack of reliability due to overestimation of adherence[214 222 223]. In recent years, objective monitoring of CPAP adherence has been the standard of care[213]. CPAP adherence and efficacy data can now be downloaded via Wi-Fi or direct download of the device's

microprocessor[224]. Information such as CPAP on and off times, duration of usage, leaks and residual AHI is available to the provider on a day to day basis.

Adequate adherence is conventionally defined as an average usage of at least four hours per night for at least 70% of nights[213-216]. A prospective study reported a dose response in SDB symptoms and CPAP usage with at least four hours of CPAP usage being associated with improvement on the Epworth Sleepiness Scale[225]. Greater CPAP usage was associated with a larger proportion of participants returning to normal daily functioning[225]. For example, six hours of CPAP usage was associated with improvement in the Multiple Sleep Latency Test and 7.5 hours of CPAP usage was associated with improvements in the Functional Outcomes associated with Sleepiness Questionnaire[225]. Furthermore, even relatively low amounts of CPAP usage (i.e. <4h/night) have shown improvement in subjective sleepiness[226].

Oral appliances are an alternative for mild to moderate SDB treatment if CPAP cannot be used or tolerated[28 227]. Mandibular advancement is the most commonly prescribed oral appliance; however, tongue-retaining devices are also used. Both appliances have been found to decrease AHI, to a relatively smaller degree than CPAP, as well as reduce sleepiness[208].

In the few studies done on CPAP treatment in pregnancy, treatment of SDB with CPAP led to improved outcomes. Accumulating evidence reveals that maternal CPAP treatment is associated with a reduction in nocturnal maternal blood pressure[228 229]. CPAP treatment has also been shown to increase fetal movements (as a surrogate marker for fetal well-being and development)[230] and changes in vascular structure thereby improving cardiac output from the mother to the fetus[231]. As mentioned above, in the only study to date including pregnant women with SDB and GDM, CPAP treatment resulted in improved insulin secretion and sensitivity; however, the authors did not find any significant differences amongst other glucose indices[163].

This may be due to the considerable limitations of this study, as previously mentioned. In addition to possibly being underpowered, the investigators' use of subjective measurements which are insensitive to diagnosing SDB in pregnancy[164-166], low CPAP adherence of 3.4 hours of nightly usage on average in the CPAP group and the use of only one form of glucose testing were flaws of their study. Overall, the literature on CPAP in pregnancy is scarce and further studies are needed.

In our pilot RCT, we found it important to assess CPAP adherence in pregnancy as this is a unique population at risk for comorbidities. Additionally, this trial assists in determining feasibility when planning future, multi-center trials examining cardiometabolic outcomes. In pregnancy, we would hypothesize that participants would be more motivated to adhere to treatment than the general population given the potential benefits available to themselves and the fetus; however, this may be offset due to sleep fragmentation and other sleep-related disturbances which may hinder adherence to treatment.

Summary of Knowledge Gaps

Accumulating evidence suggests that GDM is increasing in prevalence and is associated with poor maternal-fetal outcomes. Although SDB is common in pregnancy, it is underrecognized[232] and it has not been studied whether women with GDM and untreated SDB have worse glucose control (Objective 1). Further to this, SDB in the general population is associated with changes in glucose profiles; however, it has not been well studied how SDB in pregnancy affects glucose variability in women with GDM (Objective 2). Finally, randomized controlled trials in CPAP treatment are lacking in pregnancy and little is known as to whether CPAP can improve glucose control. It is also unknown whether pregnant women exhibit adequate CPAP adherence before pursuing larger interventional studies (Objective 3).

Chapter 3: Methods

Study Population:

Adult pregnant women ≥ 18 years of age between 24- and 34- weeks gestational age with a diagnosis of GDM[160] were recruited from obstetric and endocrinology clinics at two recruitment sites in Montreal: McGill University Health Centre and Centre Hospitalier Universitaire Sainte-Justine. All participants provided informed consent and the Research Ethics Board at the two participating sites approved the study (ID 14-004-BMB; Appendix). Participants must have spoken either English or French in order to be eligible. Ethnicity was obtained through a participant-reported questionnaire.

Women were excluded if they had diabetes before pregnancy, multiple pregnancies, active alcohol consumption, cigarette smoking, chronic renal or cardiovascular disease, active psychiatric disorders or malignancy, HIV and/or Hepatitis B or C. Additionally, potential participants with an occupation involving shift work, frequent travel across time zones or inability to provide informed consent were ineligible. All participants had a level two home polysomnogram to screen for SDB. In this study, SDB was defined as AHI ≥ 10 based on Chicago scoring criteria[27 43]. There is an existing precedence in the literature showing the use of the Chicago scoring criteria in polysomnographic studies done in pregnancy[2 146 233]. This is useful in detecting subtle respiratory events common in pregnancy, such as hypopneas associated with microarousals and hypopneas without microarousals or desaturations (relative to apneas or frequent desaturations) which may be missed with the use of other criteria and home sleep studies as previously mentioned above and has been associated with adverse maternal and fetal outcomes[158]. In the present analysis, we include all participants who underwent a level two polysomnogram, irrespective of AHI score.

Sleep Measurements:

The level II polysomnogram was completed at home for one night (Titanium unit, Natus Inc., Mississauga, ON) within one week after the initial clinic visit with the treating endocrinologist. A trained sleep technologist installed the recording equipment and verified all signals in the participant's home. The equipment captured sleep-wake measurements, arousals and limb movements in accordance with the American Academy of Sleep Medicine (AASM) criteria[38]. Respiratory events were scored by a single scorer to eliminate interscorer variability and to ensure consistency using Chicago respiratory scoring criteria[27 43]. Specifically, apneas were defined as a complete cessation of airflow lasting at least 10 seconds in duration and hypopneas as >50% reduction in airflow with or without a >3% oxygen desaturation and/or arousal. Although all details of the protocol are outlined in this thesis, the protocol for our study has also been published[117].

Habitual sleep duration and sleep/wake times were assessed with the Pittsburgh Sleep Quality Index (PSQI)[234].

CGM Measurements:

At the initial study visit, participants underwent continuous 72-hour glucose monitoring using the iPro2® device (Medtronic, Northridge, CA)[181]. The device measured interstitial glucose levels every five minutes for 72-hours with a subcutaneous sensor. CGM has been validated in normoglycemic individuals[11], in adults with type 1 or type 2 diabetes[181] and has been shown to be safe and well-tolerated in pregnant women who had type 1 diabetes[13] or who were healthy during pregnancy[179]. Interstitial glucose levels have been found to be comparable to venous blood glucose measurements[181 182]. A sterile, single-use electrode sensor (Enlite, Medtronic MiniMed, Inc., Northridge, CA) was inserted into subcutaneous abdominal tissue by a trained research study nurse after the initial clinic visit with the endocrinologist. The glucose values were stored within the

device, were blinded to the participant and did not trigger any alarms. Participants were asked to maintain their usual diet and exercise patterns during the time of CGM monitoring.

The CGM glucose recordings were calibrated with capillary blood glucose measurements taken four times a day by the participant[235]. The CGM software compares the values from the interstitial glucose and capillary blood glucose measurements (recorded and entered into the software after download), which is represented by the mean absolute difference percentage (MAD%). The MAD% is calculated by subtracting the time-specific capillary blood glucose value from the CGM sensor value, then dividing by the capillary blood glucose value. As recommended by the manufacturer and by the literature[11], major deviations from the capillary blood glucose levels were defined by a MAD% $\geq$ 18. Days with two or fewer valid calibrations and/or with major deviations from capillary blood glucose were noted for subgroup analyses based on glucose data quality.

Other Measurements:

Participants completed capillary blood glucose measurements four times daily as part of standard of care using one of two glucose meters: Contour® Next (Bayer Inc., Toronto, ON) or OneTouch Zoom® Pro (LifeScan, Inc., Markham, ON). Participants were also instructed to keep a written log of capillary blood glucose measurements. Each participant had an assigned diabetes nurse who performed weight measurements in the diabetes clinic during clinic visits. Participants self-reported their pre-pregnancy and pregnancy weights, height, medication(s) and last menstrual period. Gestational age was confirmed by a first trimester dating ultrasound.

Cross-Sectional Study

Study Design:

This is a cross-sectional analysis of baseline data collected from a randomized-controlled trial (RCT)[117] investigating CPAP (experimental group) vs. a nasal dilator strip (control group) treatment of SDB in pregnant women with GDM. Although previously discussed at the beginning of this section, the RCT protocol has been previously published[117] and the trial has been registered on clinicaltrials.gov (NCT02245659).

Objective 1: Estimating the Association between AHI and Glucose Levels using CGM

Statistical Analysis:

Participant demographic data were analyzed by the entire cohort and between SDB severity groups (AHI<10, 10≤AHI<30, AHI≥30). Since Chicago Scoring Criteria was used for scoring respiratory events, we chose AHI < 10 as the cut off to represent no significant SDB because it most closely relates to the conventional AHI cut off of 5 as per AASM scoring[27].

