Sleep-disordered breathing in pregnancy: implications for maternal and child health

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TABLE OF CONTENTS

Abstract

Rationale: Sleep-disordered breathing (SDB), as it pertains to upper airway obstruction, is characterized by recurrent respiratory pauses during sleep, with associated increased upper airway resistance or pharyngeal collapsibility resulting in snoring and/or increased respiratory effort. SDB in pregnancy is associated with an increased risk for gestational hypertension and preeclampsia, as well as a 2-3 fold increased risk for gestational diabetes (GDM). Although there are a number of observational studies confirming these associations, interventional studies in SDB and pregnancy are generally lacking. A few, smaller studies have shown improvements in blood pressure using continuous positive airway pressure (CPAP). Although SDB is very common in GDM, it is unknown whether CPAP treatment improves glucose control in pregnancy. However, prior to embarking on larger trials, it is unknown whether pregnant individuals adhere to CPAP, the standard first-line treatment of SDB. Finally, night-to-night adherence to SDB treatment with either CPAP or mandibular advancement splints (MAS), an alternative treatment to CPAP, in pregnancy has not been well characterized.

Objectives: The first objective of this thesis was to determine whether pregnant individuals with GDM and SDB adhere to CPAP and to determine whether CPAP improves 24-hour glucose profiles using continuous glucose monitoring (CGM) vs. control in a pilot randomized-controlled trial design. The second objective was to further characterize adherence in pregnancy by evaluating objective, longitudinal night-to-night adherence patterns in different treatment cohorts using CPAP and MAS.

Methods: Project 1 was a pilot randomized-controlled trial in which pregnant individuals with GDM and SDB were randomized 1:1 to either CPAP or nasal dilator strips (control). CPAP

adherence data was downloaded at every bi-weekly study visit via the memory chip or by Wi-Fi. Seventy-two hours of CGM was performed with glucose measurements taken every 5 minutes (~60,000 values) at baseline and ~4 weeks after treatment. Differences in glucose levels at various time points were analyzed using a Generalized Estimating Equations approach and multiple imputation. For Project 2, which involved night-to-night adherence analysis, three separate pregnancy cohorts evaluating treatment for SDB in the second and third trimester were used: 1) CPAP in GDM, 2) CPAP in hypertensive disorders of pregnancy (HDP), and 3) use of an alternative treatment, MAS. The first 30 days of objective adherence data obtained from CPAP and MAS devices were used in this descriptive analysis.

Results: Forty-five individuals with GDM and SDB (mean±SD age of 36.0±4.3, pre-pregnancy body mass index 29.8±7.8 kg/m^2) were randomized to either CPAP (n=22) or control (n=23). Thirty-four (n=16 CPAP, n=18 control) participants had CGM measurements at follow-up. The mean CPAP adherence was 3.0±2.3 hours/night (intention-to-treat). A complete case analysis revealed that differences in glucose levels (post-pre) were significantly lower during the early morning sleep period (3am: -0.67 mmol/L [95% CI, -1.28 to -0.06], 4am: -0.86 mmol/L [95% CI, -1.43 to -0.28], 5am: -0.74 mmol/L [95% CI, -1.37 to -0.11] and 6am: -0.79 mmol/L [95% CI, -1.42 to -0.17]) and at noon (-0.75 mmol/L [95% CI, -1.36 to -0.15]) in the CPAP vs. control group ($p<0.05$).

For Project 2, data from 36 CPAP users and 14 MAS users was analyzed. For the GDM and HDP cohorts, three patterns of adherence were observed: 1) consistent CPAP users (38%), 2) improved CPAP usage after initial adaptation (16%), and 3) inconsistent CPAP users (46%). For the MAS cohort, the three observed patterns of adherence were: 1) consistent MAS users

(47%), 2) initial usage with subsequent decrease in adherence (20%), and 3) inconsistent MAS users (33%). Participant characteristics (demographics, disease severity) were similar between adherence groups.

Conclusions: CPAP (vs. control) reduced early morning (3-6 am) and 12pm glucose levels in pregnant individuals with GDM and SDB, thus reducing fetal exposure to maternal glucose, despite overall modest adherence. Overall, objective night-to-night adherence patterns revealed that almost half of CPAP and MAS users had difficulty adapting to treatment in the first 30 days of treatment. Further research is needed to develop strategies that are shown to improve adherence to treatment of SDB in pregnancy.

Résumé

Problématique : Les troubles respiratoires du sommeil (TRS), en ce qui concerne l'obstruction des voies respiratoires supérieures, se caractérisent par des pauses respiratoires récurrentes pendant le sommeil, associées à une résistance accrue des voies aériennes supérieures ou à une pliabilité du pharynx entraînant des ronflements et/ou un effort respiratoire accru. Les TRS pendant la grossesse sont associés à un risque accru d'hypertension gestationnelle et de prééclampsie, ainsi qu'à un risque de 2 à 3 fois plus élevé de diabète gestationnel (DG). Bien que de nombreuses études observationnelles confirment ces associations, les études interventionnelles sur les TRS et la grossesse sont généralement insuffisantes. Quelques petites études ont montré des améliorations de la pression artérielle grâce à l'utilisation de la pression positive continue (PPC). Bien que les TRS soient très fréquents chez les femmes enceintes atteintes de DG, on ne sait pas si le traitement par PPC améliore le contrôle de la glycémie pendant la grossesse. Cependant, avant de lancer des essais plus vastes, il est nécessaire de savoir si les femmes enceintes adhèrent à la PPC, le traitement de première ligne standard des TRS. Enfin, l'adhésion nuit après nuit au traitement des TRS, soit par la PPC, soit par des orthèses d'avancement mandibulaire (OAM), une alternative à la PPC, n'a pas été bien caractérisée pendant la grossesse.

Objectifs : Le premier objectif de cette thèse fut de déterminer si les personnes enceintes atteintes de DG et de TRS adhèrent au traitement par PPC et de déterminer si celui-ci améliore les profils glycémiques sur 24 heures en utilisant la surveillance glycémique en continu (SGC) par rapport à un groupe témoin, dans le cadre d'un essai pilote contrôlé randomisé. Le deuxième objectif fut de caractériser davantage l’adhérence pendant la grossesse en évaluant

objectivement et longitudinalement les profils d'adhérence nocturne, nuit après nuit, dans différents groupes de traitement utilisant la PPC et l'OAM.

Méthodes : Le projet 1 était un essai pilote randomisé contrôlé dans lequel des femmes enceintes atteintes de DG et de TRS ont été réparties de manière aléatoire (1:1) pour recevoir soit une PPC (pression positive continue) soit des bandes dilatatrices nasales (groupe témoin). Les données d'adhérence à la PPC ont été téléchargées lors de chaque visite d'étude bihebdomadaire via la puce mémoire ou par Wi-Fi. Une surveillance de glucose en continu (SGC) sur 72 heures a été effectuée, avec des mesures prises toutes les 5 minutes (~60 000 valeurs), au départ et environ 4 semaines après le début du traitement. Les différences de glycémie à différents moments de la journée ont été analysées en utilisant l'approche des *Generalized estimating equations* et l'imputation multiple. Pour le Projet 2, qui impliquait l'analyse de l'adhérence nuit après nuit, trois cohortes distinctes de femmes enceintes évaluant le traitement des TRS au deuxième et au troisième trimestre ont été utilisées : 1) PPC dans le DG, 2) PPC dans les troubles hypertensifs de la grossesse (THG) et 3) utilisation d'un traitement alternatif, les OAM. Les 30 premiers jours de données d'adhérence objective obtenues à partir des appareils PPC et OAM ont été utilisés dans cette analyse descriptive.

Résultats : Quarante-cinq femmes enceintes atteintes de DG et de TRS (âge moyen ± écart-type de 36,0 ± 4,3 ans, indice de masse corporelle pré-gestationnel de 29,8 ± 7,8 kg/m^2) ont été réparties de manière aléatoire dans un groupe PPC (n = 22) ou dans un groupe témoin (n = 23). Trente-quatre participantes (n = 16 PPC, n = 18 témoins) ont eu des mesures SGC au suivi. L'adhérence moyenne à la PPC était de 3,0 ± 2,3 heures/nuit (intention de traiter). Une analyse de cas complet a démontré que les baisses des taux de glycémie (post-pré) étaient

significativement plus importantes pendant la période de sommeil en début de matinée (3h : -0,67 mmol/L [IC à 95 %, -1,28 à -0,06], 4h : -0,86 mmol/L [IC à 95 %, -1,43 à -0,28], 5h : -0,74 mmol/L [IC à 95 %, -1,37 à -0,11] et 6h : -0,79 mmol/L [IC à 95 %, -1,42 à -0,17]) et à midi (-0,75 mmol/L [IC à 95 %, -1,36 à -0,15]) dans le groupe PPC par rapport au groupe témoin ($p < 0,05$). Pour le projet 2, les données de 36 utilisateurs de PPC et de 14 utilisateurs d'OAM ont été analysées. Pour les cohortes DG et THG, trois profils d'adhérence ont été observés : 1) utilisateurs réguliers de PPC (38 %), 2) amélioration de l'utilisation de la PPC après une adaptation initiale (16 %), et 3) utilisateurs irréguliers de PPC (46 %). Pour la cohorte OAM, les trois profils d'adhérence observés étaient : 1) utilisateurs réguliers d'OAM (47 %), 2) utilisation initiale suivie d'une diminution de l'adhérence (20 %), et 3) utilisateurs irréguliers d'OAM (33 %). Les caractéristiques des participants (données démographiques, gravité de la maladie) étaient similaires entre les groupes d'adhérence.

Conclusions : La PPC (contre le groupe témoin) a permis de réduire les taux de glycémie en début de matinée (3h-6h) et à midi chez les femmes enceintes atteintes de DG et de TRS, réduisant ainsi l'exposition du fœtus au glucose maternel malgré une adhésion modeste. Dans l'ensemble, les analyses objectives de l'adhérence nocturne nuit après nuit ont révélé que près de la moitié des utilisateurs de PPC et d'OAM présentaient des difficultés d'adaptation au traitement au cours des 30 premiers jours. Des recherches supplémentaires sont nécessaires pour développer des stratégies visant à améliorer l'adhésion au traitement des TRS pendant la grossesse.

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Contribution of Authors

JS wrote the thesis and the two manuscripts that are included. For manuscript 1, SP was responsible for the conception and design. JS, CH, AD, RN and SP did the data acquisition, which was analyzed and interpreted by JS, CH, AD, RN, RJK, ZN, AB and SP. JS and SP drafted the manuscript, and JS, AB, ZN, AD, RN, SM, RJK, NG, ER, KD, RG and SP were involved in the critical revision for intellectual content and final approval of the version to be published.

For manuscript 2, JS, SP, NH and RJK were involved in the conception and design of the descriptive study. JS, NH, PP, and RJK did the data acquisition, which was analyzed and interpreted by JS and SP. JS and SP drafted the manuscript, and JS, NH, PP, RJK, SM, LDG, RN, AB, JPA, AMM, NG, ER, and SP were involved in the critical revision for intellectual content and final approval of the version to be published.

List of Abbreviations

AASM: American Academy of Sleep Medicine

AHI: apnea-hypopnea index

BMI: body mass index

CGM: continuous glucose monitoring

CPAP: continuous positive airway pressure

EEG: electroencephalograph

GDM: gestational diabetes mellitus

HAPO study: Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study

HDP: hypertension disorders of pregnancy

HSAT: home sleep apnea test

LGA: large-for-gestational age

MAD: mean absolute difference

MAD: mandibular advancement splint

ODI: oxygen desaturation index

OSA: obstructive sleep apnea

PSG: polysomnography

RCT: randomized controlled trial

RERA: respiratory effort-related arousal

SAVE study: Sleep Apnea cardioVascular Endpoint study

SDB: sleep-disordered breathing

SGA: small-for-gestational age

Chapter 1: Introduction

Rationale

Sleep-disordered breathing (SDB) is characterized by recurrent respiratory pauses during sleep, with associated increased upper airway resistance or pharyngeal collapsibility resulting in snoring and/or increased respiratory effort [1, 2]. SDB can be due to obstructive sleep apnea (OSA), central sleep apnea (CSA), or sleep-related hypoventilation/hypoxemia disorder [3]. Depending on the age group and sex, the prevalence of moderate-to-severe SDB ranges from 3% to 50% [1]. Over the last two decades, in accordance with the increasing rates of obesity, the prevalence of SDB has increased substantially, with relative increases ranging between 14% and 55% depending on the subpopulation observed [4]. The prevalence of SDB in various patient populations with certain comorbidities, namely obesity, type 2 diabetes, hypertension and stroke, exceeds that of the general population [5].

SDB prevalence increases from first to the third trimester, affecting 17-45% of women by the third trimester [6, 7]. Women with higher body mass index (BMI), increasing age and chronic hypertension are at higher risk of developing SDB in pregnancy [7, 8]. As pregnancy advances, trimester-specific physiological changes, such as weight gain, fluid retention, and upper airway edema, can significantly impact sleep [6]. Additionally, increased urinary frequency, back pain and discomfort from the enlarging uterus are additional factors that contribute to poorer sleep quality during pregnancy [6]. Mothers experiencing SDB face an elevated risk of associated adverse health outcomes, and this risk may affect the overall health of their children as well [6].

In the general population, SDB has emerged as an important risk factor for the development of hypertension, heart failure, stroke, diabetes, and other cardiovascular conditions [9-12]. Animal studies have shown that intermittent hypoxia from SDB causes sustained blood pressure increases through sympathetic nervous system activation [13, 14]. Mounting evidence also demonstrates that SDB is associated with poor glucose control [9, 15, 16]. This is also observed in pregnancy, where mothers experiencing SDB are at an elevated risk of developing gestational hypertension/preeclampsia and gestational diabetes (GDM) in comparison to those without SDB [17].

A leading cause of maternal morbidity and mortality is cardiovascular disease [18, 19]. In non-pregnancy, SDB triggers an increase in sympathetic activity, inflammatory response and oxidative stress in adults [20], and this response may also be relevant in the context of pregnancy [18, 21]. Epidemiological evidence suggests an association between the presence of SDB and an elevated risk of cardiovascular disease among pregnant individuals. For example, Bourjeily et al. found that habitual snorers had a higher likelihood of developing a hypertensive disorder during the third trimester of pregnancy (OR 2.3, 95% CI 1.4–4.0), independent of BMI, age, parity, and other pregnancy conditions [22]. An analysis of the National Perinatal Information Center database (2010–2014, >1.5 million records) found that a diagnosis of SDB was associated with an increased risk of cardiometabolic diseases, including pre-eclampsia (OR 2.22, 95% CI 1.94–2.54), eclampsia (OR 2.95, 95% CI 1.08–8.02), cardiomyopathy (OR 3.59, 95% CI 2.31–5.58) heart failure (OR 3.63, 95% CI 2.33–5.66), and GDM (OR 1.51, 95% CI 1.34–1.7) in fully adjusted models for BMI, age, race, parity and comorbidities [23]. Facco et. al. [24] also showed that in mid-pregnancy, the adjusted odds ratio for preeclampsia when SDB was present

was 1.95 (95% CI 1.18–3.23), 1.73 (95% CI 1.19–2.52) for hypertensive disorders of pregnancy, and 2.79 (95% CI 1.63–4.77) for GDM, adjusted for age, BMI, chronic hypertension, and rate of weight gain during pregnancy.

Complications during pregnancy have many adverse health effects on both the mother and the child. Pre-eclampsia is associated with long-term maternal cardiovascular risk factors and disease [25]. Gestational hypertension is associated with a 4.2-fold higher risk for developing chronic hypertension postpartum [26], and a greater risk of cardiovascular disease, coronary heart disease, and heart failure [27, 28]. The Helsinki Birth Cohort demonstrated an increased risk of type 2 diabetes in adulthood for offspring exposed to gestational hypertension in utero (HR=1.13, 95% CI 1.00–1.29) [28, 29]. Other adverse birth outcomes (e.g. small-for-gestational age), have also been associated with poor cardiometabolic health later in life [28]. As such, addressing and improving perinatal health to decrease the risk of pregnancy-related complications may have major impacts on improving the overall long-term health for both mother and baby.

GDM, prevalent in 6.9% (95% CI: 5.7–8.3) of pregnant women in Canada and the United States [30], is also associated with adverse outcomes for the mother and the offspring. The landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [31] demonstrated that maternal hyperglycemia, measured on a continuum with respect to its severity, increases the risk of pre-eclampsia, preterm delivery, caesarean section, large for gestational age (LGA) infants, admission to neonatal intensive care units (NICU) and other adverse health effects in the mother and child [31, 32]. This study suggests that there may not be one specific threshold for glucose targets, but rather, that overall tighter glucose control may be most beneficial. Long-

term complications of GDM also include an elevated risk of maternal type 2 diabetes and of obesity in the offspring [32-34].

Indeed, the prevalence of SDB in GDM is over 60% in some studies [35, 36]. Because interventional studies in this patient population have been sparse [6, 37-43], the causal relationship between SDB in pregnancy and GDM is still unclear. Therefore, it remains unknown whether treatment of SDB in GDM improves glucose control. As such, conclusive clinical trials are imperative to ascertain the degree to which interventions for SDB can mitigate the risk of adverse cardiovascular and neonatal outcomes during pregnancy [18]. Currently, guidelines do not strongly recommend screening and treatment for SDB, due to a lack of evidence [44, 45].