The primary objective was to estimate whether SDB severity, represented by AHI, was associated with glucose levels in pregnant women with GDM. The primary analysis was based on a linear mixed model with random intercept which estimated the association between AHI and mean glucose levels during various time periods available from the proprietary software download (available data included mean nocturnal glucose at two time periods: 11pm-3am and 3am-6am, as well as mean 24-hour glucose). The software output provided Excel-exported data of approximately 250 measurements of interstitial glucose values over a 24-hour period per participant for a total of 72-hours. However, the time of day for these data points were not aligned across days or between participants. For example, for a specific participant, glucose measurements may have been taken at 10:20, 10:25. 10:30, etc. on Day 1, and at 10:22, 10:27, 10:32, etc. on Day

2. Thus, in order to simplify the data for the purposes of statistical analysis, mean glucose data obtained from the pre-defined nocturnal periods by the propriety CGM software was used. However, mean hourly glucose levels were also calculated and used in our analyses (to be discussed below). Mean daytime glucose levels were also extracted separately (8am to 9pm). We also examined whether other SDB severity variables of interest including REM-AHI, AHI in non-REM sleep (NREM AHI), microarousal index, ODI, and hypopnea and apnea-related arousals (respiratory arousal index) were associated with glucose levels during these time periods.

We adjusted for two confounders in the mixed models: BMI[6 8] at enrolment and insulin and/or metformin use. Since the use of insulin and/or metformin may indicate a greater severity of underlying diabetes, it was included in the final model since diabetes severity has been linked with SDB[236]. To assess whether the linearity assumption for regression was satisfied, we tested BMI for linearity using a plot of fitted value vs. residuals with our main outcome of interest, nocturnal glucose levels, which confirmed the presence of a linear relationship. All model values were reported as per 10 unit increase of the variable (i.e. per 10 unit increase in AHI, per 10 unit increase in ODI and per 10 unit increase in microarousal index, etc.).

Hourly glucose values were calculated by averaging all glucose values measured within that hour (i.e. 9am was an average of all values at 9:05, 9:10, 9:15 …9:55). Graphically, we displayed mean glucose (y-axis) by hour (x-axis), categorized by SDB severity measured by AHI (<10, 10-30, >30). We estimated the association between AHI or REM-AHI and mean glucose levels at each hour using a mixed linear model with mean hourly glucose as the outcome variable, AHI or REM-AHI as the exposure and with adjustment of covariates (BMI at enrolment and insulin/metformin use). We included a random intercept to account for clustering by participant. AHI and REM-AHI were continuous variables in this linear mixed model to maximize power.

In a subgroup analysis, we excluded data points with significant deviations in glucose levels between CGM and capillary blood glucose measurements. Two investigators (RN, SP) evaluated the data for insufficient calibration (2 valid calibrations or less) and MAD>18% while being blinded to the AHI values of the participants. Additionally, in our cohort, 20 participants were on insulin/metformin for glucose control compared to 48 participants who were not on antidiabetic medications. Most of the participants on medication where on long-acting nighttime insulin (n=11). Using this subset of participants who were not on insulin/metformin (n=48), we conducted a sensitivity analysis using the same linear mixed models to determine if the results were similar compared to using the entire subset (after adjusting for BMI).

Objective 2: Estimating the Association between AHI and Glucose Variability

The assessment of glucose variability was an extension of the cross-sectional study. Therefore, many of the methodological aspects previously mentioned for Objective 1 are applicable to Objective 2. We estimated glucose variability through MAGE and standard deviation of glucose. The data for the glucose variability analyses was provided by the software download for different time periods. MAGE considers an arithmetic mean of all absolute glucose excursions, above 1 standard deviation of the overall glucose measurements, observed in continuous blood glucose analysis or continuous interstitial glucose monitoring within a specified time period, usually of at least 24 hours[183 237 238].

Statistical Analysis for Objective 2:

A download of the software output per participant produced CGM measured glucose values across the 72-hours. These values were analyzed per participant with Marling's proposed method of MAGE calculation[239]. Glucose values were separated by calendar day (i.e. the participant's values for each 24-hour period (day one, day two and day three) were separated in the spreadsheet).

Following this, we created a graph of glucose (y-axis) by time (x-axis) in order to calculate the average of the differences between peak-to-nadir or nadir-to-peak excursions that exceeded one standard deviation for the respective day of that participant's glucose values[239]. The standard deviation of glucose was directly provided by the software download. The automatically generated report for each participant produced a 24-hour standard deviation of glucose, standard deviation of glucose from 11pm – 3 am and a standard deviation of glucose from 3 am – 6 am.

The primary aims were to calculate a single MAGE value that reflected an average of 72-hours of data for each participant, assess standard deviation of glucose and subsequently estimate whether SDB severity, represented by AHI, was associated with glucose variability. This analysis was based on linear regression modelling. We estimated the relationship between AHI and glucose variability represented by two metrics: MAGE and standard deviation of glucose. Although MAGE was manually calculated from the CGM output values, a download of the software output per participant yielded three standard deviation values: 1) a 24-hour standard deviation considering the full 72-hours of glucose data 2) a standard deviation for the 11pm – 3am nocturnal time period and 3) a standard deviation for the 3 am – 6 am time period. We also examined whether the other, aforementioned SDB variables of interest of objective one was associated with glucose variability with adjustment for BMI at enrolment and insulin and/or metformin use as confounders in the multiple regression models. All linearity assumptions were tested and satisfied, and all model values were reported as per 10 unit increase of the variable.

Objective 3: Estimating CPAP Adherence in Pregnant Women

Study Design:

This is an unblinded pilot-RCT investigating CPAP (experimental group) vs a nasal dilator strip (control group) treatment of SDB in pregnant women with GDM[117].

Study Population and Randomization:

Participants from the baseline data of the cross-sectional analyses in objectives one and two were considered for this RCT, if they had SDB (defined by AHI ≥ 10). Participants were screened for eligibility if they were adult pregnant women ≥ 18 years of age between 24- and 34- weeks gestational age with a diagnosis of GDM[160] prior to a first study visit. Screening questions that considered SDB symptoms of snoring, witnessed apneas and other SDB symptoms were not used in the selection process as such questionnaires may not accurately predict SDB due to poor sensitivity and specificity in pregnancy[164 240]. Recruitment occurred between March 2015 and November 2018 at the aforementioned sites in Montreal. Eligible participants were randomized by a web-based system that used permuted blocks of varying size (Dacima Software, Montreal, QC).

Treatment Interventions:

In the experimental group, participants with SDB randomized to the active intervention arm received auto-CPAP, which started no later than two weeks after the initial GDM clinic visit. The device was initially set at 4-20 cmH_2O and then adjusted by the study nurse in consultation with the study physician according to participant comfort and tolerability. The final device settings ranged from minimum pressure of 4-5cmH_2O and maximum pressure of 15-20cmH_2O. Three participants were transitioned to fixed CPAP with settings between 6-11cm H_2O. Participants received an initiation session with the study nurse which included device set up, mask fitting and preference and potential side effects. The study nurse also conducted check-ins with the participants every two weeks, or more often, by telephone. Participants were encouraged to use CPAP for the duration of pregnancy for as many hours during sleep as possible. CPAP adherence data was downloaded by LL and RN from the proprietary software (EncoreAnywhere™, Koninklijke Philips N.V., The Netherlands).

In the control group, participants with SDB randomized to receive the control treatment received nasal dilator strips (Breathe Right®, GlaxoSmithKline, Brentford, UK). Therefore, adherence in this group was monitored by counting leftover strips. Our study nurse also followed up on side effects and tolerability during each clinic visit.

Follow-up Visits and Outcome Assessments:

During the antenatal period, the GDM clinics routinely followed participants every 2-4 weeks from date of diagnosis until delivery. Participants received routine care from their healthcare team (i.e. endocrinologist, diabetes nurse, maternal-fetal-medicine specialist, etc.). If possible, participants were also seen by our study nurse during the same visit to verify and record CPAP adherence and assess sleep quality through patient-reported outcomes. To achieve this, our study nurse received participant-reported feedback on device acceptance, tolerability, adherence, difficulty and adverse events. This was done during each visit or during regularly scheduled phone calls initiated by the study nurse.

Statistical Analysis:

The objectives of this study were to objectively determine CPAP adherence among women with SDB and GDM and to consider feasibility of CPAP treatment in pregnancy. Descriptive statistics were used for baseline demographic data which was stratified by treatment allocation. Continuous variables were expressed as means plus or minus standard deviations. We objectively measured adherence through a download of the adherence software output per participant resulted in data of CPAP metrics which were analyzed for all participants randomized to CPAP with data. Adherence was measured continuously in hours and minutes which began from the day of installation until the day of, or the day before, delivery (i.e. all days in the Treatment Period).

To further assess feasibility, we calculated recruitment and retention rates as well as CPAP efficacy in our study. Recruitment rates were calculated as the number of participants randomized over the number of eligible participants and the number randomized at each site over the enrolment period[117]. Retention rates were calculated as the number of participants with all baseline and post-treatment data over the total amount of participants randomized to one of the treatment interventions.