The main treatment for SDB, in pregnancy and in the general population, is continuous positive airway pressure (CPAP) [46], a device that delivers a steady stream of air through a mask to maintain airway patency during sleep. In non-pregnancy, several CPAP trials that have failed to demonstrate an improvement in metabolic outcomes were also limited by poor adherence to CPAP [47, 48]. However, when CPAP adherence was improved to 8h/night in in-laboratory proof-of-concept studies, this resulted in better cardiometabolic outcomes, including lower blood pressure, improved glucose tolerance and improved insulin sensitivity [49, 50]. In pregnancy, sleep quality is often further impaired by less deep sleep and more frequent nocturnal awakenings [48, 51], which may influence tolerability and adherence to CPAP. However, very few studies to date have examined CPAP adherence in pregnancy. To effectively power large, multi-center trials on pregnant women with SDB aimed at improving cardiometabolic outcomes, it is essential to first demonstrate the feasibility of treatment by establishing adherence to CPAP among pregnant women [48].

Interventional studies to date demonstrate that poor adherence to CPAP remains a major barrier for the effective treatment of SDB in pregnancy [37, 52, 53], with an average adherence of ~3.3 hours/night. In the general population, CPAP usage in the first few days of treatment has been shown to forecast future adherence [54]. Examining data on night-to-night CPAP adherence in non-pregnancy revealed that individuals who do not use CPAP on certain nights are prone to using it for shorter durations on the nights that they do use it [54]. This pattern becomes noticeable as early as the fourth day of treatment [54]. To our knowledge, there are no studies that have examined adherence patterns in pregnancy. Mandibular advancement splints (MAS) are oral appliances that advance the jaw and tongue forward thereby reducing the degree of upper airway obstruction. While MAS devices are better tolerated than CPAP, they tend to be less efficacious. Night-to-night adherence patterns to MAS have not been reported previously in the literature [55]. As such, longitudinal patterns of adherence to CPAP and MAS in pregnancy need to be evaluated, as these could offer valuable insights for future interventions that could improve treatment.

Hypotheses

Our study was based on two primary hypotheses. Our first hypothesis was that pregnant individuals with SDB and GDM adhere to CPAP, demonstrating feasibility of this treatment in future trials of SDB and GDM. Also, in secondary analyses, we hypothesized that pregnant individuals with GDM treated with CPAP will have better glucose control than those who are not treated. For the second project, we hypothesized that pregnant individuals demonstrate varying patterns of adherence to CPAP and MAS.

Objectives

As such, to test these hypotheses, this thesis has two objectives. Project 1 addressed the first objective: to determine whether pregnant individuals with GDM and SDB adhere to CPAP and evaluate whether treatment vs. control improves 24-hour glucose profiles (measured by continuous glucose monitoring (CGM)) in a pilot randomized controlled trial (RCT) design. Project 2 addressed the second objective, which is to further examine adherence to CPAP (and to MAS), by evaluating objective, longitudinal night-to-night adherence patterns to both treatment options in different pregnancy cohorts.

Chapter 2: BACKGROUND AND LITERATURE REVIEW – Sleep-Disordered Breathing (SDB)

Overview of SDB

OSA, the most common form of SDB, is marked by repeated episodes of cessation (apnea) or reduction (hypopnea) in airflow during sleep caused by obstruction of the upper airway [1]. In the general population, OSA poses several health risks [56], such as increased perioperative morbidity [57, 58], hypertension [59], coronary artery disease [60, 61], cardiac dysrhythmias [62], sudden death [63], stroke [64] [65], pulmonary hypertension [66], and deep vein thrombosis [67]. Clear benefit has been shown for the treatment of patients with sleepiness, cognitive or psychological dysfunction, or poor quality of life due to OSA [1, 68-70].

In pregnancy however, milder SDB is more common, which is primarily characterized by frequent flow limitation, snoring and hypopneas with arousals [6, 7, 41, 42, 71-74]. As such, consistent with the published literature, in the context of pregnancy for the purpose of this thesis, the term SDB specifically refers to the aforementioned obstructive sleep disturbances.

Pathophysiology

SDB is characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in apneas or hypopneas despite continued respiratory effort [75]. To maintain adequate airway patency during inspiration, activation of upper airway dilator muscles is necessary [76]. The most important dilator muscle in the upper airway is the genioglossus muscle [76]. The genioglossus prevents posterior collapse of the tongue by contracting with each inspiration, and it is assisted by the levator and tensor palatini muscles, which advance and elevate the soft palate (Figure 1) [76]. It is also assisted by the geniohyoid and stylopharyngeus

muscles, which work to oppose the medial collapse of the lateral pharyngeal walls [20, 76]. Patients with SDB have a narrow upper airway, typically caused by a higher volume of the soft tissue structures surrounding the upper airway [76, 77]. This oral pharyngeal region is where one or more sites are susceptible to collapse in patients with SDB [20]. The retropalatal region of the oropharynx is the most common site of collapse, but airway narrowing also often includes the retroglossal and hypopharyngeal areas [20].

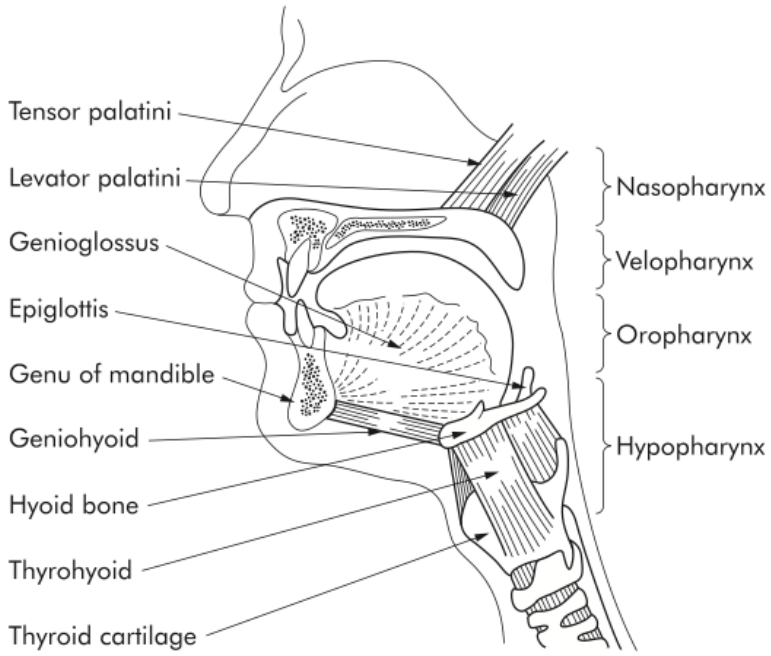

Figure 1. Anatomical representation of the upper airway and the muscles controlling airway patency (Reproduced from Fogel RB, Malhotra A, White DP. Sleep. 2: pathophysiology of obstructive sleep apnoea/hypopnoea syndrome. Thorax. 2004 Feb;59(2):159-63 with permission from BMJ Publishing Group Ltd. [78])

Fluid shift at night and during the day may also influence upper airway obstruction and risk of SDB. Throughout the day, gravity causes fluid to accumulate in the interstitial and intravascular spaces of the legs. When lying down at night, this fluid shifts rostrally towards the neck, potentially narrowing the upper airway and increasing the risk of airway collapse and SDB [79]. It has even been shown that day-to-day changes in leg fluid volume and rostral fluid shift

may partially explain the intra-individual variability in SDB severity from night-to-night [80]. Certain fluid-overload states, such as heart failure and renal disease may exaggerate the impacts of fluid shift [81, 82].

Another risk factor for SDB is smaller cranial bony structure, which is comprised of a reduced mandibular body length, an inferior positioned hyoid bone, and a retro position of the maxilla [20]. These differences in the craniofacial structures, which are primarily inherited, contribute to a compromised pharyngeal airspace [20]. The larger size of soft tissue structures both within and surrounding the airway contributes to airway narrowing and collapse in SDB patients [20]. The anterior-posterior airway diameter is compromised by an enlarged soft palate and tongue, while in the lateral plane, the constricted airway is attributed to thickened pharyngeal walls [20]. In fact, SDB treatment with CPAP, weight loss, or mandibular advancement splints has demonstrated improvements in the lateral dimensions of the pharyngeal airway [20]. Weight loss reduces soft tissue volume thereby increasing upper airway space [83]. In fact, in patients with SDB, obesity and craniofacial abnormalities contribute synergistically to increased collapsibility of the pharyngeal airway [84].

Other craniofacial and upper-airway structure characteristics may also increase the risk of OSA [85]. These include a deviated septum or turbinate hypertrophy, retrognathia or crowding of the posterior oropharynx, which can be due to larger tonsils, soft palate elongation, macroglossia or changes in dental occlusion [1]. Surgical correction of these anatomical defects can reduce the apnea-hypopnea index (AHI) and alleviate OSA symptoms [86].

To compensate for a diminished airway size, during wakefulness, SDB patients have significantly greater upper airway dilator muscle activity (namely the genioglossus and tensor palatini) compared to non-SDB patients, thereby maintaining airway patency during the daytime [75, 87, 88]. At sleep onset, genioglossal muscle activity decreases, however this reduction is much greater in SDB patients than normal controls [78, 89]. This decrease in muscle activity in SDB patients, who might already have an anatomically compromised pharynx as described above, results in the airway narrowing and/or collapsing [78]. The result of these OSA events is brief brain activation in a process called arousal or microarousal [90]. This mechanism is essential to re-establish airway patency [91], but frequent arousals interrupt sleep continuity and prevent deeper sleep [92]. Though these arousals do not generally wake the patient, they cause sleep fragmentation, which has been shown to cause excessive daytime sleepiness in SDB patients [76, 93-96].

Intermittent hypoxemia and sleep fragmentation both activate the sympathetic nervous system [97, 98]. This is the major contributor to both acute and chronic elevated blood pressure, which is a comorbidity of SDB [20, 76, 99]. Research findings from both case-control [100, 101] and observational epidemiological studies [102, 103] suggest that prolonged exposure to SDB plays a key role in the pathogenesis of cardiovascular disease [20]. The Wisconsin Sleep Cohort Study [59] is a prospective study that found a dose-dependent association between SDB severity and hypertension (OR = 1.42, 95% CI: 1.13-1.78). SDB has also been associated with left ventricular dysfunction [20]. Patients with SDB are more likely to have congestive heart failure than those without SDB (OR = 2.38, 95% CI: 1.22-4.62) [104].

Additionally, SDB has been associated with stroke, coronary artery disease, cardiac arrhythmias and pulmonary hypertension [20].

However, it is important to note that in studies demonstrating associations between SDB and cardiovascular disease, while dose-response relationships were rare, odds ratios were highest for individuals with moderate-severe SDB [20]. Collectively, these studies propose that to increase the risk of cardiovascular disease, there is a need for a certain threshold of SDB (~25–30 events/hour of sleep) and significant oxygen desaturation [20]. Additionally, in a sample derived from two cohort studies, The Outcomes of Sleep Disorders in Older Men (MrOS) [105] and the Sleep Heart Health Study (SHHS) [106], Azarbarzin et al. examined the association between hypoxic burden and cardiovascular disease (CVD) -related mortality [107]. Hypoxic burden, which encapsulates frequency, duration, and depth of the respiratory-event contribution to arterial hypoxaemia, was found to predict CVD mortality across populations [107]. Such metrics are currently being evaluated in larger cohorts to better understand their utility in clinical practice.

Diagnosis and scoring

Several studies indicate that in the United States, over 80% of individuals with OSA remain undiagnosed and untreated [108-110]. This is due to constraints in healthcare resources such as limited availability of sleep laboratories and technicians, as well as the inefficiency of current diagnostic tools [108]. Additionally, patients themselves are often unaware of their apneic episodes, and rarely report nocturnal choking related to OSA [111]. More public awareness of SDB is needed to decrease the incidence of undiagnosed or untreated SDB [112].

There is a lack of clear guidelines for screening and diagnosis of SDB in pregnancy, which may be a factor leading to it being underdiagnosed in this population [113]. There has been an effort to produce guidelines [45], but the major limitation is that the evidence is either weak or lacking, because of a lack of research in the field. Additionally, pregnant women are reluctant to undergo a sleep study [113], and even after being diagnosed, the perceived importance of SDB is low [114, 115].

There are three types of sleep apnea tests for diagnosis of SDB. The gold standard diagnostic sleep apnea test is the overnight full polysomnography (PSG), or Level 1, sleep test. PSG is the most accurate diagnostic test, as it records many different biological signals such as respiratory flow, oxygen saturation, electroencephalography (EEG), electrocardiography (ECG) and electromyography (EMG) which are all monitored in real-time by a registered sleep technician in a hospital or sleep laboratory [108]. A Level 2 sleep study monitors the same signals as a Level 1 PSG, (i.e. airflow, EEG, blood oxygen) except it is performed in the patient's home unattended and the data is screened afterwards [108]. Level 3 sleep studies, or home sleep apnea tests (HSATs), offer a convenient way to record breathing, heart rate, and oxygen levels in the participant's home. However, they do not record brain activity, making them unsuitable for diagnosing certain sleep disorders. Both at-home Level 2/3 and in-lab Level 1 sleep tests are done for diagnosing pregnant women, but the convenience and comfort of HSATs may be preferred in pregnancy [24, 115].

When determining which diagnostic method should be used, patient preferences, comorbidities and clinical setting should be considered [116, 117]. PSG has an increased diagnostic accuracy however, due to its ability to differentiate between sleep stages and to

accurately capture arousal-based events [116]. HSATs are cost-efficient diagnostic alternatives to PSGs, but are currently only recommended for use in patients with a high suspicion of moderate-to-severe OSA without significant comorbidities [116].

The American Academy of Sleep Medicine (AASM) manual recommends scoring an apnea and a hypopnea based on different criteria (i.e. drop in signal amplitude, duration of event, degree of oxygen desaturation and presence of respiratory effort) for adult vs. pediatric scoring [118]. The AHI serves as a single, comprehensive metric for case identification and for quantifying disease severity and prevalence [119]. Differences in scoring criteria (AASM vs. Chicago), especially for hypopneas, significantly impacts the AHI, which could potentially determine the presence or absence of an OSA diagnosis [119]. Chicago criteria allows for scoring of hypopneas without arousals or desaturations, thus increasing the sensitivity for scoring hypopneas. Chicago criteria describes hypopneas as 1) > 50% airflow reduction or 2) a lesser airflow reduction with associated > 3% oxygen desaturation or arousal [119, 120].

However, in pregnancy, milder SDB with frequent flow limitation and hypopneas with arousals are common [6, 7, 41, 42, 71-74]. As such, the more sensitive Chicago scoring criteria, which captures more subtle respiratory events in pregnancy (e.g. reduction in airflow without arousal), are used [7, 35, 74]. Flow limitation is especially important to measure in pregnancy because it has been associated with numerous adverse pregnancy outcomes [122]. In the prospective cohort NuMOM2b (Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-Be), greater flow limitation was associated with increased risk of preeclampsia, HDP, and lower infant birthweight [122].

Earlier studies in pregnancy relied on symptom-based assessment particularly snoring, as opposed to objective measures like PSG [6]. SDB diagnosis in pregnancy using self-reported symptoms presents several challenges. Firstly, studies often employ inconsistent definitions for both the frequency and intensity of snoring [17]. Secondly, when not pregnant, women tend to underreport symptoms of snoring compared to men [123]. Additionally, the presence of a bed partner during questioning can impact reporting of snoring among pregnant women (p=0.05) [22]. Lastly, the timing of symptom assessment across different stages of pregnancy can affect symptom prevalence, and reporting at delivery can introduce recall bias [6, 124, 125].

Despite these limitations, a significant association has been established between maternal snoring and adverse maternal-fetal outcomes [126, 127]. Screening for SDB in pregnancy is different than in the general population. Sleepiness questionnaires alone like the Epworth Sleepiness Scale (ESS) [128] cannot reliably diagnose SDB in pregnancy because they are not sensitive or specific enough [6, 129]. This is due to the already high prevalence of daytime sleepiness in pregnancy (65% in third trimester [130]) and other pregnancy-related factors, such as nocturnal awakenings and decreased sleep quality, that may contribute to daytime sleepiness [131]. The Berlin [132] and STOP-Bang [133, 134] Questionnaires incorporate questions on snoring, but they have mostly been validated in older or male-predominant populations [6, 132, 135]. These conventional questionnaire-based assessment tools perform less well among pregnant women [136].

Facco et al. [137] tested a multi-variable model which combines snoring, hypertension, age and BMI in an index to predict SDB in high-risk pregnancies [6]. It performed better in diagnosing SDB than either the ESS or Berlin Questionnaire alone (area under the curve, 0.86)

[6, 137]. A meta-analysis of four studies [137-140] that applied the Facco et al. criteria [137] to their study found a pooled sensitivity of 0.74 (95% CI 0.64–0.82) and pooled specificity of 0.64 (95% CI 0.58–0.70, AUC 0.82) [45]. Another model incorporating BMI, snoring volume and tiredness on awakening was a strong predictor for SDB diagnosis (area under the curve, 0.95) [6, 141]. However, this tool has not been validated in large groups of pregnant women [6]. Developing widely applicable pregnancy-specific clinical prediction methods that can identify women at risk for timely diagnosis and potential treatment of SDB remains an important objective [6]. Identifying biomarkers for SDB would be a very useful way to assess risk for SDB, but this approach has not been well explored to date [6]. Objective PSG sleep recordings are the current best way for definitive diagnosis of SDB in pregnancy.

Epidemiology

In 2009, the Public Health Agency of Canada reported that 26% of Canadian adults have symptoms of OSA, but the absence of studies using objective sleep testing make it difficult to estimate accurate prevalence measurements in Canada, where only 3% of adults reported a formal diagnosis [1].

Depending on age and sex, SDB prevalence rates differ. Additionally, SDB becomes more common as people age in the general population [142]. For mild SDB (AHI 5-15 events/h), adult men have a prevalence rate ranging from 13% to 33%, whereas prevalence rates were 6% to 19% for adult women [142]. The Wisconsin Sleep Study Cohort revealed that among individuals aged 30 to 49, 10% of men and 3% of women exhibited moderate to severe SDB (AHI 15-30) [4, 143]. Among those aged 50 to 70, 17% of men and 9% of women had moderate to severe SDB

[4, 143]. This is in line with the finding of various studies across multiple countries indicating that males are at higher risk for severe SDB compared to females, pre-menopause [5, 144]. However, post-menopause, SDB prevalence rates in women doubles, independent of age and BMI [145, 146].

In addition, the Wisconsin Sleep Cohort study showed that the prevalence of SDB is increasing with trends of increased obesity [147]. In a subset of this cohort (n=690), a 10% weight gain was associated with a 6-fold greater risk of developing SDB [148]. Obesity is the main risk factor for SDB and has increased in prevalence worldwide over the past four decades [144]. The global epidemic of obesity is contributing to increased rates of SDB, in both children and adults [144].

SDB occurs in 17-45% of pregnant women by the third trimester of pregnancy [6]. This wide range is due to differences in BMI, gestational age, SDB symptoms, type of sleep test, and scoring criteria in the studies that were used to obtain these prevalence rates [6]. As pregnancy progresses, the prevalence of SDB rises significantly: according to one study that used objective PSG testing, the occurrence rate of SDB (defined by Chicago scoring criteria [120]) escalates from 10% in the first trimester to 27% by the third trimester [6, 7]. The NuMoM2b study [24], which has the largest prospective cohort to date in pregnancy (n=3,702), found that the prevalence of SDB went from 3.6% in early pregnancy to 8.3% in mid-pregnancy. This study used Level 3 HSATs without EEG [24, 149], and so the assessment could not capture hypopneas with microarousals, which are a predominant form of SDB in pregnancy [7, 74].

Maternal SDB and adverse health outcomes

In pregnancy, airway dimensions are reduced, which could increase the risk of developing SDB [6, 150, 151]. This could be due to several factors, such as increased abdominal girth and reduced functional residual capacity [6, 152]. Additionally, an increase in adipose tissue associated with weight gain or underlying obesity could also increase the risk of SDB [6]. Though this mechanism has not yet been explored in pregnancy, increased blood volume [153] and elevated estrogen levels [154] in pregnancy may cause a buildup of mucosal edema, which in turn could lead to narrowing of the upper airway [6]. There may also be hormonal influences which may predispose pregnant women to SDB. Over 20% of women experience gestational rhinitis as a result of elevated estrogen and placental growth hormone levels [155, 156], which predisposes them to SDB by causing nasal obstruction, more specifically nocturnal congestion [6, 157]. This is a known risk factor for SDB in the general population [158, 159], and as such it is possible that gestational rhinitis could increase the risk of SDB. Though progesterone increases upper airway muscle dilator activity [160], it also increases ventilatory drive [161, 162], which results in respiratory instability and more negative intraluminal pressures, thereby worsening SDB [6]. As such, the observed increase in progesterone levels during pregnancy also exerts an influence.

During pregnancy, respiratory events predominantly manifest as obstructive rather than central [6, 163]. Pregnant women present increased inspiratory flow limitation more often than conventionally defined apneas or hypopneas, which is associated with adverse health outcomes [6].

SDB has been associated with various HDP, such as pre-existing or chronic hypertension, gestational hypertension, and preeclampsia [17, 24]. Preeclampsia is caused by various

pathogenic mechanisms, such as ischemia-reperfusion injury, oxidative stress, and endothelial dysfunction [6, 164]. The way these mechanisms work is similar to how SDB causes cardiovascular issues in the general population [6, 165, 166].

Preeclampsia is also associated with volume overload, which can potentially lead to upper airway narrowing caused by nocturnal rostral fluid shift during recumbency at night [6, 167, 168], as demonstrated in a study that found decreased airway dimensions in pregnant women with preeclampsia relative to healthy pregnant women [150]. This is consistent with findings from studies on non-pregnant populations, which show that patients with conditions causing fluid overload, such as end-stage renal disease (ESRD) have a higher prevalence of SDB (50-60%) [169-172]. Patients with chronic heart failure have a higher prevalence of OSA (26%) and CSA (21%) as well [81]. One study found that ESRD patients with SDB (AHI ≥15) have a higher extracellular fluid volume than those without SDB, which is correlated with SDB severity [82]. This effect was most marked in males, but nonetheless is consistent with the evidence that fluid overload contributes to the pathogenesis of SDB. Given that preeclampsia involves fluid overload, it is pertinent to consider fluid shift as a factor contributing to the etiology of SDB in pregnant populations.

Additionally, various other studies with differing definitions of SDB, either symptom-based or by objective sleep recordings, found a significant relationship between maternal SDB and gestational hypertension and/or preeclampsia (OR, 2.5; 95% CI, 1.8-3.5) [6, 24].

Independent of obesity, SDB is associated with both poor glucose control and type 2 diabetes in the non-pregnant population [6, 47, 173]. In pregnancy, the mother undergoes physiologic changes that predispose patients to hyperglycemia [174, 175]. Early on in

pregnancy, insulin sensitivity increases resulting in an increased uptake of glucose into adipose tissue to meet the high energy demands of later stages of pregnancy [176, 177]. However, as pregnancy advances, an increase in certain hormone levels, including estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone together increase the body's resistance to insulin [177, 178]. As a result, there is a slight increase in blood glucose during pregnancy [177].

The evolution of SDB remains unknown in the postpartum period, however. Several studies have shown an improvement in SDB from three months to two years postpartum [6, 179-181]. However, more frequent sleep studies spanning various intervals before, during, and after pregnancy are necessary to draw conclusive findings [6].

Maternal SDB and gestational diabetes (GDM)

GDM is glucose intolerance first recognized during pregnancy [174]. Based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [182], the most used screening method worldwide, a meta-analysis reported the global prevalence of GDM was 14.7% [183]. However, the prevalence of GDM varies widely across the world. Different countries use different diagnostic criteria [177, 184], Additionally, even when the same criteria and screening methods are used, prevalence ranges from 1% to 28% [183]. This is due to differences in population characteristics, such as age [185], ethnicity [32, 186, 187], obesity [188], lifestyle and diet [175]. Across most populations however, GDM prevalence is increasing [186], most likely due to the rising prevalence of obesity among pregnant individuals.

GDM has been associated with adverse health outcomes in the mother and the child [174]. GDM increases the risk of complications in pregnancy, especially HDP [189, 190]. After adjusting for age, BMI, ethnicity, parity and prenatal care, GDM was associated with an increased risk of severe preeclampsia (OR=1.5, 95% CI: 1.1, 2.1), mild preeclampsia (OR=1.5, 95% CI: 1.3, 1.8), and gestational hypertension (OR=1.4, 95% CI: 1.2, 1.6) [189]. The HAPO Study followed over 25,000 women in the second-through-third trimester of pregnancy [31]. It found that higher maternal glycemia was associated with increased frequency of birth weight above the 90th percentile, caesarean section, clinical neonatal hypoglycemia, C-peptide level (a measure of hyperinsulinemia) above the 90th percentile, admission to NICU and neonatal hypoglycemia [31, 191].

GDM is also associated with long-term adverse health outcomes in the mother and the child. After pregnancy, 20 to 50% of women with GDM develop type 2 diabetes, and this risk has doubled in the last decade [6, 192-195]. A meta-analysis that included 20 studies and over 675,000 women found that GDM patients had an increased risk of developing type 2 diabetes compared with women who had a normoglycemic pregnancy (RR=7.43, 95% CI 4.79-11.51) [196]. GDM is associated with subsequent cardiovascular morbidity [197-199]. In a study following up on ~63,000 women, even only 7 years after pregnancy, GDM was significantly associated with a higher risk of CVD (adjusted OR=1.25, 95% CI: 1.09–1.43) [199]. Women with a history of GDM were also found to have a higher risk of malignancies, such as breast, uterine, and ovarian cancer (adjusted HR=1.3, 95% CI: 1.2-1.6) [200], ophthalmic morbidity (adjusted HR=2.0, 95% CI: 1.5-2.8) [201], and renal morbidity (OR=2.34, 95% CI: 1.4-3.7) [202, 203].

Maternal hyperglycemia is also strongly associated with development of type 2 diabetes in the offspring later in life. In a multi-ethnic retrospective case-control study, exposure to maternal diabetes was independently associated with type 2 diabetes in the offspring (OR=5.7, 95% CI: 2.4–13.4) [204]. Additionally, GDM is associated with obesity in the offspring (OR=1.53, 95% CI:1.03-2.27) [205, 206], and long-term endocrine disease during childhood (adjusted OR=3.1, 95% CI: 2.2–4.4) [207], among other conditions such as cardiovascular, neurodevelopmental, and ophthalmic morbidity [203]. This is consistent with Barker's hypothesis on fetal origins of disease, which states that an adverse intrauterine environment is associated with epigenetic disruptions in the developing fetus' metabolic genome, thereby predisposing the offspring to chronic and metabolic disorders later in life [208-210].

After diagnosis of GDM, treatment starts with lifestyle and behaviour modifications, including nutrition counselling, physical activity and weight management. These measures alone can be effective in 70-85% of GDM patients [211], but are sometimes not achieved. Lifestyle modification does not achieve adequate glucose control in 15% to 30% of GDM patients [212], necessitating pharmacologic treatment with insulin or other antidiabetics therapy [213], thus, highlighting the need to investigate for other risk factors that worsen glucose control in pregnancy. Insulin is the first line agent recommended for treatment of GDM in Canada [214], after which other non-insulin agents like metformin and glyburide can be prescribed. However both of these latter agents cross the placenta [213], and no long-term safety data is available for any oral agent [215].

Despite current strategies to manage GDM, adverse neonatal outcomes such as neonatal hypoglycemia and NICU admissions still occur, prompting further investigation into the

identification of novel, reversible risk factors to improve overall glucose control. A meta-analysis of observational studies found a strong association for SDB and GDM with an OR=2.11, 95% CI: 1.38- 3.23 [17]. Another meta-analysis of ~10,000 participants enrolled in observational studies found that after adjusting for BMI, women with SDB had a more than threefold increased risk of GDM, with a pooled OR=3.06, 95% CI: 1.89-4.96 [9]. However, a case-control study of non-obese women (BMI < 35) found no association between GDM and sleep-disordered breathing in pregnant women [216], but another observational case-control study found a strong association between SDB and GDM in an obese population (OR=6.60, 95% CI: 1.15–37.96) [217]. As such, it is still unclear whether the interaction between SDB and GDM is independent of obesity.

Continuous glucose monitoring (CGM) tracks glucose levels in real-time with periodic measurements every 5 minutes. This offers a more dynamic understanding of blood glucose control compared to traditional markers like HbA1c, which misses daily fluctuations. Using CGM, our group has previously shown that a 10-unit increase in the AHI was associated with increased nocturnal (11pm-3am: 0.2 mmol/L [95% CI, 0.04-0.4]) and morning (8am: 0.3 mmol/L [95% CI, 0.08- 0.4]) glucose levels in GDM, even after adjusting for BMI and diabetes medications (Figure 2) [35]. Interventional studies examining GDM and SDB are lacking [6, 37-42, 179], and so it remains unknown whether treatment of SDB in GDM improves glucose control.

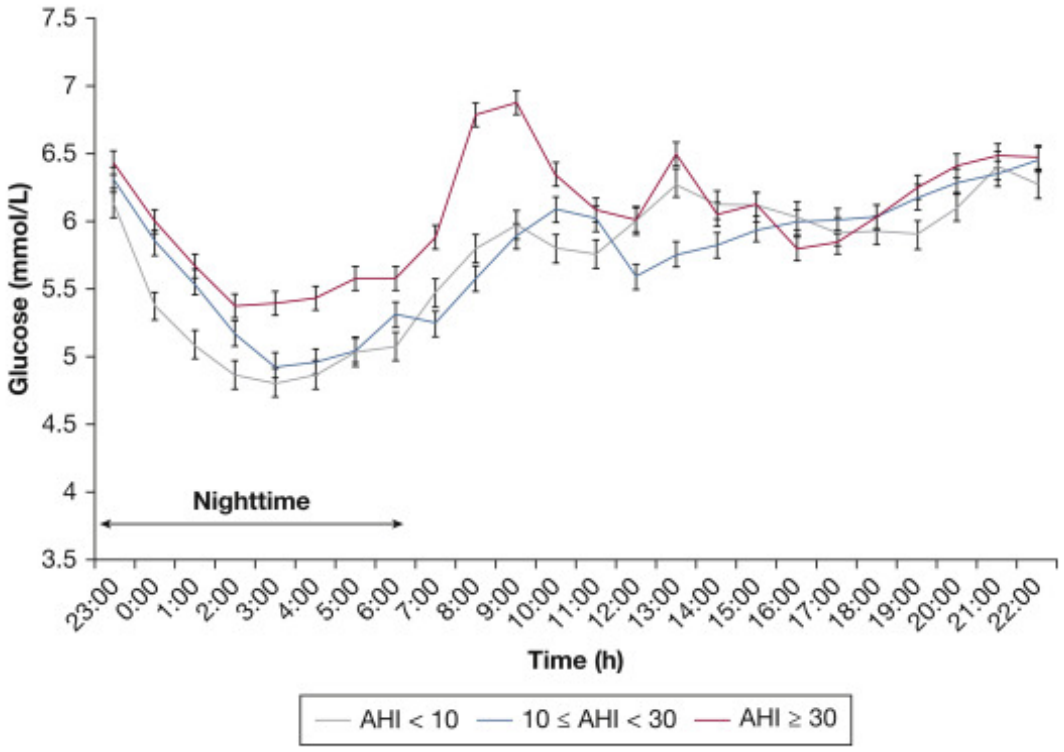

Figure 2. Mean hourly 24-hour glucose profiles in relation to category of sleep-disordered breathing severity. SE bars are shown. (Reprinted from: Newbold, R., Benedetti, A., Kimoff, R. J., Meltzer, S., Garfield, N., Dasgupta, K., Gagnon, R., Lavigne, L., Olha, A., Rey, E., & Pamidi, S. (2021). Maternal Sleep-Disordered Breathing in Pregnancy and Increased Nocturnal Glucose Levels in Women with Gestational Diabetes Mellitus. *Chest*, *159*(1), 356–365, with permission from Elsevier [35])

Maternal SDB and child health outcomes

There are limited studies examining the effects of maternal SDB on fetal outcomes. In nonpregnant SDB patients, cardiac output and left ventricular stroke volume both decrease with a concurrent drop in oxygen saturation, which compromises tissue oxygen delivery [218]. As such, it is plausible that maternal SDB could disrupt hemodynamics and reduce placental tissue perfusion, which in turn decreases fetal growth potential [6]. Small for gestational age (SGA) infants face an increased risk of developing cardiometabolic health issues and mortality later in life [6]. Recent studies using PSG have demonstrated that maternal SDB was related to the

delivery of SGA infants [74, 122, 219]. As such, mild maternal SDB, even without major oxygen desaturation, could pose a risk of negative health outcomes for the developing baby [74].

Maternal SDB has also been associated with preterm birth (OR = 1.47, 95% CI = 1.14–1.91) [220], which increases the risk for mortality and a variety of other health concerns later in life, including respiratory, gastrointestinal, immunologic, and cognitive problems, among many others [221]. A recent study found that even mild maternal SDB during pregnancy is linked to a smaller head circumference in newborns [222]. These infants also exhibited a unique pattern of head growth during the following three years of life. While newborns with slightly smaller head circumferences (still within normal ranges) might catch up quickly within the first year, this early difference could have lasting effects [222]. Recent research suggests that head circumference growth reflects brain development and that atypical head growth patterns are linked to an increased risk of developing neurodevelopmental disorders [222, 223].

In addition, maternal SDB during pregnancy affects adiposity acquisition from birth until infancy [222]. Offspring of mothers with mild SDB have a compromised weight-to-length ratio at birth in addition to exhibiting rapid subsequent catch-up growth, which increases the risk for coronary heart disease [222, 224]. They also have an increase in weight and an increase in adiposity acquisition in the next three years of life [222].

Adverse fetal outcomes of maternal SDB have also been modeled in animals. Gozal et al. demonstrated in a gestational rat model that exposure to intermittent hypoxia and sleep fragmentation, the two hallmarks of SDB, results in an increased risk for catch-up growth in the male offspring and worse glucose control, which are both risk factors for developing obesity

later in life [225, 226]. To fully understand the long-term effects of maternal SDB on children's health, we need well-designed studies involving human subjects.

Treatments of SDB

The gold standard treatment for OSA is CPAP for its benefits regarding sleep-related symptoms as well as quality of life [227]. A CPAP machine generates airflow that is delivered through a nasal or oronasal mask into the upper airway, thereby maintaining a generally constant pressure in the upper airway throughout the respiratory cycle [228]. CPAP works like a pneumatic splint, using air pressure to keep the upper airway open throughout each breath, resulting in decreased respiratory effort and gas-exchange perturbations [228].