Chapter 4: Results

Cross-Sectional Analysis

Study Participants:

Of 68 participants with GDM and evaluation for SDB, three were excluded (two without CGM data and one with major deviations in capillary vs. CGM measurements). Most participants were of European ethnic origin (40%; Table 1), 18% were of African origin, 18% were West Asian participants, 12% of participants were East Asian while ~12% belonged to other ethnicities. Data from the PSQI questionnaires showed that the mean bedtime of participants was ~10:30 pm while mean waking time was ~7:00am. On average, most participants were overweight or mildly obese based on their pre-pregnancy BMI. Increasing severity of SDB was associated with greater pre-pregnancy BMI, greater percentage use of medication and other characteristics (Table 1). Severity of SDB, however, was not associated with gestational weight gain.

Objective 1: Estimating the Association between AHI and Glucose Levels

Sixty-six percent of the study sample had an AHI>10 (Table 2). The majority of respiratory events were related with arousals rather than oxygen desaturation. The mean REM-AHI was almost 30 events/hour and was substantially greater than the NREM-AHI.

In models adjusted for BMI and diabetes medications, a 10 unit increase in AHI was associated with a statistically significant increase in glucose by 0.2 mmol/L between 11pm – 3am (Table 3). AHI was not associated with daytime nor 24-hour glucose levels (Table 4). REM-AHI was also associated with glucose levels during the nighttime period in the adjusted models. A ten unit increase in REM-AHI was associated with a 0.1 mmol/L increase in glucose between 11pm – 3am and a 0.07 mmol/L increase in glucose between 3am – 6am. Non-REM AHI, however, was not significantly associated with glucose levels during the day or night. The sensitivity analysis

estimating the association between AHI and REM-AHI on nocturnal glucose levels using the data from the subgroup of participants on antidiabetic medications produced similar beta coefficients in unadjusted and adjusted models (Table 5).

The total microarousal index and ODI were not statistically associated with glucose levels at either of the two nocturnal periods. The obstructive hypopnea and apneas associated with microarousals index was significantly associated with a 0.3 mmol/L increase in glucose levels in the unadjusted model between 11pm-3am, but was not significant in adjusted models. Between 3-6 am, a 10 unit increase in the respiratory arousal index was associated with a significant increase of 0.2 mmol/L glucose increase in adjusted models.

When adjusting for pre-pregnancy BMI instead of BMI at enrolment, the results remained similar to those presented above. Furthermore, the mean self-reported sleep and wake times were 10:27pm and 7:10am, respectively. Self-reported sleep duration was not associated with daytime or nighttime glucose levels. In a sensitivity analysis excluding 8 participants with MAD>18%, estimates were also similar. When adding gestational weight gain to the adjusted model with BMI at enrolment and insulin/metformin use, the associations of AHI and REM-AHI with glucose levels during the nocturnal time periods did not substantially differ.

Based on mean hourly 24-hour glucose profiles, glucose levels were greater during the nocturnal and early morning periods in women with AHI>30 when compared to women with AHI<10 (Figure 1). From the linear mixed model, AHI remained associated with nocturnal glucose levels at 11pm and 12am and in the early morning hours from 4am-8am (Figure 1, Table 6). The AHI was most strongly associated with increased glucose levels at 8 am (Figure 1). REM-AHI, on the other hand, was significantly associated with elevated hourly mean glucose levels from 11pm to 1am and 6am to 8am.

Objective 2: Estimating the Association between AHI and Glucose Variability

In both unadjusted models and in models adjusted for BMI and medications, a ten unit increase in AHI was not statistically associated with MAGE based on 24-hour glucose data (Table 7). Likewise, REM-AHI, NREM-AHI, microarousal index, ODI and respiratory arousal index were also not associated with MAGE.

When replacing MAGE with 24-hour standard deviation of glucose in the model, the results remained similar to those of MAGE (Table 7). Additionally, In the analysis of standard deviation of glucose from 11pm – 3am, the microarousal index was associated with standard deviation of glucose in both unadjusted and adjusted models. However, all other SDB variables were unassociated with standard deviation of glucose during this time period. Similarly, SDB variables were not associated with standard deviation of glucose from 3am – 6am in unadjusted and adjusted models.

Objective 3: Estimating CPAP Adherence in Pregnant Women

Study Participants:

Between March 2015 and November 2018, 1,634 participants were assessed for eligibility and 46 were randomized (23 randomized to CPAP; 23 randomized to nasal dilator strips, Figure 2). In our sample of 46 participants, all of whom were diagnosed with both SDB and GDM, one participant withdrew due to an early induced pregnancy and was unable to start the allocated treatment. The average age of the entire sample was 35.9 ± 4.4 years. Most participants self-identified as European descent (44%; Table 8). On average, most participants were overweight or mildly obese based on their pre-pregnancy BMI. Across the entire sample, participants exhibited moderate SDB; however, the control group had a slightly higher AHI, on average, than the experimental group at

randomization (Table 8). Although ODI was generally low overall (3.9 ± 5.5), the control group exhibited a slightly higher ODI, on average, compared to the experimental group (Table 8).

CPAP Treatment and Adherence

CPAP adherence was measured across all nights during the treatment period which was defined by CPAP start and stop date. The mean treatment duration was 37 ± 17 days. Based on the average adherence data across the treatment period, participants used CPAP 55% of the time for at least four hours per night. The mean usage was 3 hours and 48 minutes across all nights in the treatment period (Table 9). Using conventional criteria (>4h nightly usage for at least 70% of nights), only seven participants (32%) demonstrated adequate adherence. Over half of the participants reported complications while using CPAP (64%; Table 9) with five dropouts in the CPAP group due to sleeping and breathing difficulties, anxiety with device usage and intolerable side effects such as vomiting and acid reflux. The majority of complications were due to sleep difficulty with CPAP (n=7; Table 9), mask difficulty (n=3; Table 8) or some combination of two or more complications (n=3; Table 9).

In terms of CPAP efficacy, the average AHI in the CPAP group decreased from 19.4 ± 8.7 at baseline to 1.6 ± 1.4 after treatment (Table 9). Of 18 participants with residual AHI data, 17 participants (94%) had AHI<5 on CPAP while one participant had an AHI>5 (residual AHI of 5.2). On average, the time with large leaks per day was 3 minutes and 6 seconds (Table 9).

For the entire recruitment period, out of a full sample of 68 participants, the recruitment rate was 0.07 suggesting an average of one participant per centre per month. Out of the entire sample of 46 randomized participants, with 12 participants not completing the study (five dropouts from the CPAP group and seven from the control group), the retention rate was calculated to be 73.9.

Chapter 5: Discussion

Objective 1: Estimating the Association between AHI and Glucose Levels

In this novel study using CGM in pregnant women with SDB, we demonstrated that increasing severity of SDB in women with GDM was associated with higher levels of glucose during nighttime which persisted into the early morning periods. These associations remained significant even after adjusting for BMI and use of antidiabetic medications. In adjusted models, increasing AHI during REM sleep was also found to be associated with elevated nocturnal glucose levels, but AHI during NREM sleep was not. Neither AHI nor REM-AHI were associated with mean daytime (8am-9pm) or mean 24-hour glucose levels. To our knowledge, this is the first analysis characterizing the relationship between SDB severity and temporal glucose patterns in pregnancy.

Overall, the circadian system regulates 24-hour rhythms of behavioural and physiological processes in response to the environment, in particular, light[241]. The circadian system also influences and regulates glucose metabolism. An impaired circadian rhythm can lead to lower glucose tolerance including decreased insulin sensitivity, excess hepatic glucose production and decreased beta-cell function[241]. In normal, healthy participants who are not pregnant, the influence of the circadian rhythm on glucose metabolism reveals stable or a minimal decrease in glucose at night despite the overnight fast associated with sleeping[241 242].

The Dawn Phenomenon may also result in diurnal changes in glucose. The Dawn Phenomenon refers to a dynamic surge in glucose levels in the dawn period relative to stable nocturnal glucose[243]. This is often seen in persons with type 1 or 2 diabetes[244]. It is plausible that SDB may augment the Dawn Phenomenon due to abnormal secretion or sensitivity to nocturnal growth hormone or cortisol, however further study is required to further explore this hypothesis.

It is unlikely that the increases in nocturnal glucose levels in our cohort were driven by variations in sleep patterns or circadian rhythm disruption since the cohort as a whole had relatively stable bedtime and wake time (10:27pm, 7:10am; Table 1) and a sufficient amount of hours of sleep per night (7.4 hours; Table 1). Shift work also has the potential to offset circadian functioning and lead to an increased risk of developing type 2 diabetes[245-247]. In our study, participants engaging in shift work were excluded. Furthermore, as mentioned above, the self-reported sleep times and wake times of participants did not indicate substantial circadian rhythm disruptions.

Our findings are consistent with studies in non-pregnant participants. In one such study, SDB was associated with greater nighttime but not daytime glucose levels in type 2 diabetes[95]. In the MESA community-based study, moderate-severe SDB was also associated with elevated fasting glucose in adjusted models[248], suggesting a possible persistent effect from nighttime SDB disturbances. More recently, a CPAP withdrawal study resulting in re-emergence of SDB showed that respiratory events were dynamically associated with elevations in nocturnal glucose levels[59]. SDB has been associated with elevated sympathetic activity[70], cortisol levels[59] and systemic inflammation[249], all of which are thought to be potential mechanisms underlying SDB-associated glucose dysregulation. Elevated glucose levels at night have also been associated with clinical outcomes such as target organ damage in the form of atherosclerosis and increased brachial-ankle pulse wave velocity[250]. Interestingly, fasting glucose and Hemoglobin A1C were not associated with these outcomes[250]. Having higher nocturnal glucose may also contribute to greater glucose fluctuations (i.e. when compared to daytime), which in itself has been linked with oxidative stress activation[189] and cardiovascular mortality. Thus, there may be adverse cardiometabolic implications associated with nocturnal hyperglycemia. However, the above mechanisms and outcomes need further investigation in pregnancy and other populations.