Despite the high efficacy of CPAP, treatment effectiveness relies on patients' adherence to prescribed therapy. In the non-pregnant population, using the conventional 4 h/night cut-off, 29 to 83% of patients are non-adherent to CPAP [229]. Patterns of adherence are usually established early, within the first week of treatment, and they predict the patient's long-term use [54]. Skipping nights of CPAP therapy is also associated with shorter nightly use durations, averaging 3 h/night [54].

This level of detailed adherence has not been described in pregnancy. Interventional CPAP studies have given similar adherence rates to the general population. For example, in a recent RCT of 340 participants evaluating the effects of CPAP on blood pressure and preeclampsia in women with high-risk pregnancy, CPAP adherence rate was 32.7% with average use of 2.5 h/night [230]. Another smaller RCT of CPAP in a GDM population revealed that 46.7% of participants were adherent to CPAP with average adherence 3.39 h/night [37]. Night-to-night

adherence in pregnancy is an important gap in knowledge in this field and needs to be examined for improving our understanding of patterns of adherence in pregnancy, which may provide clues for novel interventions to improve overall adherence.

Oral appliances offer an alternative treatment option for SDB patients who are intolerant to CPAP or simply prefer a different approach [1]. Either a mandibular advancement splint (MAS) or tongue-retaining device is fitted and worn to bed nightly, though tongue-retaining devices have been less frequently used in recent years due to intolerability, being almost completely replaced by MAS [231]. MAS are considered a less invasive, tolerable, and silent treatment option for mild-to-moderate SDB [231, 232]. MAS push the jaw forward, thereby opening the airway. This position, however, might put stress on the teeth and jaw muscles due to constant counterbalancing forces trying to return the jaw to its natural position. This stress could potentially affect tooth alignment and jawbone health in up to 24% of oral appliance patients [231]. While oral appliances can help reduce sleepiness, a systematic review and meta-analysis found they are less effective than CPAP in lowering the AHI in non-pregnant individuals (weighted mean difference: -7.08, 95%CI: -9.06∼-5.10) [233]. However, patients often find them much easier to tolerate (80-90% adherence vs. 50-70% for CPAP) [1]. This higher adherence might make them just as effective overall for mild to moderate cases of OSA [234]. Additionally, like CPAP, oral appliances can slightly improve blood pressure [234-237]. However, further research is needed to see if they offer other cardiovascular benefits.

In addition to CPAP and MAS, alternative treatments for SDB include upper airway surgery, namely tonsillectomy or tracheostomy [1]. Maxillomandibular advancement surgery is a major procedure reserved for SDB patients who cannot tolerate other treatments, but the risk

of major complications that require readmission is high, and minor complications can occur as well [1]. Bariatric surgery for weight loss is also an option to help treat SDB, but in general, surgery for SDB only becomes an option when conventional therapies fail to significantly improve a patient's quality of life, and diagnostic tests reveal clear anatomical reasons for the airway blockage [238].

Beyond traditional treatments for SDB, simple lifestyle adjustments can offer additional benefits for an improvement in sleep quality. Behavioural interventions like weight loss, a healthy diet and exercise can decrease SDB severity and may be the most effective first-line treatment, before any pharmacological or surgical intervention [238]. Smoking cessation, quitting alcohol and positional therapy are other behavioural lifestyle changes that SDB patients can consider to compliment conventional therapies [238].

Knowledge gaps

SDB is associated with an increased risk of GDM in pregnant individuals which can cause adverse health outcomes in both the mother and the child [6]. It is still unknown if treatment with CPAP, the main treatment for SDB, 1) demonstrates adequate adherence in pregnancy, and 2) improves glycemic profiles of pregnant women with SDB and GDM (Objective 1). Additionally, since CPAP is the first-line treatment for pregnant women with SDB, to assess whether it improves metabolic outcomes in pregnancy, it is necessary to evaluate in detail adherence to CPAP (and alternative forms of treatment for SDB) in this population, and characterize any ensuing patterns of adherence (Objective 2).

Chapter 3: Manuscript 1 – Original Research Article

Impact of Continuous Positive Airway Pressure (CPAP) on Glucose Profiles in Gestational Diabetes: A Pilot Randomized-Controlled Trial

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ABSTRACT

Rationale:

Sleep-disordered breathing (SDB) in pregnancy is associated with a 2-3 fold increased risk for gestational diabetes (GDM). It is unknown whether continuous positive airway pressure (CPAP) treatment of SDB improves glucose control in pregnancy.

Objectives:

In pregnant individuals with GDM, to assess 1) the objective adherence to CPAP and 2) the impact of CPAP on 24-hour continuous glucose monitoring (CGM) profiles.

Methods:

In this pilot randomized-controlled trial, pregnant individuals with GDM and SDB were randomized 1:1 to either CPAP or nasal dilator strips (control). Seventy-two hours of CGM was performed at baseline and ~4 weeks after treatment. Differences in glucose levels at various time points were analyzed using a generalized estimating equations approach.

Measurements and Main Results:

Forty-five individuals with GDM and SDB (mean±SD age of 36.0±4.3, pre-pregnancy body mass index 29.8±7.8 kg/m^2) were randomized to either CPAP (n=22) or control (n=23). Thirty-four (n=16 CPAP, n=18 control) participants had CGM measurements at follow-up. The mean CPAP adherence was 3.0±2.3 hours/night (intention-to-treat). Differences in glucose levels (post-pre) were significantly lower during the early morning sleep period (3am: -0.67 mmol/L [95% CI, -1.28 to -0.06], 4am: -0.86 mmol/L [95% CI, -1.44 to -0.28], 5am: -0.74 mmol/L [95% CI, -1.37 to -0.11] and 6am: -0.80 mmol/L [95% CI, -1.42 to -0.17]) and at noon (-0.75 mmol/L [95% CI, -1.36 to -0.15]) in the CPAP vs. control group ($p<0.05$) (per-protocol).

Conclusions:

CPAP (vs. control) reduced overnight early morning glucose levels in pregnant individuals with GDM and SDB, thus reducing fetal exposure to maternal glucose.

Abstract word count: 250

Key words: sleep apnea, sleep-disordered breathing, pregnancy, gestational diabetes, continuous positive airway pressure, glucose monitoring

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first recognized during pregnancy [1]. The global prevalence of GDM is up to 30% [2, 3], with rates increasing worldwide [4]. Importantly, elevated maternal glucose in GDM is associated with poor neonatal outcomes, such as large-for-gestational age infants [5], neonatal hypoglycemia and neonatal intensive care unit admissions [3, 6-8]. Long-term complications of GDM also include an elevated risk of maternal type 2 diabetes and of obesity in the offspring [3, 9, 10]. Gestational sleep-disordered breathing (SDB) is common, occurring in ~17-45% of pregnant individuals by the third trimester [11-15]. Moreover, the prevalence of SDB in GDM is over 60% in some studies [16, 17]. SDB has also been shown to be associated with a 2-3 fold increased risk of GDM, even after adjusting for body weight [18].

Continuous glucose monitoring (CGM) allows for the measurement of dynamic and temporal changes in glucose, with measurements taken every five minutes, providing a comprehensive measure of fetal exposure to maternal glucose levels [19, 20]. Additionally, CGM allows for nocturnal glucose assessments, which are not measured with conventional daytime capillary blood glucose testing. Even small elevations in glucose in pregnancy are clinically relevant [21], and elevations in nocturnal glucose, rather than daytime glucose, have been associated with the delivery of large-for-gestational age infants [22].

We have previously shown that a 10-unit increase in the apnea-hypopnea index (AHI) was associated with elevated nocturnal (11pm-3am: 0.2 mmol/L [95% CI, 0.04-0.4]) and morning (8am: 0.3 mmol/L [95% CI, 0.08- 0.4]) glucose levels in GDM, even after adjusting for BMI and diabetes medications [16]. However, the causal relationship between SDB in pregnancy

and GDM is still unclear, as interventional studies in this patient population have been sparse [11, 23-29]. Thus, it remains unknown whether treatment of SDB in GDM improves glucose control.

Previous CPAP trials in non-pregnancy that did not show improvements in metabolic outcomes have also been limited by poor adherence. Higher CPAP adherence improves cardiometabolic outcomes. In pregnancy, there are unique sleep complaints that could affect CPAP adherence, and so to power larger, multi-center trials for improving cardiometabolic outcomes in pregnant women with SDB, adherence to CPAP in this population must first be assessed. As such, CPAP adherence is the primary outcome of this trial. In this pilot randomized-controlled trial, we therefore assessed whether individuals with GDM and SDB were able to adhere to CPAP, and whether CPAP improves 24-hour glucose profiles using CGM.

Some of these results have been previously reported in the form of an abstract [30].

METHODS

This was a pilot, multicenter, unblinded randomized-controlled parallel-group study comparing CPAP treatment vs. nasal dilator strip (NDS) control for the treatment of SDB in pregnant individuals with GDM. Participants were recruited from specialized gestational diabetes clinics at the McGill University Health Centre (MUHC) and Centre Hospitalier Universitaire Sainte-Justine (CHU Ste-Justine) in Montreal, Quebec, Canada. The study was registered under clinicaltrials.gov (NCT02245659) and was approved by the Research Ethics Board at both sites (14-004-BMB). All study participants provided informed consent prior to any

study assessments. The protocol and design of this study has previously been reported [31]. Additional details on the methods can also be found in the Online Supplement.

In brief, participants were screened for eligibility if they were pregnant, aged ≥ 18 years and before 34-weeks gestational age with a diagnosis of GDM during their current pregnancy. The criteria for diagnosis of GDM was based on the preferred two-step approach (i.e. initial 50g glucose challenge test followed by a 75g oral glucose tolerance test if indicated) as recommended by the 2013 Canadian Diabetes Association Clinical Practice Guidelines [32]. Participants with pre-existing or pregestational diabetes and multiple pregnancy were not eligible. Other eligibility criteria are available on the Online Supplement.

Participants with GDM were subsequently screened for SDB using a one-night Level 2 screening home polysomnogram. The polysomnogram (Titanium unit, Medcare, Natus Inc., Mississauga, ON) was set up by a sleep technologist in the participant's home. Further details are available in the Online Supplement. A diagnosis of SDB was made if the apnea-hypopnea index (AHI) was ≥ 10, based on Chicago respiratory scoring criteria [33]. During pregnancy, since milder SDB with frequent flow limitation and hypopneas with arousals are common [11, 14, 15, 27, 28, 34-36], the more sensitive Chicago scoring criteria were used [14-16].

Within two weeks of the diagnostic screening sleep study, participants who screened positive for SDB were randomized 1:1 to CPAP vs. control groups using web-based randomization with permuted blocks of varying size (Dacima software, Montreal, Quebec). Participants randomized to the CPAP arm were initiated on nightly auto-adjusted PAP (APAP; 5-18 cm H2O; Philips Respironics). Standard initial CPAP adaptation and education was performed by a respiratory therapist and study nurse. For the control group, nightly nasal dilator strips

(NDS; Breathe Right, GlaxoSmithKline, Brentford, UK) were provided to participants as a control, as has been previously reported [38]. Both groups had follow-up visits every two weeks by the study nurse for education and troubleshooting of side effects until delivery, and for download of the CPAP adherence data via the memory chip in the machine or by Wi-Fi [37]. Participants assigned to CPAP were encouraged to use the device for as many hours as possible until delivery. The strips function by widening the nasal passages, thereby easing breathing and reducing snoring; however, they have not been shown to treat SDB in the pregnant population [39]. Participants in the NDS group were also assessed every two weeks for comfort, side effects and subjective adherence to therapy.

Since this was a pilot study, the primary outcome was objective adherence to CPAP. The secondary outcome was glucose levels at various time points measured by CGM. Intention-to-treat (ITT) was used for assessing objective CPAP adherence from CPAP initiation to delivery by downloading CPAP usage reports at each study visit (every two weeks) to document nightly CPAP hours of usage. At the baseline visit, and again at a follow-up visit 2-4 weeks after starting CPAP or the NDS, the study nurse inserted a subcutaneous single-use, sterile electrode (Enlite, Medtronic Minimed Inc., Northridge, CA) in the abdomen, connected to the CGM device (iPro2®, Medtronic, Northridge, CA). The well-validated iPro2® [40-43] measured interstitial glucose levels every five minutes over a 72-hour period [44]. To obtain accurate measurements, the CGM was calibrated against capillary blood glucose measurements that were measured ~four times/day by the participant, and were verified for accuracy using the minimal mean absolute difference, as previously described [45, 16, 68]. The CGM was blinded so participants could not see their glucose levels. Insulin doses (if applicable) at each visit were documented.

All participants received education on diet and exercise by a dietician and/or nurse in the GDM clinics as part of routine clinical care.

CPAP adherence was reported as the mean usage (h/day) and percent acceptable usage (using the conventional definition of ≥ 4h/night average nightly use for >70% of nights) over all days of the treatment period during pregnancy. Intention-to-treat analysis for adherence to CPAP was performed by assigning an overall of 0h/night of adherence to the individuals who did not use CPAP at all. Completer analysis (per-protocol) included the usage of CPAP among individuals who completed the study.

Analysis of 24-hour glucose profiles was performed using ITT with multiple imputation (primary analysis), and also, using a complete case analysis (secondary analysis). The study statisticians and CGM outcome assessors were blinded to treatment allocation. Statistical analyses were performed using R version 4.3.0 and SAS version 9.4. Between group differences in imputed CGM data was compared using a Welch two-sample t test. In the complete case analysis, the within-group (CPAP, NDS) and between-group (CPAP vs. NDS) differences in glucose levels at all time points (i.e. every five minutes over the 72-hour period) was determined using a generalized estimating equations (GEE) approach for repeated measures to account for the correlation in the data. Pre-pregnancy BMI was selected as an *a priori* confounder in these analyses and the same model was fit while adjusting for BMI [17, 46]. At baseline and follow-up visits, CGM-derived mean 24h, daytime (6am-11pm), late night (11pm-3am) and early morning (3am-6am) glucose values were calculated over the 72-hour CGM measurement period and at each individual hourly time point. Between-group differences in baseline characteristics and

insulin doses were assessed by performing the Wilcoxon Rank sum test. Significance level was set at 0.05.

For this pilot study, the sample size calculation was based on achieving acceptable CPAP adherence rates, similar to what would be expected in the non-pregnant population [31]. For instance, a sample size of 20 in the CPAP group was needed to observe an adherence rate of ≥ 4h/night of usage for 70% of nights with a confidence interval width of ≤ 0.36 with >90% probability.

RESULTS

Participants were recruited from March 2015 until December 2018. A total of 45 pregnant individuals with GDM and SDB were randomized 1:1 to CPAP vs. NDS (Figure 1). Of the 22 participants allocated to CPAP, one participant did not receive CPAP because she was induced and thus delivered early. Four participants discontinued CPAP due to intolerance and were lost to follow-up, and one participant was intolerant to CGM with CPAP data transmission issues, leaving 16 with complete follow-up data available. 5/16 (31.3%) of participants on CPAP were on fixed-CPAP ranging between 6-11 cmH2O, and 11/16 (68.8%) had their device set to auto-CPAP between 4-20 cmH2O. Of the 23 individuals who were randomized to NDS, one delivered early and did not receive the control intervention, and an additional four were lost to follow-up and/or discontinued the NDS (Figure 1), leaving 18 with follow-up data available. Analyses for 24-hour glucose profiles were performed in completers (16 individuals from the CPAP group and 18 in the NDS group). The participants (mean±SD age of 36.0±4.3) who were randomized (n=45) were recruited at an average gestational age of 29 weeks, with a mean pre-pregnancy BMI of

29.8±7.8 kg/m^2. Out of all participants, 58% (26/45) had moderate-severe OSA (AHI ≥ 15 events/h). The mean oxygen desaturation index (ODI) was 4.0±5.5 events/hour. Baseline characteristics, including insulin requirements, were balanced between groups except for a higher total sleep time in the CPAP group (p=0.028; Table 1). Though mean 4% ODI was higher in the control group, the difference was not significant (p=0.20). Baseline characteristics between CPAP and control groups among completers (i.e. n=16 and n=18, respectively) were similar to those who were randomized, except for mean early morning (3am-6am) glucose and total sleep time being slightly higher in the CPAP vs. NDS group (Table 1).

Complete data on the primary outcome, objective adherence to CPAP, was available for 16 out of 22 participants allocated to CPAP. In ITT analysis (n=22), including the 4 participants who discontinued CPAP, the mean objective adherence was 3.0±2.3 hours/day. Complete adherence data was not available for 6 participants (n=4 discontinued CPAP and were lost to follow-up; n=1 had data transmission issues; n=1 had induced delivery before CPAP treatment could begin). More details on adherence data are in the Online Supplement. In the per-protocol analysis (n=16), mean objective adherence was 3.9±2.0 hours/day over a treatment period (CPAP initiation until delivery) of 41.8±18.1 days, and 44% of participants used CPAP for greater than or equal to 4 hours/day for at least 70% of days (Table 2). The mean time interval from CPAP initiation to the post-treatment CGM measurements was 25.7±10.9 days. CPAP adherence was 2.8±2.8 hours/day (ITT) or 4.1±2.5 hours/day (per-protocol) in the two weeks preceding and including the 72-hour CGM measurement period. Additionally, at time of CGM, mean usage of CPAP was 53.4±39.5%.

There were 6/16 (38%) participants on insulin at baseline in the CPAP group vs. 7/18 (39%) in the NDS group. At the post-treatment follow-up visit when CGM measurement occurred (mean gestational age 35.5±2.37 weeks), 11/16 (69%) were on insulin in the CPAP group vs. 11/18 (61%) in the NDS group. The total 24-hour (19.8 vs. 19.1 units) and nighttime (14.7 vs. 11.1 units) insulin requirements at baseline were slightly higher in the NDS group vs. CPAP group (Table 3), but these were not significantly different (p=0.96 and p=0.67 respectively). At the post-treatment follow-up visit at time of CGM measurement, the mean 24-hour (47.7 vs. 39.7 units) and nighttime (34.2 vs. 26.6 units) insulin requirements remained higher in the NDS group vs CPAP group, though not significant (p=0.70 and p=0.52 respectively), and daytime insulin requirements were also similar between groups (p=0.98). Gestational age at follow-up CGM was higher for the CPAP than for the control group (p=0.0096).

In the primary analysis of CGM data using multiple imputation (missing post-treatment CGM data in 11 participants; n=6 CPAP and n=5 NDS), the difference of differences (CPAP-NDS; post-pre) was -0.28 mmol/L, 95% CI -0.80 to 0.25 mmol/L for mean 24-hour glucose, -0.34 mmol/L, 95% CI -0.92 to 0.24 mmol/L for mean glucose values from 11pm-3am, and -0.67 mmol/L, 95% CI -1.2 to -0.16 mmol/L for mean glucose values from 3am-6am, the latter being statistically significant (p=0.01). In a secondary, complete case analysis of CGM data (n=16 in CPAP and n=18 in NDS; ~60,000 total glucose values), the GEE model was fit with an exchangeable correlation structure based on the QIC metric. The model demonstrated that the mean reduction in 24-hour glucose levels was -0.40 mmol/L, 95% CI -0.86 to 0.05 mmol/L, p=0.08 from pre- to post-treatment in the CPAP vs. NDS groups. The mean reduction in glucose levels during the daytime (6am-11pm) was -0.36 mmol/L, 95% CI -0.82 to 0.10, p=0.12, during

late night (11pm-3am) was -0.21 mmol/L, 95% CI -0.86 to 0.44, p=0.52, with a statistically significant reduction during early morning hours (3am-6am) of -0.71 mmol/L, 95% CI -1.27 to -0.16 mmol/L, p=0.01, in CPAP vs. NDS groups. Hourly post-pre and between-group differences are shown in Table 4. Twenty-four-hour continuous glucose monitoring profiles showed that glucose levels in the CPAP group post-intervention vs. baseline were generally lower starting at 3am until mid-afternoon, with significant within-group reductions from 4-8am (Figure 2A). Increases in glucose post-intervention were observed from late afternoon to the following evening, with significant differences at 4pm and 9-10pm. For the NDS control group, post- vs. pre-intervention glucose levels were generally higher from mid-afternoon until early morning the next day. Within-group significantly higher levels were observed in NDS post- vs. pre- at 12pm, 4pm, from 7-10pm and midnight to 2am (Figure 2B). Analysis of the difference of differences using GEE between the CPAP and the control groups revealed that there was a greater reduction in glucose levels in the CPAP vs. control group in a 24-hour period (Figure 2C). Significant reductions were observed from 3-6am (range of glucose reduction -0.7 to -0.8 mmol/L), and again at 12pm (Table 4). Similar results were observed when adjusting the model for pre-pregnancy BMI.

DISCUSSION

To our knowledge, this is the first randomized controlled trial assessing the impact of CPAP treatment on 24-hour glycemic control in pregnant individuals with GDM and SDB. This pilot study showed that CPAP adherence was ~3h/night in intention-to-treat analysis (3.9h/night in per protocol analyses), which is similar to recent large cardiovascular trials in SDB involving

non-pregnant participants (eg. 3.3h/night in the SAVE trial [47], 2.8h/night in ISAAC trial [48]). Two weeks prior to follow-up CGM testing, mean CPAP usage improved to 4.5h/night, suggesting a possible adaptation period for CPAP in individuals with GDM. Despite the modest CPAP adherence, in post-hoc analyses, we found that the between-group (CPAP vs. control) CGM results showed that overnight, and especially in the early morning, glucose levels were significantly lower in the CPAP vs. control groups.

By using CGM monitoring, we were able to show novel findings assessing the impact of CPAP on longitudinal and temporal changes in glucose levels in pregnancy. Our results indicate that while there were no significant differences between groups in 24-hour mean glucose levels, improved glycemic control for the CPAP group was observed in the early morning hours (3-6am) and at 12pm. Insulin requirements were similar in both groups. Thus, it is unlikely that the lower glucose levels observed in the CPAP group are due to the actions of insulin. The increase in glucose levels observed in the control group in our study at post vs. pre-treatment assessments (~ 35 vs. 29 weeks gestation) likely reflect a physiologic increase in insulin resistance in GDM as pregnancy progresses, resulting from growth of the placenta, and subsequent increases in hormone levels (e.g. human placental lactogen, estrogen, progesterone) which are known to interfere with the actions of insulin [49-51]. Thus, it is possible that CPAP may partly mitigate the increase in glucose levels (and potentially insulin resistance) as pregnancy progresses, with untreated SDB and GDM likely exacerbating this process.

Our findings suggest that SDB may be a novel reversible risk factor for GDM by contributing to poor overnight glucose control in pregnancy [16-18, 52, 53], independent of obesity. One RCT of 36 pregnant participants with GDM by Chirakalwasan et al. showed that

there was improved insulin secretion among those adherent to CPAP vs. controls after two weeks (per protocol analysis) [23]. However, no significant differences were identified in the primary or secondary metabolic outcomes in the intention-to-treat analysis. This study did not use CGM to measure 24-hour glucose profiles. Our observations of a reduction in early morning glucose levels, rather than daytime glucose, in the CPAP vs. control groups may be due to reversal of SDB-specific increases in glucose [54]. In one study, Rahmi et al. showed that obesity in pregnancy was associated with elevated mean nocturnal glucose levels at night vs. non-obese controls [55]. However, this study did not screen individuals for SDB, making it plausible that a substantial proportion of the study population had undetected and untreated SDB. In one study of CPAP withdrawal in a non-pregnant population, SDB dynamically increased nocturnal glucose levels in individuals without diabetes, but morning oral glucose tolerance testing remained normal, suggesting possible rapid recovery of metabolic function upon awakening or compensation by endogenous insulin secretion [56]. As has been shown in another study [57], there may also be a carryover effect of CPAP with possible improvement in postprandial glucose levels, as suggested by significant improvements in lunch-time glucose levels in our study in CPAP vs. controls. However, given the small sample size and lack of reliable documentation of timing of meals, these findings would need to be replicated in future, larger studies.

In a recent paper by Law and colleagues [22], who used CGM to measure glucose control in 162 pregnant individuals with GDM, elevated nocturnal glucose levels (12:30am-6am) were significantly higher (~ 6.0 vs. 5.5 mmol/L) among women who delivered a large-for-gestational-age (LGA) infant vs. non-LGA infant. Importantly, there was no difference in the glucose values during the daytime between groups nor the time in range between the groups, suggesting that

nocturnal glucose levels, even with the relatively modest mean difference of 0.5 mmol/L, were the most important factor driving the overall differences. Importantly, SDB was once again not assessed in this study. While we were not powered to assess for LGA infants in our study, CPAP-related reductions by ~0.7mmol/L in early morning glucose levels as shown in our study is therefore an important justification for future studies powered to examine whether CPAP reduces the incidence of LGA infants in GDM. Infants born LGA are at high risk for birth complications, hypoglycemia and fetal death, and as such, LGA is a critical outcome in the prevention and control of GDM [58, 59].

Based on our results, it is plausible that fetuses of individuals with GDM and untreated SDB are exposed to higher nocturnal glucose levels than those treated with CPAP. This is consistent with our prior work showing that greater severity of SDB was associated with elevated nocturnal and morning glucose levels in GDM [16]. Moreover, another study in pregnant individuals without GDM also showed that increasing severity of SDB and oxygen desaturation index was associated with higher levels of glucose using 24-hour CGM [60]. Extrapolating from the HAPO study [21], these observations may suggest an elevated risk of perinatal complications related to fetal exposure to maternal hyperglycemia. Undiagnosed and undetected SDB may be especially relevant since many babies with macrosomia are born to mothers who are obese, but without GDM [61]. Thus, SDB may be an additional factor related to obesity contributing to macrosomia, that currently is not routinely screened for in GDM [62, 63].

Our findings may also be relevant to the theory of the developmental origins of health and disease. Developmental programming is the phenomenon by which events occurring in the

early stages of development, even before pregnancy, can affect the occurrence of various health conditions like diabetes, cardiovascular diseases, asthma and more [64]. Accordingly, high circulating levels of glucose in mothers with GDM have been associated with significant changes in the epigenome of the infants, more specifically in the DNA methylation patterns, resulting in an increased susceptibility to metabolic disease later in life [65]. As such, if CPAP therapy could potentially contribute to lowering glucose levels in patients with GDM and SDB, this could offer a protective mechanism against obesity and diabetes later in life. Animal studies by Gozal et al. [66, 67] have shown that exposure to sleep fragmentation and intermittent hypoxia during the gestational period increases insulin resistance and markers of obesity in the offspring.

Our study is not without limitations. Since this is a pilot trial, all results are considered preliminary and should be interpreted with caution. Importantly, possible lifestyle differences between groups may have occurred, such as different nutritional habits and levels of physical activity. This was mitigated to some extent by both groups receiving standard of care with respect to education on lifestyle measures from the dietician and treating physician. Since we did not exclude individuals who required insulin, variations in dosing may influence our glycemic outcomes. However, we carefully examined insulin doses at baseline and at time of follow-up CGM to ensure the effect could not be explained by different insulin doses between the two groups. Due to the small sample size of the pilot trial, we did not do further analyses on adherent vs. non-adherent participants.

Our study demonstrated improved glycemic profiles of pregnant women, particularly in the early morning sleep period. Assessing for nocturnal glycemic control is normally missed with conventional daytime-only capillary blood glucose checks that are part of monitoring

recommendations for individuals with GDM. As such, our pilot study results indicate that SDB may be an undetected reversible risk factor for fetal exposure to elevated maternal glucose levels. Future, larger studies with strategies to improve overall adherence to therapy of SDB in this population are needed to replicate our findings and to assess for the impact of CPAP on improving perinatal outcomes in GDM. If verified, these results might suggest that screening and treatment for SDB may reduce the burden of GDM.

FIGURE LEGENDS

Figure 1: Participant flow diagram

CONSORT flow diagram. CONSORT = Consolidated Standard of Reporting Trials. CPAP = Continuous Positive Airway Pressure. CGM = Continuous Glucose Monitoring. The number of participants who were enrolled, assessed for eligibility, randomized to each treatment arm, and included in the analysis.

Figure 2: Mean 24-hour glucose profiles during pre- and post-treatment continuous glucose monitoring (CGM)

(A) Difference of mean glucose levels pre- and post-intervention for the CPAP group. **(B)** Difference of mean glucose levels pre- and post-intervention for the NDS group. **(C)** Difference of differences between CPAP and NDS groups. 95% confidence interval bands are shaded around respective curves. Significant differences between groups ($p < 0.05$) are identified by red star symbols.

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Table 1. Baseline Characteristics of the Study Population*

	Intention-to-treat (n=45)		Per-protocol (n=34)	
	CPAP (n=22)	**Control (n=23)**	**CPAP (n=16)**	**Control (n=18)**
Age, years	36.5 (4.7)	35.5 (4.0)	38.4 (4.9)	35.3 (4.5)
Race, n (%)				
White	13 (59.1)	8 (34.8)	9 (56.3)	7 (38.9)
Black	3 (13.6)	3 (13.0)	2 (12.5)	1 (5.6)
Middle Eastern	3 (13.6)	5 (21.7)	2 (12.5)	3 (16.7)
Other	3 (13.6)	7 (30.4)	3 (18.8)	7 (38.9)
Gestational age at baseline (weeks)	30.1 (2.9)	28.7 (4.6)	32.0 (2.8)	27.6 (4.6)
Gestational weight gain (kg)	10.0 (7.3)	8.8 (6.6)	10.8 (7.5)	9.4 (6.9)
Pre-pregnancy BMI (kg/m^2)	29.1 (9.1)	30.5 (6.4)	31.0 (9.8)	29.1 (5.4)
Neck circumference (cm)	36.8 (3.1)	35.7 (3.3)	39.5 (3.0)	35.7 (3.7)
Hypertension disorder of pregnancy, n (%)	3 (13.6)	1 (4.3)	1 (6.3)	1 (5.6)
Mean fasting glucose (mg/dL)	93.2 (8.3)	92.6 (16.1)	99.1 (7.2)	91.9 (18.0)
Mean 24-hour glucose (mg/dL)	105.4 (8.3)	104.5 (12.6)	113.4 (8.4)	103.5 (13.3)
Mean late night (11pm-3am) glucose (mg/dL)	103.0 (16.3)	99.6 (13.6)	110.2 (17.3)	98.5 (14.1)
Mean early morning (3am-6am) glucose (mg/dL)	94.7 (10.4)	90.0 (12.3)	**104.1 (8.2)**	**89.9 (12.2)**
Use of insulin at enrolment (yes), n (%)	9 (40.9)	11 (47.8)	6 (37.5)	7 (43.8)
Mean 24-hour insulin dose (units)	18.0 (32.4)	23.5 (42.4)	19.1 (36.8)	21.0 (45.2)
Mean total daytime insulin dose (units)	6.4 (19.7)	5.4 (18.9)	7.9 (22.9)	5.2 (20.5)
Mean total nighttime insulin dose (units)	11.6 (19.0)	17.9 (26.8)	11.1 (20.4)	15.5 (27.8)
Use of metformin (yes), n (%)	1 (4.5)	1 (4.3)	1 (6.3)	1 (5.6)
Epworth sleepiness scale score	7.0 (4.0)	7.2 (5.0)	8.6 (4.0)	8.1 (5.1)
Total sleep time (hours)	**6.9 (1.1)**	**6.3 (1.1)**	**7.6 (1.2)**	**6.4 (1.1)**
Apnea-hypopnea index (events/hour)	19.4 (8.7)	21.1 (10.5)	21.7 (9.6)	22.3 (11.3)
4% oxygen desaturation index (events/hour)	2.6 (3.3)	5.2 (6.8)	3.2 (3.7)	5.9 (7.5)

Microarousal index (events/hour)	30.6 (7.5)	30.3 (10.4)	34.4 (7.7)	31.4 (11.2)

Definition of abbreviation: CPAP = Continuous Positive Airway Pressure.

Data are mean ± SD unless otherwise specified. Hypertension was considered to be present if systolic or diastolic blood pressure >140 or >90 mm Hg respectively. Gestational weight gain was defined from pre-pregnancy to date of enrolment. Mean fasting glucose levels were obtained from oral glucose tolerance tests (OGTT). Mean 24-hour, evening, sleeping and daytime glucose levels were obtained from continuous glucose monitoring (CGM) for three consecutive days. Total sleep time, apnea-hypopnea, oxygen desaturation and microarousal indices were obtained from a level 2 screening home polysomnogram. * All available data was used in the primary analysis (i.e. all participants who were randomized and completed baseline assessments). In **bold** are significant differences ($p<0.05$) found between groups (CPAP vs NDS) using the Wilcoxon Rank-sum test.

Table 2. CPAP Adherence Data*

	CPAP (n=16)
Duration of treatment period (CPAP start to delivery) (days)	41.8 (18.1)
Average usage (all days) (hours/day)	3.87 (2.01)
Average usage (days used) (hours/day)	4.58 (2.01)
% Days used minimum of 4h/day	54.5 (31.0)
CPAP used < 2 hours/night, n (%)	3 (19)
CPAP used 2-4 hours/night, n (%)	6 (38)
CPAP used ≥ 4 hours/night, n (%)	7 (44)
Days with device usage	37.9 (18.5)
Days without device usage	4.27 (3.31)
P90 (cm H_2O)	9.14 (2.95)
Residual AHI	1.62 (1.23)
Time in Large Leak (avg per day) (min)	1.95 (3.34)
Time interval from CPAP start to CGM measurement (days)	25.7 (10.9)
Average CPAP usage 2 weeks before CGM (hours/day)	4.53 (2.18)

Data are mean ± SD unless otherwise specified. Treatment period corresponds to time of CPAP start until delivery. P90 was defined as the pressure delivered by the CPAP device in auto- mode for ≥ 90% of the time. Residual AHI (Apnea Hypopnea Index) was the AHI after being on auto-CPAP. * All available CPAP data was used in the per-protocol analysis shown here. Average usage (days used), % Days used minimum 4h/day, Days with and without device usage, Time in large leak and Average CPAP usage 2 weeks before CGM was missing for n =1 participant.