In this study, we also showed that REM-AHI rather than NREM-AHI was associated with elevated nocturnal glucose levels between 11pm-3am, even after adjustment for BMI and diabetes medications. The association between AHI and nocturnal glucose was statistically significant between 11pm-3am; however, this association was not statistically significant between 3am-6am. This may have likely been due to a lack of power as the beta coefficients between the two nocturnal periods are similar (Table 3). Our results also remained similar in our sensitivity analysis using data from participants not on diabetes medication (Table 5). In a subgroup analysis of 22 participants with REM-only SDB (categorized by AHI>15, REM-AHI/NREM-AHI and NREM AHI <15), the association between AHI and glucose levels was between 3-6am, when REM sleep generally predominates. A ten unit increase in AHI was associated with a 0.6 mmol/L increase in glucose (95% CI 0.03, 1.2; p-value 0.04; not shown). This was consistent with the results of the mean hourly glucose analysis showing an association between severity of SDB and increasing glucose levels in the early morning hours (Figure 1, Table 6).

In studies with non-pregnant participants, REM-AHI has also been more strongly associated with hyperglycemia than NREM-AHI[94]. In type 2 diabetes, REM-AHI but not NREM-AHI, was also associated with increasing Hemoglobin A1C levels[39]. REM sleep is associated with greater sympathetic activity[55], longer duration of hypopneas and apneas and a greater number and severity of oxygen desaturation episodes when compared to NREM sleep[41]. Both the increase in event duration and the greater oxygen desaturation characteristic of REM-related SDB is likely to worsen glucose homeostasis[93 96]. Thus, our results demonstrate that SDB in REM sleep may also be quite relevant with respect to glucose dysregulation in pregnant women with GDM. Our results are consistent with the results of a recent case-control study that showed SDB is associated with newly diagnosed GDM[251]. The investigators found that women with SDB had a higher risk of

GDM (OR: 4.71 95% CI 1.05, 21.04). The authors also showed that REM-AHI was associated with an increased risk of GDM . The above-mentioned studies help to support our findings as we found significant associations with REM-AHI and glucose levels, but not NREM-AHI.

In our study, the microarousal index and the ODI were not associated with nocturnal glucose levels. However, the mean ODI in our cohort was very low (3 events/hr), consistent with other studies in pregnant women with SDB[2 8]. On the other hand, the respiratory arousal index (microarousal associated with hypopneas and apneas) was significantly associated with glucose levels from 11pm-3am in unadjusted analyses. In our sample, SDB mostly comprised of respiratory-related arousals. Our findings suggest that respiratory-related sleep fragmentation has a significant impact on nocturnal glucose control in GDM. Considering our results show that it is possible that arousals associated with respiratory events may play an important role in glucose dysregulation in pregnancy, particularly during the early morning hours when REM sleep predominates, further studies warrant investigations into the mechanistic pathways involved in this process.

We did not find any significant associations between SDB and mean daytime or mean 24-hour glucose levels. In a recent study in non-pregnant participants, glucose levels were elevated at night in relation to respiratory events in SDB, but the morning oral glucose tolerance test normalized after awakening in the morning[59]. Thus, it is possible that there is restoration of normal glucose homeostasis during the daytime or that pregnant women are able to compensate with increased insulin secretion during the day in the absence of respiratory events. Alternatively, the magnitude of increase in mean daytime glucose was small and we may have lacked power to detect statistical significance.

In our study, we observed that the AHI and REM-AHI were most strongly associated with glucose levels at 8 am. Since many women may have had breakfast by this time, this increase may also reflect an increase in postprandial glucose levels that are associated with increased severity of SDB. Of note, data from non-pregnant OSA patients suggests that increased SDB severity predisposes to greater postprandial glucose levels[93]. The lack of observed association between AHI and hourly glucose levels from 1am to 3am may be due to a lack of power caused by limiting the data set to hourly glucose levels, in addition to adjustment of the confounders (BMI and insulin/metformin). The beta coefficients and corresponding confidence intervals were very similar at 1-3am compared to the rest of the hourly glucose levels at night, suggesting that lack of power was likely (Table 4).

The strengths of our study include being the first to describe the relationship between SDB severity and glucose control over a 24-hour period in pregnancy. While the Hemoglobin A1C is the conventional measure of glycemic control in non-pregnant individuals, its utility in pregnancy is limited due to increased erythrocyte turnover and inability to detect short-term changes in glucose control[176]. In contrast to Hemoglobin A1C, CGM permits the detailed evaluation of changes in glucose over a short period of time, in addition to information on 24-hour glucose rhythms during normal daily activities. Furthermore, since even mildly elevated levels of maternal glucose (i.e. fasting glucose increases of 0.4 mmol/L)[153 159] are associated with birth and childhood complications, use of the Hemoglobin A1C alone may miss clinically important hyperglycemia. However, to our knowledge, no prior studies have used CGM in pregnant women with SDB to characterize glucose control. In this study, we also used complete polysomnography for accurate diagnosis and characterization of SDB severity, since in pregnancy, SDB is largely characterized by hypopneas associated with arousals[2 146], which are not captured on more simplified home, level

III sleep recordings[8]. We also had participants who did not have SDB (AHI <10) in our study population, thus enabling us to examine a range of SDB severity, including normals, in association with glucose.

Our study had some limitations. The sample size was relatively small and power was likely limited in adjusted hourly glucose analyses. Furthermore, nutritional factors and activity levels may have also affected glucose levels. However, since our main positive results occurred at nighttime, activity is less likely to be major contributing factor. Due to the observational nature of this study, we cannot conclude on the causal nature of the relationship between SDB and glucose levels. Finally, since the protocol did not involve polysomnogram being performed concurrently with CGM, we cannot conclude the sleep and wake times for the participants, and therefore cannot be certain that participants were actually sleeping during the nighttime periods of 11pm-3am and 3am-6am. Unmeasured sleep disruption and fragmentation unrelated to respiratory events may have also played a role.

Objective 2: Estimating the Association between AHI and Glucose Variability

To our knowledge, our study is one of the first studies to assess the association between SDB and glucose variability in pregnancy. We demonstrated that, with the exception of the microarousal index between 11pm – 3am, there were no statistically significant associations between glucose variability and SDB variables in pregnancy.

Although our finding of a significant association between the microarousal index and standard deviation of glucose from 11pm – 3am should be cautiously interpreted, it is consistent with other studies showing significant associations between the microarousal index and other glucose metrics in pregnancy. In a landmark study, the first using polysomnography to assess interactions between pregnancy, SDB and GDM, the authors showed that increased microarousal

indices in pregnancy was significantly associated with increased Hemoglobin A1C and fasting glucose levels after adjustment for pre-pregnancy BMI[252]. When focusing specifically on pregnant women with GDM, the authors showed evidence of more fragmented sleep based on a higher microarousal index in this group compared to normo-glycemic pregnant women[252].

The lack of significance in both the day and nocturnal glucose variability models may be in part due to glucose variability being more sensitive in identifying hypoglycemia rather than hyperglycemia as it is an adaptation of the hypoglycemia-driven M value, as previously mentioned. There are accumulating studies supporting the associations between hypoglycemia and glucose variability in non-pregnancy[253 254]. In fact, one study has shown that glucose variability is associated with an increased risk of overall and nocturnal hypoglycemia[255]. As our sample is entirely based off of hyperglycemia in pregnancy, there is a possibility that MAGE is not well-adjusted for considering significant hyperglycemia, which can be driven by both fasting and postprandial glycemia.

Additionally, our sample consisted of 20 participants who were on medication to control their diabetes with the remainder of participants being diet controlled. It is therefore plausible that we were unable to find significant associations between SDB and glucose variability due to insulin and/or metformin contributing to overall reduced glucose fluctuations. Studies done in participants with type 2 diabetes show that oral drugs used to manage diabetes is associated with significantly reduced glucose variability due to a minimization effect of acute hyperglycemia periods[256-258].

Our study was amongst the first to estimate the association between SDB and glucose variability. Limitations of the glucose variability data include the lack of consensus as to which metrics best represent glucose variability in clinical settings and lack of clear definitions for

calculating MAGE[184]. Additionally, it might be possible that useful glucose data might have been missed as MAGE requires excursions to be greater than 1 standard deviation[194].

Objective 3: Estimating CPAP Adherence in Pregnant Women

An important aspect of CPAP adherence is the method of measurement. Early studies examining CPAP adherence in non-pregnancy relied on subjective, participant-reported measures inclusive of verbal confirmation and the use of diaries[220 221]. However, such subjective measurements have been argued to be unreliable due to overestimation of adherence[214 222 223]. More commonly, adherence is defined objectively through the use of automated reports from the CPAP device microprocessor[224]. In one prospective study in non-pregnancy comparing the accuracy between subjective and objective reports, objectively measured adherence was lower (5 ± 0.3 hours/night) compared to participant-reported adherence (6.1 ± 0.3 hours/ night)[223]. This is consistent with a Korean-based study showing a discrepancy between subjective (34%) and objective (~21%) adherence rates[259].

Current conventional adherence is defined as >4h nightly usage for at least 70% of nights[213-216]. A few studies have highlighted relatively effective adherence rates ranging between 2.5 to 5 hours per night, depending on which outcome (e.g. sleepiness and respiratory disturbance) was being assessed[223 226 260]. Another important consideration is the dose-dependent relationship between SDB symptoms and CPAP usage which was investigated in a prospective study[225]. In this study, the authors treated participants with CPAP for three months to estimate the likelihood of obtaining normal levels of sleepiness and daily functioning based on hours of CPAP usage[225]. The results revealed that greater use of CPAP was associated with a higher number of participants returning to normal, daily functioning depending on the outcome being measured[225]. Improvement on the Epworth Sleepiness Scale required at least four hours of usage, while the Multiple Sleep

Latency Test required 6 hours and 7.5 hours of usage for improvement on the Functional Outcomes of Sleep Questionnaire[225]. The results demonstrate a dose-dependent effect of CPAP, where the threshold of CPAP usage needed to improve health outcomes is dependent on the measurement and outcome of interest[224 225]. A repeat polysomnography to assess efficacy of treatment was not performed on CPAP to minimize participant burden and drop-out rates. For the purposes of assessing efficacy, the data obtained from the CPAP device download was used, consistent with the current standard of practice (residual AHI<10 from CPAP accompanied by a low mask leak value)[213 261]. Download AHI from the CPAP device has not been compared to Chicago scoring criteria.

There are few studies on CPAP adherence in women. In one Montreal-based study assessing CPAP adherence in women with SDB (mean age 56 ± 10 years)[262], approximately half of the participants were adherent to CPAP (52% n=15)[262]. When considering our specific sample of pregnant women, it is unclear whether adequate adherence should be defined by 4 hours per night for 70% usage[213-216]. In the literature, a few small studies in pregnancy have reported objective CPAP adherence rates ranging from 5 to 7 hours[229 263 264]. However, primary data for these studies was not available. The small sample sizes of such studies, short treatment periods and the lack of detailed reporting of adherence over the entire period of use are limitations that our study has overcome. Possible reasons why adherence rates of our sample (3 hours and 48 minutes across all nights) were lower than other studies could be due to the added burden and stress that may have been associated with participants' management of their gestational diabetes.

Although studies have shown associations between SDB and the risk of GDM and other maternal complications[6-8], there are few studies that have assessed the therapeutic influence of CPAP treatment in pregnancy[228]. In one study of pregnant women with preeclampsia, one-night

CPAP use was associated with reduction in nocturnal blood pressure compared to a night without treatment[228]. Another study including pregnant women with pre-existing hypertension also showed reduction in maternal blood pressure in addition to higher infant Apgar scores compared to the control group[229]. Contrary to this, one study considering women with gestational hypertension found no significant improvements in blood pressure between the CPAP and mandibular appliance with nasal dilator strips group; however, this study only included one night in the lab[265].

In the first published study to investigate CPAP use in obese pregnant women with both SDB and GDM, two-week nightly CPAP use resulted in improved insulin secretion and sensitivity, but no significant differences in other glucose indices when compared to the wait-listed control group[163]. In this study, low adherence rates and a small sample size that may have left the authors underpowered to detect differences may partially explain the lack of improved glucose outcomes.

Studies investigating maternal CPAP usage in pregnancy have also shown improved fetal outcomes[230 231]. Maternal treatment of SDB with CPAP was associated with increased fetal movements, as a surrogate of fetal well-being[230], and improved cardiac output[231].

To our knowledge, our study is the first to report on detailed CPAP adherence data in pregnancy across an extended period (average of 37 days compared to two weeks in a previous study in women with GDM[163]). In our pilot study, pregnant women randomized to CPAP exhibited similar adherence rates (3 hours and 48 minutes across all nights) to the general population[213-216]. The retention rate of 74% in both treatment arms was similar, but slightly better compared to another study assessing SDB and GDM in pregnancy (69%)[163].

In the general population, there are a variety of factors that predict CPAP adherence. Predictors include treatment method (i.e. negative associations with CPAP such as side effects and stigma), lifestyle changes, familial support and physician support[266]. In one recent RCT including

participants with SDB, inclusive of women and underrepresented ethnic groups, the authors showed that the first week of use is a strong surrogate for overall adherence[267]. Given the increasing discomfort associated with pregnancy and specific sleeping positions, in addition to women typically being caregivers inclusive of caring for other children outside of the current pregnancy, there may be unique factors that influence adherence during this time in addition to the factors of the general population. Further analyses are needed to examine the determinants of adherence in pregnancy. This warrants further interventional studies to also consider unique strategies associated with increased adherence in this population such as familial support and educational interventions. Multiple reviews considering strategies to improve CPAP adherence in non-pregnancy suggest that psycho-educational strategies (e.g. written information, informational videos and motivational enhancement) and troubleshooting interventions (e.g. home visits, phone calls from healthcare providers) are highly useful in improving CPAP usage compared with usual care[218 268 269]. More recently, telemonitoring of CPAP adherence has become increasingly relevant showing associations to increased 90-day CPAP adherence[270]; however, the evidence regarding this has been inconsistent[271]. Participants in the CPAP group of our study were subjected to auto-CPAP and also received educational support from her study nurse. Interventional strategies in our sample, and in pregnant women using CPAP, may need to be further explored and tailored to best support their unique needs and address niche gaps.

The results of our pilot-RCT provides novel information regarding the feasibility and acceptance of CPAP treatment in women with SDB and GDM, in addition to the recruitment and retention rates which will be useful in planning larger RCTs in the future to further examine the impact of CPAP treatment in pregnant women with GDM and associated maternal-fetal outcomes. Our pilot-RCT had a small sample size. We also did not stratify our participants based on treatment

duration period (i.e. there were no adjustments made based on how long participants were undergoing treatment which would have been useful for estimating dose-dependent relationships and better accounting for CPAP acclimation). Due to the limited sample size and treatment duration range, it is likely that we would have lacked statistical power for such adjustments. Finally, side effects and intolerance associated with CPAP made it difficult for some participants (n=14) and no online transmission of data from some machines (n=2) resulted in incomplete for some participants. The required dose of CPAP to improve maternal-fetal outcomes is still unknown.

Chapter 6: Conclusion and Implications

While recent studies have identified that SDB during pregnancy is a risk factor for GDM with adjusted odds ratios of 1.9-3.5[6-8], it is unclear if SDB worsens glucose control. Our results indicate that increased severity of SDB is associated with worse glycemic control during the night and early morning in women with GDM. The HAPO study has demonstrated that even mild elevations in glucose that are still below the conventional threshold for a diagnosis of diabetes are harmful[10]. Our results suggest that SDB may be a commonly unrecognized risk factor for elevations in glucose at night and early in the morning. Long term prospective studies are needed to further determine whether such fluctuations in glucose are harmful for the pregnancy and health of the child. Since SDB is a reversible risk factor with the appropriate treatment, interventional studies will also be important in determining whether SDB treatment improves glucose control in GDM and whether this favourably impacts on maternal and fetal outcomes of pregnancy.

Although CPAP is considered the gold standard of treatment for SDB, it is unclear whether CPAP is an accepted and tolerable form of treatment in pregnancy. Our pilot-RCT provides insight into CPAP adherence in pregnant women with SDB and GDM which, may be similar to that of the general population, but still is relatively low overall. There are limited studies done on CPAP in pregnancy; however, CPAP has been shown to lead to a variety of positive maternal outcomes[163 228-231]. Overall, our results suggest that CPAP may be an acceptable and feasible method of SDB treatment; however, further studies are needed to thoroughly examine pregnancy-specific predictors of CPAP adherence. Given the side effects associated with CPAP use, it is also important to consider mitigation strategies that may aid in increasing adherence during pregnancy. An important future consideration for CPAP interventional trials in GDM will be to determine the

relationship between glucose levels and early morning periods of CPAP usage, when REM sleep is predominant.

In this thesis, we have successfully completed all three objectives. In the first study, our cross-sectional analysis, we showed that SDB severity is associated with greater nocturnal glucose levels, but not daytime or mean 24-hour glucose levels in pregnant women with GDM (Objective 1). We have also demonstrated that SDB severity is not statistically associated with greater glucose variability in GDM (Objective 2). Finally, in the second study, our pilot-RCT, we have shown that women with SDB and GDM exhibit similar adherence rates to that of the general population and that CPAP may be accepted in pregnancy (Objective 3). However, further interventional studies may be needed to determine optimal strategies to improve CPAP adherence in pregnancy. Secondly, CPAP studies are needed to determine whether treatment of SDB in GDM improves health outcomes for both the mother and baby.