Table 3. Insulin doses at baseline and at time of post-treatment follow-up visit

	CPAP (n=16)	**NDS (n = 18)**	**p-value**
Gestational age at baseline (weeks)	29.7 (2.77)	27.6 (4.61)	0.30
Gestational age at post-treatment follow-up visit (weeks)	**36.6 (2.11)**	**34.5 (2.20)**	0.0096
Total 24-hour insulin (units) at baseline	19.1 (36.8)	19.8 (44.1)	0.92
Total 24-hour insulin (units) post-treatment	39.7 (53.9)	47.7 (64.4)	0.78
Change in total insulin (units)	20.6 (24.4)	27.8 (34.7)	0.62
Total daytime insulin (units) at baseline	7.94 (22.9)	5.17 (20.5)	0.52
Total daytime insulin (units) post-treatment	13.1 (32.7)	13.4 (34.0)	0.68
Change in daytime insulin (units)	5.19 (14.4)	8.28 (18.2)	0.31
Total nighttime insulin (units) at baseline	11.1 (20.4)	14.7 (27.2)	0.86
Total nighttime insulin (units) post-treatment	26.6 (30.4)	34.2 (37.2)	0.62
Change in nighttime insulin (units)	15.4 (16.0)	19.6 (20.8)	0.63

Data are mean ± SD. Post-treatment assessment of insulin doses occurred at the time of the visit for the post-treatment CGM measurement. Participants who were not lost to follow-up (i.e. analyzed groups) are represented in this table. Change in insulin represents post-treatment minus baseline. Daytime insulin indicates short-acting insulin doses taken during the day. Nighttime insulin indicates long-acting insulin doses taken at bedtime.

Table 4. Between-group differences of glucose levels (mmol/L) unadjusted for BMI

24-hour time	NDS POST-PRE difference	CPAP POST-PRE difference	Difference of differences (CPAP – NDS)
00:00	**0.60 (0.09 to 1.11)**	0.46 (-0.11 to 1.02)	-0.15 (-0.91 to 0.62)
01:00	**0.50 (0.07 to 0.94)**	0.38 (-0.24 to 1.00)	-0.13 (-0.88 to 0.63)
02:00	**0.53 (0.07 to 0.99)**	0.05 (-0.45 to 0.55)	-0.48 (-1.15 to 0.20)
03:00	0.43 (-0.07 to 0.94)	-0.24 (-0.58 to 0.10)	**-0.67 (-1.28 to -0.06)**
04:00	0.42 (-0.07 to 0.91)	**-0.44 (-0.74 to -0.13)**	**-0.86 (-1.44 to -0.28)**
05:00	0.13 (-0.37 to 0.62)	**-0.61 (-1.00 to -0.23)**	**-0.74 (-1.37 to -0.11)**
06:00	-0.04 (-0.45 to 0.36)	**-0.84 (-1.32 to -0.36)**	**-0.80 (-1.42 to -0.17)**
07:00	-0.25 (-0.73 to 0.22)	**-0.75 (-1.24 to -0.26)**	-0.49 (-1.18 to 0.19)
08:00	-0.26 (-0.74 to 0.22)	**-0.69 (-1.28 to -0.10)**	-0.42 (-1.18 to 0.34)
09:00	-0.12 (-0.51 to 0.27)	-0.53 (-1.41 to 0.34)	-0.41 (-1.37 to 0.55)
10:00	0.07 (-0.25 to 0.40)	-0.44 (-0.90 to 0.03)	-0.51 (-1.08 to 0.06)
11:00	0.24 (-0.20 to 0.67)	-0.02 (-0.40 to 0.36)	-0.26 (-0.83 to 0.32)
12:00	**0.65 (0.37 to 0.92)**	-0.11 (-0.65 to 0.43)	**-0.75 (-1.36 to -0.15)**
13:00	0.19 (-0.14 to 0.52)	-0.35 (-0.97 to 0.27)	-0.54 (-1.24 to 0.16)
14:00	0.22 (-0.08 to 0.52)	-0.17 (-0.72 to 0.37)	-0.39 (-1.01 to 0.23)
15:00	0.29 (-0.13 to 0.70)	0.20 (-0.27 to 0.68)	-0.08 (-0.71 to 0.55)
16:00	**0.63 (0.14 to 1.11)**	0.36 (-0.03 to 0.76)	-0.26 (-0.89 to 0.36)
17:00	0.41 (-0.18 to 0.99)	0.16 (-0.38 to 0.70)	-0.24 (-1.04 to 0.56)
18:00	0.37 (-0.09 to 0.82)	0.14 (-0.49 to 0.77)	-0.23 (-1.01 to 0.55)
19:00	**0.52 (0.17 to 0.87)**	0.21 (-0.33 to 0.75)	-0.32 (-0.96 to 0.33)
20:00	**0.50 (0.12 to 0.89)**	0.26 (-0.20 to 0.73)	-0.24 (-0.84 to 0.36)

21:00	**0.59 (0.07 to 1.10)**	**0.64 (0.21 to 1.06)**	0.05 (-0.62 to 0.71)
22:00	**0.62 (0.00 to 1.24)**	**0.53 (0.00 to 1.07)**	-0.09 (-0.90 to 0.73)
23:00	0.39 (-0.14 to 0.93)	0.45 (-0.02 to 0.93)	0.06 (-0.66 to 0.77)

Data are mean (95% confidence interval). Glucose levels were obtained from continuous glucose monitoring for three days and averaged on the hour, which was performed pre-intervention (NDS or CPAP) and 2-4 weeks post-intervention. At hours 3, 4, 5, 6 and 12, the difference between the groups is statistically significant (shown in bold).

Figure 1. Participant flow diagram

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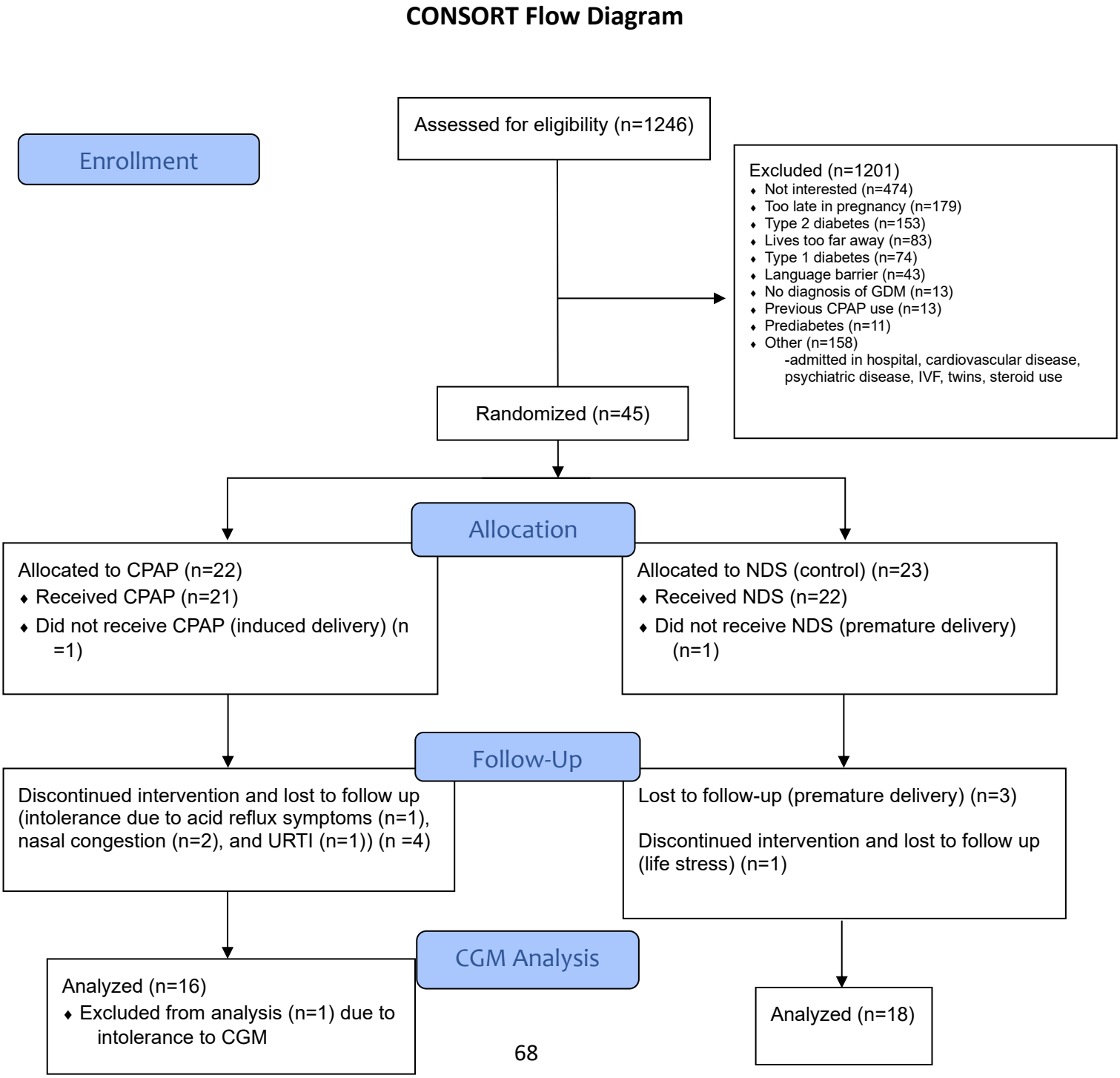


Figure 2A. Difference of mean glucose levels pre- and post-intervention for the CPAP group.

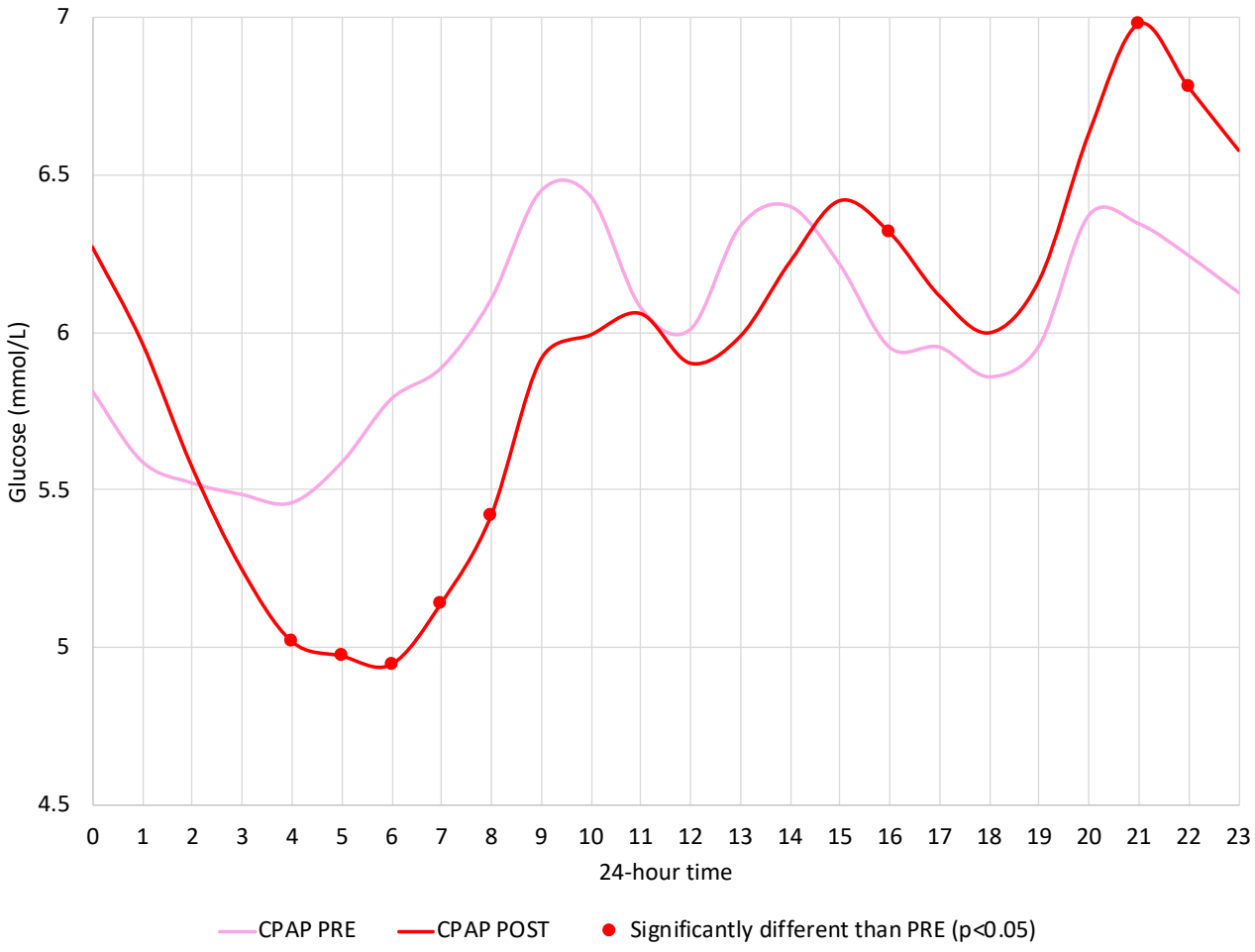


Figure 2B. Difference of mean glucose levels pre- and post-intervention for the nasal dilator strip (NDS) group

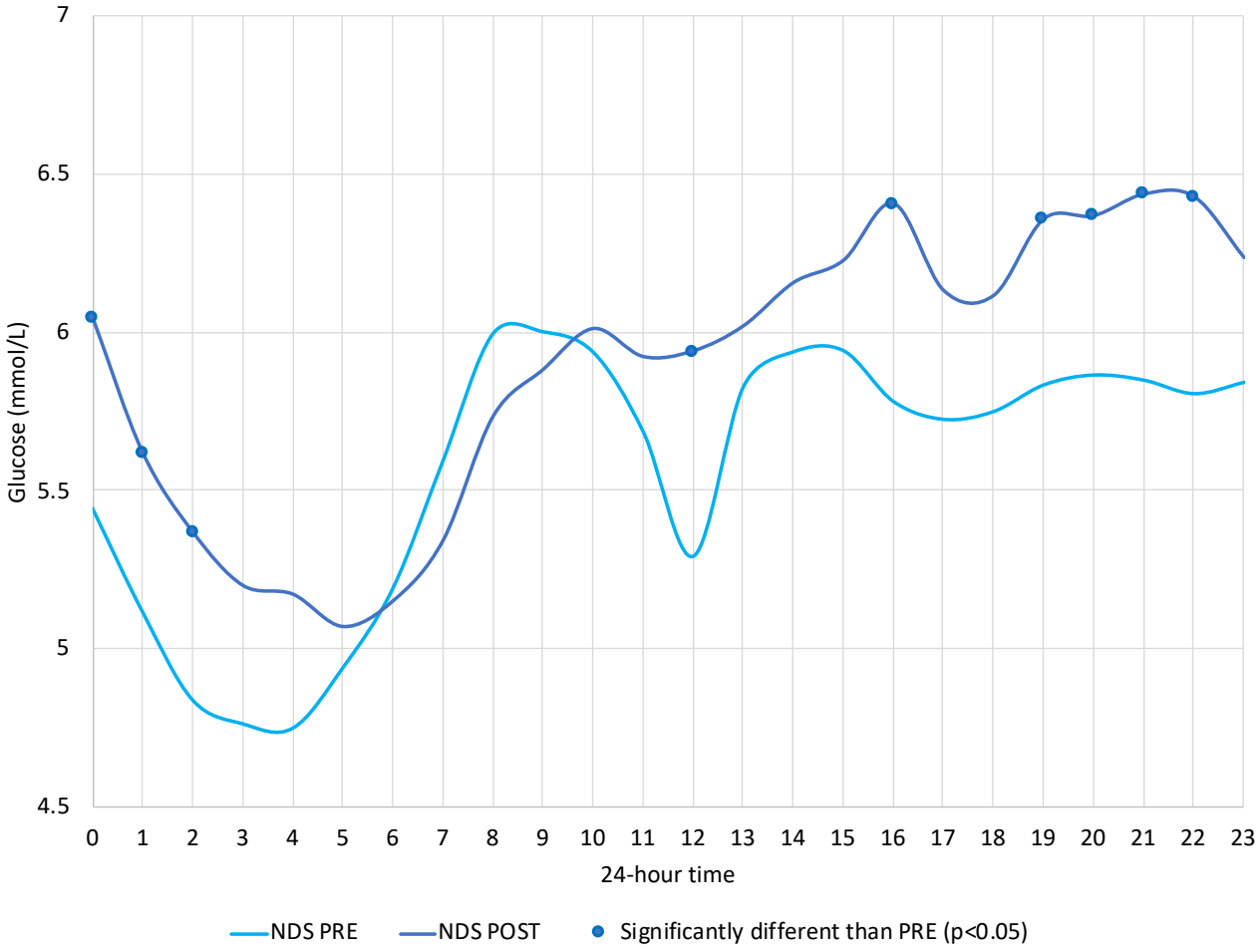
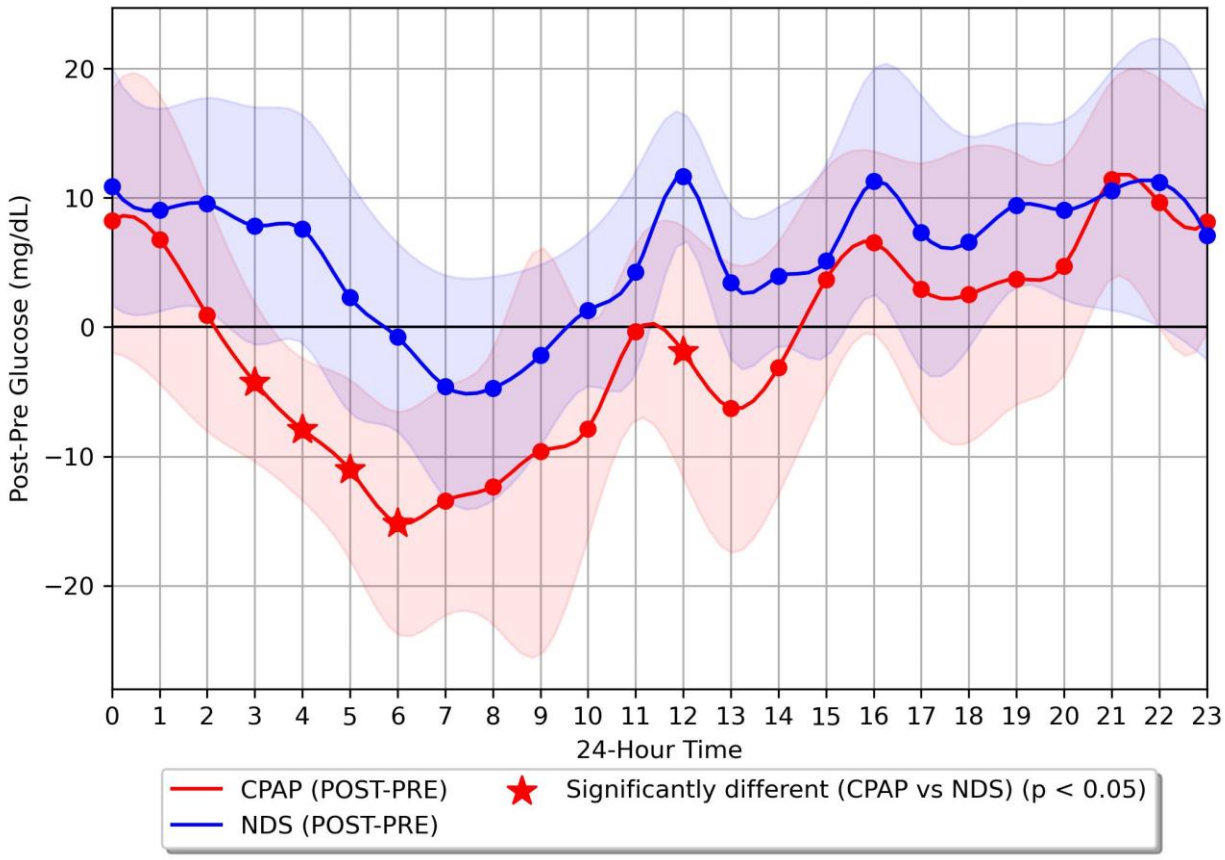