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Table 1. Participant demographic characteristics based on SDB severity

	Entire Sample (n=65)	AHI < 10 (n=20)	10≤AHI<30 (n=35)	AHI ≥ 30 (n=10)
Age, years	35.4 ± 4.7	34.2 ± 5.0	35.6 ± 4.7	36.8 ± 3.4
Gestational Age at Recruitment, weeks	29.8 ± 3.6	30.4 ± 3.4	29.8 ± 3.6	29.0 ± 2.5
Caucasian	26 (40.0%)	6 (30.0%)	15 (43.0%)	5 (50.0%)
Coexisting Hypertension	6 (9.0%)	1 (5.0%)	4 (11.0%)	1 (10.0%)
BMI at enrolment, kg/m2	32.7 ± 6.9	29.7 ± 7.3	34.1 ± 6.2	33.6- ± 7.5
Pre-pregnancy BMI, kg/m2	29.2 ± 7.4	26.6 ± 8.5	31 ± 6.5	28.2 ± 6.9
Gestational weight gain, kg	9.3 ± 6.2	8.0 ± 5.6	8.8 ± 5.2	13.6 ± 9.4
Bedtime, hh:mm pm	10:27	10:41	10:14	10:48
Wake Time, hh:mm am	7:10	6:22	7:02	7:24
Sleep Duration, hours	7.4 ± 1.3	7.6 ± 0.9	7.3 ± 1.3	7.1 ± 1.9
Medications for Diabetes	20 (31.0%)	4 (20.0%)	12 (34.0%)	4 (40.0%)
Daytime Insulin	1 (5.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Nighttime Insulin	11 (55.0%)	2 (50.0%)	6 (50.0%)	3 (75.0%)
Both Daytime & Nighttime Insulin	5 (25.0%)	0 (0.0%)	4 (33.3%)	1 (25.0%)
Metformin	2 (10.0%)	1 (25.0%)	1 (8.3%)	0 (0.0%)
Both Insulin & Metformin	1 (5.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)

Values are means ± SD or numbers (%). BMI, body mass index

Table 2. Polysomnography characteristics of all study participants (n=65)

AHI, events/hour	16.2 ± 10.6
AHI ≥ 10, events/hour	43 (66.0%)
REM-AHI, events/hour	29.9 ± 19.0
NREM-AHI, events/hour	12.9 ± 9.7
ODI, events/hour	3.0 ± 4.9
Obstructive hypopnea and apneas associated with microarousals - index, events/hour	10.0 ± 3.0
Microarousal index, events/hour	27.5 ± 9.4
Total Sleep Time, hours	6.6 ± 1.2

Values are means ± SD or numbers (%). AHI: apnea-hypopnea index;
REM-AHI: rapid eye movement apnea-hypopnea index, NREM-AHI: non-REM AHI; ODI: oxygen desaturation index.

Table 3: Beta coefficients in unadjusted and adjusted linear mixed models in the relationship between SDB variables and glucose across the nighttime periods of 11pm-3am and 3am-6am.

Mean Glucose Levels from 11pm-3am (95% CI)			
	Unadjusted	Adjusted for BMI	Adjusted for BMI and insulin/metformin use
AHI	0.23 (0.08, 0.4)	0.19 (0.03, 0.4)	0.2 (0.04, 0.4)
REM-AHI	0.12 (0.02, 0.2)	0.1 (0.03, 0.2)	0.1 (0.04, 0.2)
NREM-AHI	0.16 (-0.01, 0.4)	0.1 (-0.02, 0.3)	0.16 (-0.02, 0.3)
Microarousal index	0.1 (-0.08, 0.3)	0.09 (-0.1, 0.3)	0.09 (-0.09, 0.3)
ODI	0.3 (-0.07, 0.6)	0.2 (-0.2, 0.5)	0.2 (-0.2, 0.5)
Obstructive hypopnea and apneas associated with microarousals - index,	0.3 (0.06, 0.5)	0.3 (0.02, 0.5)	0.3 (-0.03, 0.5)

Mean Glucose Levels from 3am-6am (95% CI)			
	Unadjusted	Adjusted for BMI	Adjusted for BMI and insulin/metformin use
AHI	0.17 (0.02, 0.3)	0.13 (-0.03, 0.3)	0.14 (-0.02, 0.3)
REM-AHI	0.06 (-0.03, 0.2)	0.07 (-0.02, 0.2)	0.07 (-0.03, 0.2)
NREM-AHI	0.1 (-0.06, 0.3)	0.09 (-0.08, 0.3)	0.1 (-0.07, 0.3)
Microarousal index	0.04 (-0.1, 0.2)	0.03 (-0.1, 0.2)	0.03 (-0.1, 0.2)
ODI	0.3 (-0.07, 0.6)	0.20 (-0.2, 0.5)	0.2 (-0.2, 0.5)
Obstructive hypopnea and apneas associated with microarousals - index,	0.2 (-0.03, 0.5)	0.2 (-0.08, 0.4)	0.2 (-0.08, 0.4)

AHI, apnea-hypopnea index. REM-AHI, rapid eye movement apnea-hypopnea index. ODI, oxygen desaturation index. All SDB variables are per unit 10 increase. The beta of each variable represents an increase in glucose in units of mmol/L.

Table 4: Beta coefficients in unadjusted models in the relationship between SDB variables and daytime glucose and mean 24-hour glucose periods.

Mean Daytime Glucose Levels (95% CI)	
	Unadjusted
AHI	0.08 (-0.06, 0.23)
REM-AHI	0.05 (-0.04, 0.14)
NREM-AHI	0.04 (-0.11, 0.18)
Microarousal index	0.01 (-0.15, 0.18)
ODI	0.16 (-0.15, 0.47)
Respiratory arousal index	0.13 (-0.10, 0.36)

Mean 24-Hour Glucose Levels (95% CI)	
	Unadjusted
AHI	0.05 (-0.10, 0.21)
REM-AHI	-0.01 (-0.11, 0.08)
NREM-AHI	0.10 (-0.06, 0.27)
Microarousal index	0.13 (-0.04, 0.30)
ODI	0.04 (-0.29, 0.37)
Respiratory arousal index	0.09 (-0.15, 0.34)

AHI, apnea-hypopnea index. REM-AHI, rapid eye movement apnea-hypopnea index. ODI, oxygen desaturation index, Respiratory arousal index, obstructive hypopnea and apneas associated with microarousals - index. All SDB variables are per unit 10 increase. The beta of each variable represents a change in glucose in units of mmol/L.

Table 5: Beta coefficients in unadjusted and adjusted linear mixed models in the relationship between AHI and REM AHI and glucose across the nighttime periods of 11pm-3am and 3am-6am using the data from participants not on diabetes medication.

Mean Glucose Levels from 11pm-3am (95% CI)		
	Unadjusted	Adjusted for BMI
AHI	0.22 (0.08, 0.40)	0.15 (-0.04, 0.35)
REM-AHI	0.13 (0.01, 0.26)	0.1 (-0.03, 0.23)

Mean Glucose Levels from 3am-6am (95% CI)		
	Unadjusted	Adjusted for BMI
AHI	0.15 (0.02, 0.30)	0.07 (-0.13, 0.27)
REM-AHI	0.07 (-0.06, 0.20)	0.04 (-0.09, 0.16)

AHI, apnea-hypopnea index. REM-AHI, rapid eye movement apnea-hypopnea index. All SDB variables are per unit 10 increase. The beta of each variable represents a change in glucose in units of mmol/L.

Table 6: Association between AHI and REM-AHI with hourly glucose values from 11pm until 8am.

	AHI	**REM-AHI**
Time	**β (95% CI)**	**β (95% CI)**
11pm	0.17 (-0.01, 0.33)	0.11 (0.01, 0.2)
12am	0.18 (0.01, 0.35)	0.11 (0.01, 0.22)
1am	0.16 (-0.01, 0.33)	0.12 (0.02, 0.23)
2am	0.12 (-0.05, 0.29)	0.08 (-0.02, 0.19)
3am	0.12 (-0.05, 0.29)	0.03 (-0.07, 0.14)
4am	0.12 (-0.05, 0.33)	0.04 (-0.06, 0.14)
5am	0.2 (0.03, 0.37)	0.07 (-0.03, 0.18)
6am	0.2 (0.03, 0.37)	0.12 (0.02, 0.22)
7am	0.19 (0.02, 0.36)	0.14 (0.03, 0.24)
8am	0.28 (0.11, 0.45)	0.15 (0.05, 0.26)

Beta coefficients and 95% confidence intervals are unadjusted and reported for AHI per 10 and REM-AHI per 10. The beta of each variable represents a change in glucose in units of mmol/L.

Table 7: Beta coefficients in unadjusted and adjusted regression models in the relationship between SDB variables and glucose variability

Mean Amplitude of Glucose Excursion (95% CI)			
	Unadjusted	Adjusted for BMI	Adjusted for BMI and insulin/metformin use
AHI	-0.14 (-0.29, 0.26)	-0.05 (-0.34, 0.25)	-0.07 (-0.36, 0.21)
REM-AHI	-0.03 (-0.19, 0.14)	-0.07 (-0.25, 0.11)	-0.08 (-0.25, 0.10)
NREM-AHI	0.05 (-0.25, 0.35)	0.03 (-0.31, 0.36)	-0.03 (-0.36, 0.29)
Microarousal index	0 (-0.30, 0.32)	-0.02 (-0.34, 0.30)	-0.04 (-0.35, 0.26)
ODI	0.04 (-0.55, 0.64)	0.04 (-0.59, 0.68)	-0.07 (-0.68, 0.55)
Respiratory arousal index	-0.04 (-0.48, 0.40)	-0.10 (-0.56, 0.37)	-0.14 (-0.59, 0.30)

Standard Deviation of Glucose from 11pm-3am (95% CI)			
	Unadjusted	Adjusted for BMI	Adjusted for BMI and insulin/metformin use
AHI	-0.06 (-0.16, 0.05)	-0.06 (-0.17, 0.06)	-0.06 (-0.18, 0.08)
REM-AHI	-0.05 (-0.12, 0.01)	-0.05 (-0.13, 0.02)	-0.06 (-0.13, 0.01)
NREM-AHI	-0.05 (-0.17, 0.07)	0 (-0.17, 0.09)	-0.05 (-0.18, 0.07)
Microarousal index	-0.14 (-0.26, -0.03)	-0.15 (-0.27, 0.03)	-0.15 (-0.27, -0.03)
ODI	-0.08 (-0.31, 0.15)	-0.06 (-0.31, 0.18)	-0.09 (-0.34, 0.15)
Respiratory arousal index	-0.04 (-0.18, 0.1)	0.04 (-0.19, 0.11)	-0.05 (-0.2, 0.1)

Standard Deviation of Glucose from 3am-6am (95% CI)			
	Unadjusted	Adjusted for BMI	Adjusted for BMI and insulin/metformin use
AHI	-0.03 (-0.15, 0.08)	-0.03 (-0.15, 0.09)	-0.04 (-0.16, 0.08)
REM-AHI	-0.07 (-0.13, 0)	-0.07 (-0.14, 0)	-0.07 (-0.14, 0)
NREM-AHI	0 (-0.13, 0.12)	0.01 (-0.13, 0.15)	-0.01 (-0.15, 0.12)
Microarousal index	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.08)	-0.06 (-0.19, 0.06)
ODI	-0.14 (-0.38, 0.1)	-0.15 (-0.41, 0.11)	-0.19 (-0.45, 0.06)
Respiratory arousal index	-0.06 (-0.24, 0.12)	-0.05 (-0.24, 0.14)	-0.07 (-0.26, 0.12)

AHI, apnea-hypopnea index. REM-AHI, rapid eye movement apnea-hypopnea index. ODI, oxygen desaturation index, Respiratory arousal index, obstructive hypopnea and apneas associated with microarousals - index. All SDB variables are per unit 10 increase. The beta of each variable represents a change in the standard deviation of glucose.

Table 8. Participant demographic characteristics based on RCT treatment allocation

	Entire Sample (n=45)	Control Group (Nasal Strip) (n=23)	Experimental Group (CPAP) (n=22)
Age, years	35.9 ± 4.4	35.5 ± 4.0	36.3 ± 4.8
Gestational Age at Recruitment, weeks	29.3 ± 3.9	28.7 ± 4.6	30.0 ± 2.9
Caucasian	20 (44.4%)	12 (52.2%)	8 (36.4%)
BMI at enrolment, kg/m2	34.4 ± 7.2	34.0 ± 7.8	34.8 ± 6.7
Pre-pregnancy BMI, kg/m2	29.9 ± 7.7	30.6 ± 6.4	29.2 ± 9.0
AHI, events/hour	20.2 ± 9.6	21.1 ± 10.5	19.4 ± 8.7
ODI, events/hour	3.9 ± 5.5	5.2 ± 6.8	2.5 ± 3.2

Values are means ± SD or numbers (%). BMI, body mass index

Table 9. CPAP metrics of participants randomized to CPAP (n=22)

AHI residual	1.6 ± 1.4
Mean percent of nights used ≥ 4 hours/night (%)	55.4%
Mean usage for all nights in the treatment period	3 hours 48 minutes
Mean usage when CPAP was used	4 hours 24 minutes
Mean time with large leaks per day	3 minutes 6 seconds
Adequate adherence (n(%))	7 (31.8%)
Experiencing complications (n(%)) **Sleep difficulty** **Mask difficulty (i.e. adjustments, device connection)** **Breathing difficulty** **Combination of ≥ 2 complications**	14 (63.6%) 7 (31.8%) 3 (13.6%) 1 (4.50%) 3 (13.6%)

Adequate adherence is defined as at least four hours of usage for at least 70% of all nights

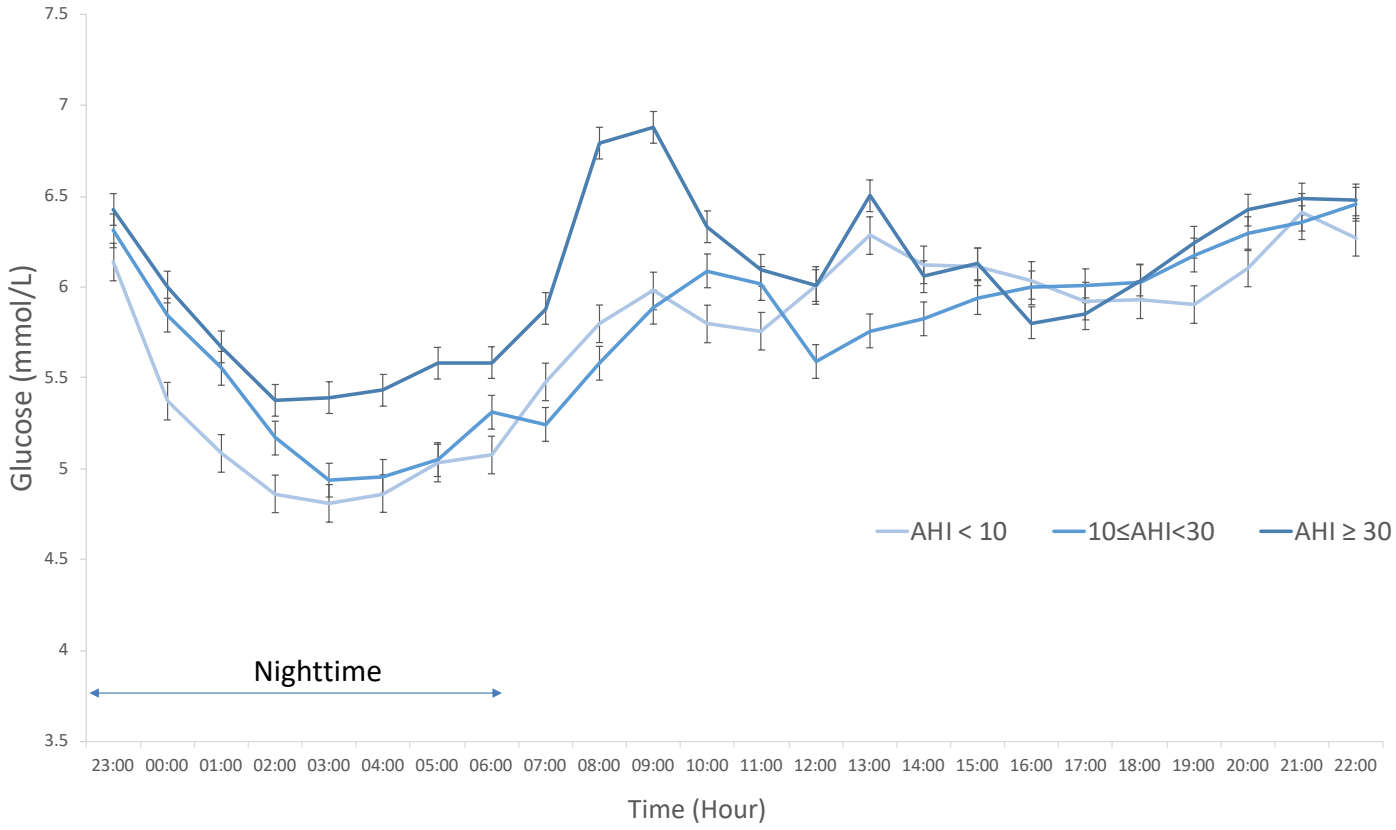

Figure 1. Mean hourly 24-hour glucose profiles in relation to category of SDB severity (AHI<10, 10≤AHI<30, AHI≥30). Standard error bars are shown.