Figure 2C. Difference of differences between CPAP and NDS groups



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Impact of Continuous Positive Airway Pressure on Glucose Profiles in Gestational Diabetes: A Pilot Randomized-Controlled Trial

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ONLINE DATA SUPPLEMENT

METHODS

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were described in a previously published protocol (1). Participants were screened for eligibility if they were pregnant, aged ≥ 18 years and between 20- and 34-weeks gestational and referred to the gestational diabetes mellitus (GDM) clinic at the McGill University Health Centre (MUHC) or the Centre Hospitalier Universitaire Sainte-Justine (CHU St-Justine).

A) Diagnosis of GDM: The criteria for diagnosis of GDM was based on the preferred two-step approach. A positive screening non-fasting 50-g glucose load (24-28 weeks gestation) of >11.1 mmol/L indicated a diagnosis of GDM. If the 50g test was abnormal but not in the diabetic range (7.8-11.1 mmol/L), then a fasting, standard, 75-g oral glucose tolerance test (OGTT) was performed. GDM was diagnosed in our study with either an abnormal 50-g glucose tolerance test with level ≥11.1 mmol/L or from one of the following from the 75-g OGTT: 1) fasting glucose ≥5.1 mmol/L, 2) 1-h glucose ≥10.0 mmol/L, or 3) 2-hr glucose ≥8.5 mmol/L (2). These results needed to occur in the absence of pre-existing or pregestational diabetes.

B) Diagnosis of SDB: Participants were scheduled for a one-night level 2 home polysomnogram within one week of their initial GDM clinic visit. The complete polysomnogram (Titanium unit, Medcare, Natus Inc., Mississauga, ON) was set up by a sleep technologist in the participant's home and all signals were verified. The sleep recording device was then picked up by a driver in the morning and returned to the

sleep laboratory after the sleep recording was completed. The data from the recorder was then downloaded and the Registered Polysomnographic Technologist scored the sleep studies, which were then reviewed by one of the study's sleep physicians. To ensure scoring reliability, standard quality assurance measures such as ensuring a minimum of ~4h total sleep time were applied. To ensure accurate scoring of respiratory events, oximetry, electroencephalogram (EEG) and nasal cannula signals were verified for adequate signal quality. American Academy of Sleep Medicine (AASM) criteria were used to score sleep-wake state, arousals and periodic limb movements (3), and respiratory events were scored using Chicago criteria (4). A diagnosis of SDB was made based on features indicative of SDB (AHI ≥ 10 according to Chicago criteria). During pregnancy, milder SDB with less oxygen desaturation but frequent flow limitation and arousals is common (5-10). As such, the more sensitive Chicago scoring criteria was used for diagnosis of SDB, as has been used in prior studies in pregnancy (11, 12).

Participants were excluded if they had known pre-gestational Type 1 or 2 diabetes, multiple pregnancy, conception by IVF, chronic renal disease, cardiovascular disease, stroke, active psychiatric disease, active malignancy, HIV infection, Hepatitis C or B, prior treatment for SDB, occupation involving shift work or travel across time zones, or inability to provide informed consent. Cigarette smoking, alcohol consumption and the use of illicit drugs was also exclusion criteria. Participants who had severe SDB (AHI ≥30 events per hour) accompanied by notable daytime sleepiness (ESS ≥15), or significant oxygen desaturation (4% oxygen desaturation index ≥30 or sustained hypoxia <80%), were excluded from the study and were referred for urgent evaluation at the Sleep Clinic in our establishment.

NDS as a control

For CPAP studies, there has been significant uncertainty on the optimal control group. A sham CPAP device is similar in appearance to a therapeutic CPAP, but it can cause sleep disruption because of discomfort and frustration from wearing a mask that delivers suboptimal treatment pressures (13). In a recent large RCT that randomized participants to sham-CPAP or therapeutic CPAP, mean nightly usage of sham-CPAP was less than therapeutic CPAP (3.4h vs. 4.2h) (14). In pregnant individuals, due to the greater sleep disturbances resulting from pregnancy itself (15), a sham CPAP device may interfere with sleep quality and shorten sleep duration. This in turn might worsen glucose control and therefore bias the results in favor of the active intervention arm, since sleep fragmentation is independently associated with poor glucose metabolism (16). Thus, sham CPAP was not used as the control in this study.

Randomization and treatment

Eligible participants were randomized 1:1 to CPAP vs control groups, using web-based randomization with permuted blocks of varying size (Dacima software, Montreal, Quebec). Once all complete participant information concerning eligibility was entered (i.e. age, AHI, GDM diagnosis, medical problems, etc.), the website then displayed the group to which the participant was randomized. Participants allocated to CPAP were given a variety of nasal masks to try, and if mouth-breathing or intolerance occurred, then an oronasal mask was fitted. Supplementary ad-hoc visits or telephone calls were made by the study nurse if difficulties with adaptation occurred.

Repeated CGM at follow-up

Some individuals (n=15) had another repeated CGM measurement two weeks after the first follow-up CGM, but many delivered prior to this so only the first follow-up CGM was used for all participants.

RESULTS

Table 1 - Baseline characteristics: missing data

All available data was used in the primary analysis for CPAP adherence (i.e. all participants who were randomized and completed baseline assessments). Gestational weight gain and pre-pregnancy BMI were missing from n=1 participant in the Control group. Mean fasting glucose was missing in a total of n=9 participants (n=3 in the CPAP group and n=6 in the Control group). Mean 24-hour, late night and early morning glucose levels were missing from n=1 participant in the CPAP group. Epworth Sleepiness Scale score was missing from n=1 participant in the CPAP group and n=2 participants in the Control group. 4% oxygen desaturation index and microarousal index was missing from n=1 participant in the CPAP group.

Adherence data

Intention-to-treat analysis included all 22 participants randomized to CPAP:

- 16 who completed the study.

- 4 who discontinued the study and were lost to follow-up (3 of which did not use CPAP at all and so were assigned 0 h/night average usage, and one who had an average usage of 0.40 h/night).
- One who did not receive CPAP because she delivered early (assigned 0h/night).
- One who did not complete the post-treatment CGM and had some CPAP data transmission issues, who had an average usage of 2.72 h/night.

Per-protocol analysis included only the 16 participants who completed the study (pre- and post-CGM).

CGM data

For the CPAP group, CGM data was complete in 13/16 participants. 1/16 participant was missing 1 day of pre-treatment CGM data, and 2/16 participants were missing half a day of post-treatment follow up-visit CGM data. For the NDS group, CGM data was complete for 15/18 participants. 2/18 participants were missing 1 day of post-treatment CGM data and 1/18 participants was missing half a day of post-treatment CGM data. All other available data from these participants was still used in the analysis.

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Linking section: Importance of adherence to therapy in SDB

The first-line treatment for SDB is CPAP therapy. However, a major hurdle exists – adherence rates are low, between 30-60% [240]. Inconsistent CPAP use significantly weakens its effectiveness, leaving many patients with SDB vulnerable to its associated complications, such as an increased risk of comorbid cardiometabolic disorders [59, 103, 241], persistent daytime sleepiness [242, 243], and a significantly diminished quality of life [240].

Therefore, for pregnant women with SDB to experience the optimal benefits of CPAP therapy, such as reduced blood pressure and reduction in preeclampsia risk [38, 39], adherence to treatment is imperative. As such, to examine the systemic and metabolic effects of CPAP in pregnant patients with SDB and GDM, it is first important to assess adherence and ensure optimal CPAP use in this population.

A key study by Kribbs et al. [244] investigated objectively measured CPAP adherence in the general population. This study found that only 46% of participants met the criteria for regular use, defined as using CPAP for at least 4 hours on at least 70% of the nights [244, 245]. Further studies using objective monitoring confirmed similar average nightly CPAP use of around 4.7 hours [246, 247]. As such, a trend of less-than-optimal adherence emerged, and it became clear OSA patients have difficulty using CPAP consistently throughout the night. It is unknown what threshold for adherence is optimal, but one study in the non-pregnant population found a dose-dependent relationship between increased CPAP use and reducing daytime sleepiness, but only up to 7 hours of use [248]. Studying adherence to treatment in pregnancy is especially important because of the higher prevalence of SDB in this population (17-45% [6]), and the implications for both maternal and fetal health and well-being.

Beyond investigating adherence rates, Kribbs et al. [244] aimed to identify factors that could help predict which patients were more likely to be adherent to CPAP therapy. Specifically in this study, it was found that patients who adhered to CPAP therapy tended to have higher levels of education and professional occupations [244]. More recent studies have confirmed that socioeconomic status may play a role in CPAP adherence, suggesting that patients with higher income have an increased odds of CPAP adherence [249-251]. Other factors like marital status, partner involvement, attitude towards treatment, and partner's sleep quality have also all been suggested to predict long-term adherence behaviour [252].

Indeed, a central theme in CPAP research has become the identification of significant predictors for adherence [252-254]. Investigators have touched on a wide range of elements that might influence how well patients adhere to CPAP therapy. These factors fall into five main categories: patient characteristics, disease severity and characteristics, the design and features of the CPAP machine itself, how the therapy is initially introduced, and the patient's emotional and social well-being [240]. Several studies have identified an association between daytime sleepiness and CPAP adherence [244, 255, 256].Despite this comprehensive examination, no single factor has emerged as a consistent predictor of adherence [240]. Instead, the evidence suggests that a complex interplay of unique factors for each individual likely determines how well they adapt and adhere to CPAP treatment [240].

Adherence to CPAP in pregnancy is not well characterized, as there have been few interventional trials exploring this to date. One study found the average reported CPAP usage was 6 hours per night for 7 days a week, however the sample size was small (n=7) [42]. Two other studies with small sample sizes (n=12) demonstrated high mean CPAP adherence as well

(5.4 h/night [41] and 7 h/night [40]), yet a more recent trial with a larger sample randomized to CPAP (n=153) found a mean average-CPAP use of 2.5 h/night [230]. As such, pregnant individuals' adherence to CPAP remains to be better characterized.

Therefore, a key research goal in treating pregnant women with SDB is to identify and better characterize CPAP adherence in pregnancy. This includes investigating specific factors that distinguish women who consistently use CPAP from those who do not. Night-to-night adherence in pregnancy remains unclear, but understanding these patterns could offer valuable insights, particularly since adherence during the first week of treatment is a strong predictor of long-term usage in the general population [54, 255, 257, 258]. With the emergence of alternative treatments like MAS, it is also important to understand how pregnant women adhere to this form of treatment. It would be particularly interesting to address whether adherence patterns for MAS differ from those observed with CPAP, specifically in the pregnant population. Subjective adherence is often overestimated by the patient (by 69±110 min) and inaccurate [244]. As such, with embedded electronic chips, it is now possible to obtain objective measures of adherence.

Thus, a critical gap exists in our understanding of how pregnant women adhere to SDB treatments like CPAP and MAS on a night-to-night basis over time (longitudinal adherence patterns). This knowledge gap hinders the development of optimal treatment plans for this vulnerable population. The next chapter aims to bridge this gap by investigating these patterns, ultimately paving the way for improved treatment regimens and efficacy for pregnant women with SDB.

Chapter 4: Manuscript 2 – Research Letter

Patterns of Adherence to Continuous Positive Airway Pressure and Mandibular Advancement Splints in Pregnant Individuals with Sleep-Disordered Breathing

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ABSTRACT

Purpose: Night-to-night adherence to sleep-disordered breathing (SDB) treatment with either continuous positive airway pressure (CPAP) or mandibular advancement splints (MAS) in pregnancy has not been well characterized. The objective of this study was to assess night-to-night adherence patterns from existing CPAP and MAS data in pregnancy.

Methods: Three separate pregnancy cohorts evaluating treatment for SDB in the second and third trimester were used: 1) CPAP in gestational diabetes mellitus (GDM), 2) CPAP in hypertensive disorders of pregnancy (HDP), and 3) mandibular advancement splints (MAS). The first 30 days of objective adherence data obtained from CPAP and MAS devices were used in this descriptive analysis.

Results: Data from 37 CPAP users and 15 MAS users was analyzed. For the GDM and HDP cohorts, three patterns of adherence were observed: 1) consistent CPAP users (38%), 2) improved CPAP usage after initial adaptation (16%), and 3) inconsistent CPAP users (46%). For the MAS cohort, the three observed patterns of adherence were: 1) consistent MAS users (47%), 2) initial usage with subsequent decrease in adherence (20%), and 3) inconsistent MAS users (33%). Participant characteristics (demographics, disease severity) were similar between adherence groups.

Conclusion: Overall, objective night-to-night adherence patterns revealed that almost half of CPAP and MAS users had difficulty adapting to treatment in the first 30 days of treatment. Early usage patterns in pregnancy may provide insight into identifying patients who are at risk for poor adherence and for developing tailored and timely interventions to enhance adherence to therapy.

Abstract word count: 245 words

Key words: sleep apnea, sleep-disordered breathing, pregnancy, continuous positive airway pressure, oral appliance, mandibular advancement splint, night-to-night adherence

INTRODUCTION

Maternal sleep-disordered breathing (SDB) occurs in 17-45% of women by the third trimester of pregnancy and is associated with adverse pregnancy outcomes [1-3]. Interventional studies to date demonstrate that poor adherence to CPAP remains a major barrier for the effective treatment of SDB in pregnancy [4-6].

Among nonpregnant individuals, CPAP usage patterns in the first few days has been shown to forecast future adherence [7]. Analysis of night-to-night CPAP usage data revealed that those who skip nights of CPAP are more likely to use it for a shorter duration on the nights they do use it [7], with this trend becoming evident as early as the fourth day of treatment [7]. There is a scarcity of studies, however, evaluating CPAP usage patterns in pregnancy [4-6]. Mandibular advancement splints (MAS) are a well-tolerated alternative treatment to CPAP in pregnancy [8], but night-to-night usage patterns of MAS in pregnancy have not been reported. As such, the aim of this study was to evaluate objective, longitudinal adherence patterns to CPAP and MAS in pregnant individuals, as they may provide important insights for future interventions aimed at improving treatment.

Some of these results have previously been reported in the form of an abstract [9].

METHODS

Three separate pilot studies assessing treatment for SDB in the second to third trimester were used for this study: 1) CPAP in a gestational diabetes mellitus (GDM) population [5], 2) CPAP in hypertensive disorders of pregnancy (HDP) [6] and 3) mandibular advancement splints (MAS) in pregnancy [8]. All studies were conducted in Montreal, Quebec, Canada. The Research Ethics Board at the McGill University Health Centre (MUHC) and Centre Hospitalier Universitaire

Sainte-Justine (CHU Ste-Justine) approved the above studies. All participants provided informed consent.

For the GDM study, participants were recruited from GDM clinics at MUHC and CHU Ste-Justine (2015-2018) [10]. Participants were eligible if they were diagnosed with GDM and were found to have SDB (apnea-hypopnea index; AHI ≥ 10, Chicago scoring criteria [11]) using a level 2 home polysomnogram (Titanium unit, Medcare, Natus Inc., Mississauga, ON). Individuals randomized to CPAP were started on nightly auto-titrated CPAP for the remainder of pregnancy.