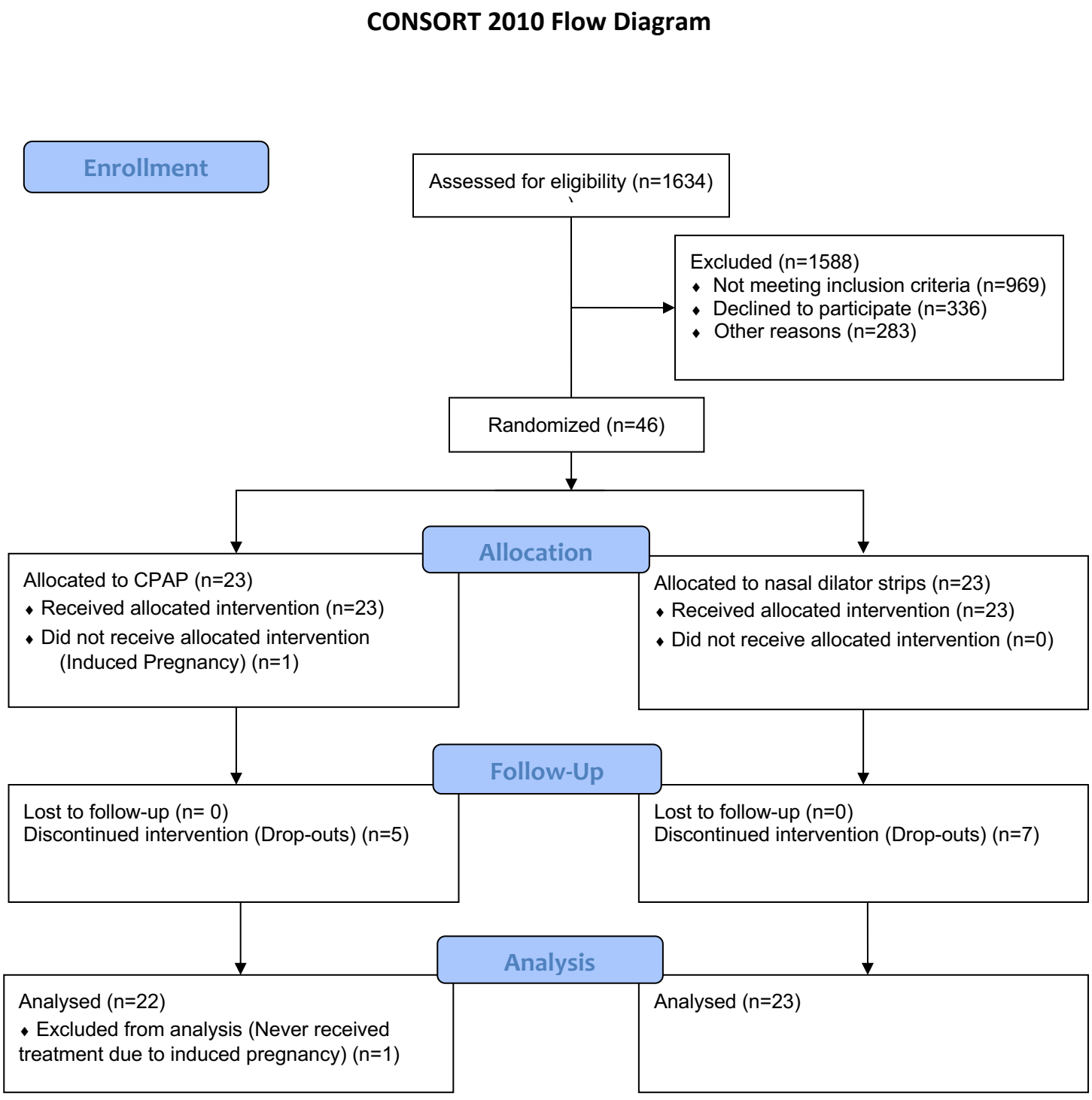

Figure 2. Detailed CONSORT flow diagram for pilot-RCT investigating CPAP (intervention) vs. nasal dilator strips in women with SDB and GDM

APPENDIX: RESEARCH ETHICS BOARD APPROVAL

Centre universitaire de santé McGill | McGill University Health Centre

Annual renewal submission

Submit date: **2019-04-16 11:09**

Submitted by: **Tremblay, Genevieve**

Project's REB approbation date: **2014-05-02**

Nagano identifier: **14-004-BMB**

Project number: **2015-1845, 14-004-BMB, eReviews_3405, MP-CUSM-14-004-T.pdf**

Form: **F9 - 42172**

Form status: **Approved**

Administration

1. **MUHC REB Panel & Co-chair(s):**
   Clinical Trials 2 (CT2)
   Co-chairs: Bertrand Lebouché,Thomas Maniatis, Sonya Page

2. **REB Decision:**
   Approved - REB delegated review

3. **Renewal Period Granted:**
   from 2019-05-12 until 2020-05-11

4. **Date of the REB final decision & signature**
   2019-04-26
   Signature

   Sheldon Levy
   MUHC REB Coordinator
   for MUHC REB Co-chair mentioned above

5. FWA 00000840 - FWA 00004545

A. General information

1. **Indicate the full title of the research study**

The Effect of Continuous Positive Airway Pressure (CPAP) Treatment on Glycemic Control in Gestational Diabetes: A Pilot Randomized-Controlled Trial

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2. **If relevant, indicate the full study title in French**

L'effet du traitement par ventilation en pression positive continue (CPAP) sur le contrôle glycémique du diabète gestationnel : Étude pilote avec répartition aléatoire.

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3. **Indicate the name of the Principal Investigator in our institution (MUHC)**

Pamidi, Sushmita

From which department is the principal investigator?

Medicine

Division

Respiratory Medicine

---

4. **Are there local co-investigators & collaborators involved in this project?**

Yes

List all the local co-investigators & collaborators involved in the research study

Kimoff, John

Department of co-investigators & collaborators

Medicine

Division

Respiratory Medicine

Meltzer, Sara J.

Department of co-investigators & collaborators

Medicine

Division

Endocrinology

Dasgupta, Kaberi

Department of co-investigators & collaborators

Medicine

Division

Endocrinology

GAGNON, ROBERT

Department of co-investigators & collaborators

Obstetrics/Gynaecology

Division

Obstetrics

5. **For each participating centre part of the Québec health and social services network (RSSS), indicate the name of the external investigator**

Dr. Rey

What is the name of the participating center(s)?

CHU-SJ

6. **Indicate the name and the affiliation of the external collaborator(s),(if any)**

none

B. Project development

1. **Study start date:**

2014-05-02

2. **Expected ending date of the study:**

- ☐ Determined date
- ☑ Undetermined date

3. **Date of recruitment of the first participant?**

- ☑ 1st enrollment date is...
- ☐ No participant enrolled

1st participant enrollment date:

2015-03-12

4. **Indicate the current study status at MUHC.**

Study in progress and closed to recruitment.

Give specifcs

Closed to recruitment but participants are in long -term follow-up

5. **Add a brief statement on the study status**

Recruitement is closed. Long term follow-ups are in progress as well as data analysis.

6. **Information about the participants at this institution, since the beginning of the project**

Number of participants to be recruited according to protocol

60

Number of participants who have been recruited

45

Number of minors

0

Number of incompetent adults

0

Number of participants who have not yet completed the study (still in progress)

0

Number of participants who've completed the study

40

Number of participants who were recruited to the study, but who were then excluded or withdrawn:

3

Indicate the reasons the participants were withdrawn

GDM17 - to be induced in one week; no time to start treatment GDM52 - Premature labor, bed rest; limited time for treatment GDM46 - Labor started; limited time for treatment

Number of participants who dropped out (voluntary withdrawal):

2

Please indicate the reasons for the participant(s) withdrawing from the study

GDM57 - Did not wish to continue in the study GDM49 - did not want to continue CPAP after getting sick

Number of participants who died during the study

0

7. **Information about the participants at this institution (MUHC) since the previous REB approval**

Number of participants who have been recruited

10

Number of minors

0

Number of incompetent adults

0

Number of participants who have not yet completed the study (still in progress)

0

Number of participants who've completed the study

9

Number of participants who dropped out (voluntary withdrawal):

1

Please indicate the reasons the participant(s) stopped

GDM57 - Did not wish to continue in the study

Number of participants who died during the study

0

8. **Since the previous REB approval (annual renewal or initial approval):**

Were there any changes to the protocol (or to the databank management framework) ?

No

Specify the current version/date:

2018-06-07

Date approved by the REB:

2018-06-22

Were there any changes to the information and consent form?

No

Specify the current version/date:

2018-05-08

REB approval date:

2018-06-22

Were there any reportable adverse events at this site (or, for multi-center projects, at an institution under the jurisdiction of our REB) that should be reported to the REB under section 5.2.1 of " SOP- REB- 404001 " ?

https://muhc.ca/cae/page/standard-operating-procedures-sops

No

Has there has been any new information likely to affect the ethics of the project or influence the decision of a participant as to their continued participation in the project ?

No

Were there any deviations / major violations protocol (life -threatening or not meeting the inclusion / exclusion criteria)?

No

Was there a temporary interruption of the project?

No

Have the project results been submitted for publication, presented or published?

No

Has the REB been notified of a conflict of interest - (apparent , potential or actual), of one or more members of the research team - that was not known when it was last approved project?

No

Do you want to bring any other info to the REB's attention?

No

9. **For all external participating institutions, please answer the following questions:**

Please select the name of the institution concerned and attach the "Formulaire de renouvellement annuel pour les projets sites externes - Projets multicentriques":

CHU-SJ

Please print a copy of the "Formulaire de renouvellement annuel pour les sites externes" (see link below), have it completed by other institutions and attach it here.

Formulaire de renouvellement pour les sites externes (MP project)

This form is accessible to external researchers, via our web page.

Renouvellement annuel sites externes_CHUSJ_Signé_Avril2019.pdf

Is there any institution's info (pdf form) missing?

No

10. **Is there a data safety monitoring committee analyzing data on the safety and efficacy of the treatment?**

No

C. Signature

1. **I confirm that all information is complete & accurate.**

First & last name of person who completed the submission

Genevieve Tremblay