For the HDP study, pregnant participants with a diagnosis of hypertension were recruited from obstetrics clinics at the MUHC (2017-2021) [12]. SDB was also diagnosed as above but with an AHI cut-off ≥ 5 [11].

Both GDM and HDP studies used objective adherence data obtained from periodic online or manual downloads from the CPAP devices' microchip and troubleshooting was provided as needed [6, 10].

For the MAS study, participants were recruited from obstetrics clinics at the MUHC (2016-2017) and were eligible if they had mild-moderate SDB (AHI 10-29 events/h, Chicago criteria) [8]. Eligible participants were treated with MAS (SomnoDent Flex, SomnoMed, USA), with rapid titration based on comfort [8]. Dental sleep specialists performed troubleshooting on a weekly basis by telephone. An embedded thermosensor/DentiTrac® (Braebon Medical Corporation, Kanata, ON) measured objective adherence [13], from which data was downloaded at the end of the study.

The first 30 days of objective adherence data obtained from these 3 studies was used. An *a priori* definition for consistent adherence (≥ 4h/night for at least 70% of nights [14]) was

used to ascertain consistent vs. inconsistent users. In exploratory analyses, statistical comparisons were performed using a Student's t-test (R version 4.3.0) to evaluate for differences in baseline characteristics between consistent and inconsistent users. Patterns of night-to-night usage were assessed by visual inspection of the 30-day adherence data displayed graphically for individual participants. Since this was an exploratory analysis with relatively small sample sizes for each cohort, error bars were omitted from the curves to reflect the preliminary nature of these findings and to avoid implying statistical significance.

RESULTS

For the GDM CPAP cohort, complete 30-day night-to-night objective adherence data was available for 15/21 participants who were randomized to and received CPAP vs. control (nasal dilator strip). Adherence data was not available for 6 participants due to intolerance (n=4) or data transmission issues (n=2). Of those accepting to use CPAP, the mean objective adherence was 3.9 ± 2.0 h/night. Three mean patterns of night-to-night adherence were observed: 1) consistent CPAP users (≥ 4h/night at least 70% of nights; n=7 (47%)), 2) improved CPAP usage after initial adaptation (initial usage <4h/night but improved and sustained to ≥ 4h/night later on; n=4 (27%)), and 3) inconsistent CPAP users (<4h/night; n=4 (27%)) (Figure 1). Various interventions (i.e. mask interface change, switch to fixed CPAP, addition of expiratory pressure relief) were instituted for participants in Group 2. The residual AHI for the GDM cohort was (mean±std) 1.6±1.3 events/hour, and no patients had a residual AHI>5.

For the HDP CPAP cohort, complete 30-day night-to-night objective adherence data was available for 22/27 participants randomized to CPAP vs. control (nasal dilator strip) (n=5 participants were intolerant). The mean objective adherence was 3.2±2.3 h/night [6]. The same

three mean patterns of adherence from the GDM CPAP cohort were also observed in this cohort (Figure 2). 7/22 (32%) participants were consistent CPAP users, 2/22 (9%) had improved CPAP usage after an initial adaptation period and 13/22 (59%) were inconsistent CPAP users. The residual AHI for the HDP cohort was 0.4±0.5 events/hour, and no patients had a residual AHI>5.

In the MAS cohort, 15/17 participants had objective adherence data available (n=2 participants had chip malfunction) with a mean adherence of 6.9±1.9 h/night. In this cohort, the three different patterns of adherence observed were: 1) consistent MAS users (n=7 (47%)), 2) Discontinued MAS treatment after initial consistent usage (n=3 (20%)) and 3) Inconsistent MAS users (n=5 (33%)), of which n=2 barely used the MAS and n=3 used it for ~50% of nights (Figure 3). A total of n=12/15 participants had residual sleep apnea (AHI>10) (9 mild, 3 moderate cases), however due to the time delay of 79 ± 42.4 days between baseline (second trimester) and on-treatment PSG (third trimester), this could be due to the worsening of SDB severity as pregnancy progresses [8, 15].

Participant characteristics were examined between consistent and inconsistent users of each cohort (Table 1). In the GDM cohort, total sleep time was higher in the consistent (8h) vs inconsistent (6.3h) CPAP users ($p = 0.02$). In the HDP cohort, consistent CPAP users had a higher gestational age (28.3 weeks) than inconsistent users (23.2 weeks) ($p = 0.04$). No other significant differences were found between consistent and inconsistent MAS users. Additionally, there were no differences in patient characteristics between those who completed the CPAP studies and those who dropped out or were lost-to-follow-up.

DISCUSSION

To our knowledge, this is the first description of night-to-night objective adherence patterns to CPAP and MAS in the pregnant population. For the CPAP studies, adherence rates ranged from 32-47%, and the MAS study had 47% of participants who were adherent. The CPAP data from the GDM and HDP patient populations showed the same three patterns of adherence: 1) consistent usage, 2) improved usage after initial adaptation period, and 3) inconsistent usage. Almost half of participants used CPAP consistently in the GDM study, whereas only a third had consistent usage in the HDP study. While patient characteristics between the two groups may play a role, it is also important to note that ~20% of patients in the GDM and HDP groups did not have data available because of early drop out due to intolerance to CPAP. Pattern 2 indicates the possibility of an adaptation period during the first few days of treatment. The MAS study showed the same consistent and inconsistent patterns of adherence, but surprisingly, there was a group who started with consistent MAS usage and then discontinued treatment. Additionally, participants in Group 1 (adherent users) in the MAS cohort averaged a higher usage time (~8 hours/night) vs. in the CPAP cohorts (~6 hours/night).

Initial reports of adherence to MAS in non-pregnancy suggested higher adherence rates compared to CPAP therapy [16]. However, many of these studies were based on self-reported rather than objective adherence [17]. In our analysis, although the MAS cohort had a higher proportion of adherent patients, it was also the only cohort where a group of patients started consistently then discontinued treatment in the first 30 days. This could be due to increases in AHI as pregnancy advances [15], and a lack of further titration (i.e. advancement) of MAS later in pregnancy. Future protocols may benefit from reassessment of SDB severity later in pregnancy to determine if additional MAS advancement is necessary.

Other than an increase in total sleep time during the night of the sleep test (GDM) and being more advanced in pregnancy (HDP), we did not identify any other patient factors (i.e. demographics or underlying SDB severity) that were associated with consistent or inconsistent usage. Larger studies with more broader cohorts and diverse populations are needed to examine potential predictors of adherence to SDB therapy in pregnancy.

While this is the first description of objective night-to-night adherence patterns in both CPAP and MAS users during pregnancy, our study also has important limitations. In addition to small sample sizes, we limited our analyses to descriptive analyses given that we were not powered to compare groups for statistical differences. Thus, our findings should be considered exploratory and need to be replicated in future, larger studies. We also did not have qualitative data to explain our usage patterns. Finally, all our CPAP data was from individuals who had either GDM or HDP. These comorbidities could affect adherence by possibly adding an additional burden to frequent medical visits. However, it is particularly relevant to study adherence in the context of GDM and HDP, as the most compelling evidence to date linking SDB with adverse pregnancy outcomes pertains to these two conditions [2]. Additionally, nasal congestion, a common side-effect, could affect mask and pressure tolerance.

Night-to-night adherence may provide important information on adaptation and barriers to therapy in pregnancy. Qualitative research is needed in future studies to help explain the reasons behind usage patterns, and how we can use novel, patient-oriented methods to improve the effectiveness of treatment of SDB.

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The data that support the findings of this study are available from the corresponding author, SP, upon reasonable request.

FIGURE CAPTIONS

Fig. 1: CPAP adherence patterns in GDM cohort

Night-to-night CPAP adherence patterns of three groups in GDM pregnancy cohort. Group 1: Consistent CPAP users (n=7). Group 2: Improved CPAP users after initial adaptation period (n=4). Group 3: Inconsistent CPAP users (n=4). The dotted line represents 4 hours of usage per night, corresponding to the conventional threshold for adherence.

Fig. 2: CPAP adherence patterns in Hypertensive Disorders of Pregnancy (HDP) cohort

Night-to-night CPAP adherence patterns of three groups in HDP pregnancy cohort. Group 1: Consistent CPAP users (n=7). Group 2: Improved CPAP users after initial adaptation period (n=2). Group 3: Inconsistent CPAP users (n=13). The dotted line represents 4 hours of usage per night, corresponding to the conventional threshold for adherence.

Fig. 3: Adherence patterns in Mandibular Advancement Splint (MAS) cohort

Night-to-night MAS adherence patterns of three groups in MAS pregnancy cohort. Group 1: Consistent MAS users (n=7). Group 2: Discontinued MAS treatment after initial consistent usage

(n=3). Group 3: Inconsistent MAS users (n=5). The dotted line represents 4 hours of usage per night, corresponding to the conventional threshold for adherence.

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Table 1. Patient characteristics of consistent and inconsistent users of 3 pregnancy cohorts *

	GDM		HDP		MAS	
	Consistent CPAP users (n=7)	**Inconsistent CPAP users (n=4)**	**Consistent CPAP users (n=7)**	**Inconsistent CPAP users (n=13)**	**Consistent MAS users (n=7)**	**Inconsistent MAS users (n=5)**
Ethnicity n (%)						
White	4 (57.1)	1 (25)	3 (42.9)	5 (38.5)	4 (57.1)	3 (60)
Black	1 (14.3)	1 (25)	3 (42.9)	4 (30.8)	2 (28.6)	2 (40)
Arab/West Asian	0 (0)	1 (25)	0 (0)	2 (15.4)	1 (14.3)	0 (0)
East Asian	1 (14.3)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)
Latin American	1 (14.3)	1 (25)	0 (0)	2 (15.4)	0 (0)	0 (0)
Age (years)	36.7 (5.8)	35.5 (3.1)	36.9 (4.9)	35.8 (5.1)	35.6 (4.7)	35.6 (3.8)
Gestational age at baseline (weeks)	29.8 (1.2)	28.5 (5.4)	**28.3 (3.7)**	**23.2 (3.5)**	24.4 (7.3)	27.5 (5.8)
Pre-pregnancy BMI (kg/m^2)	30.4 (14.3)	26.5 (4.9)	35.5 (8.3)	32.5 (8.2)	28.8 (5.4)	26.7 (5.7)
Hypertension, yes/no n(%)	0 (0)	0 (0)	7 (100)	13 (100)	2 (28.6)	0 (0)
Insulin, yes/no n(%)	2 (28.6)	2 (50)	2 (28.6)	1 (7.7)	-	-
Total sleep time (hours/night)	**8 (0.7)**	**6.3 (1.0)**	6.2 (0.9)	6.0 (1.9)	6.7 (0.9)	5.9 (1.4)
Apnea-hypopnea index pre-treatment (events/hour)	17.9 (7.3)	28.1 (13.8)	27.2 (26.6)	19.3 (9.1)	15.8 (5.8)	18.4 (4.5)
Oxygen desaturation index, 4% (events/hour)	1.1 (1.1)	7.7 (3.6)	2.3 (2.2)	1.2 (1.8)	3.5 (4.9)	1.8 (2.0)
Epworth Sleepiness Score	9.7 (4.1)	8.7 (2.9)	10 (4.1)	11.4 (3.0)	11 (6.2)	11.2 (5.4)

Data are mean ± SD unless otherwise specified. Bolded are those that are significantly different ($p < 0.05$, from Student's t-test). * All available data was used in the primary analysis (i.e. all participants who were randomized and completed baseline assessments).

Figure 1. CPAP adherence patterns in GDM cohort

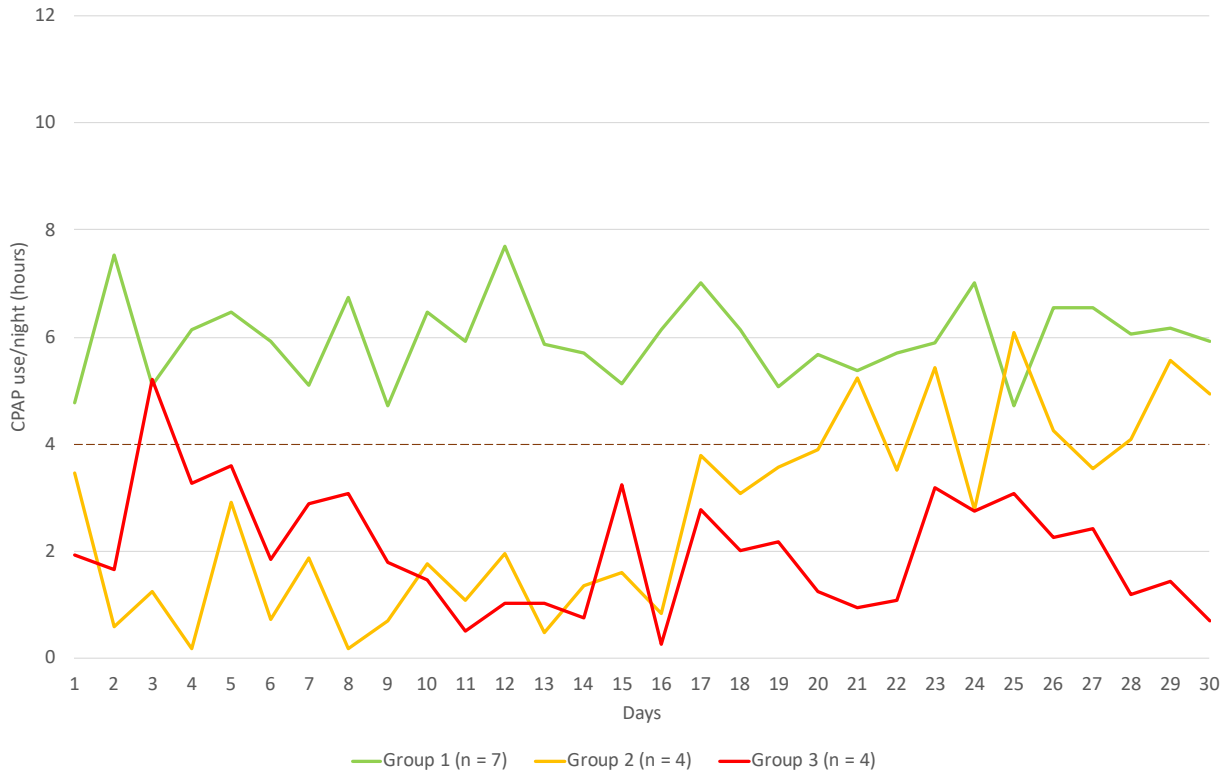


Figure 2. CPAP adherence patterns in Hypertensive Disorders of Pregnancy (HDP) cohort

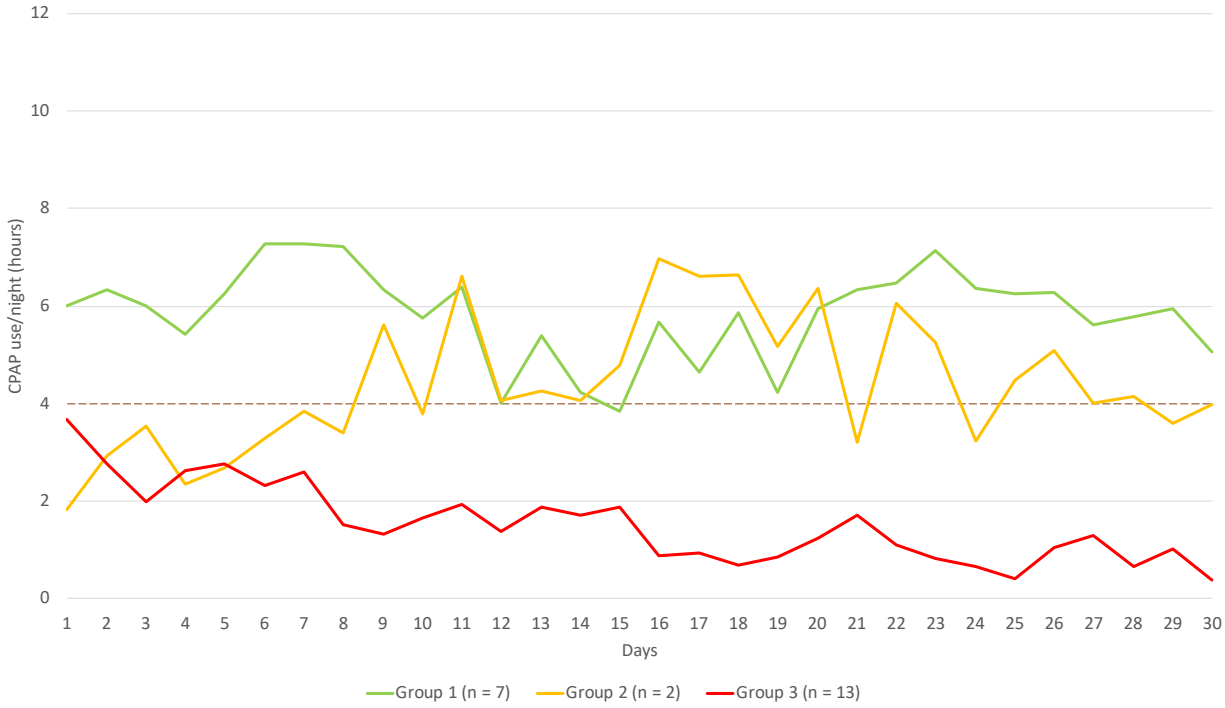
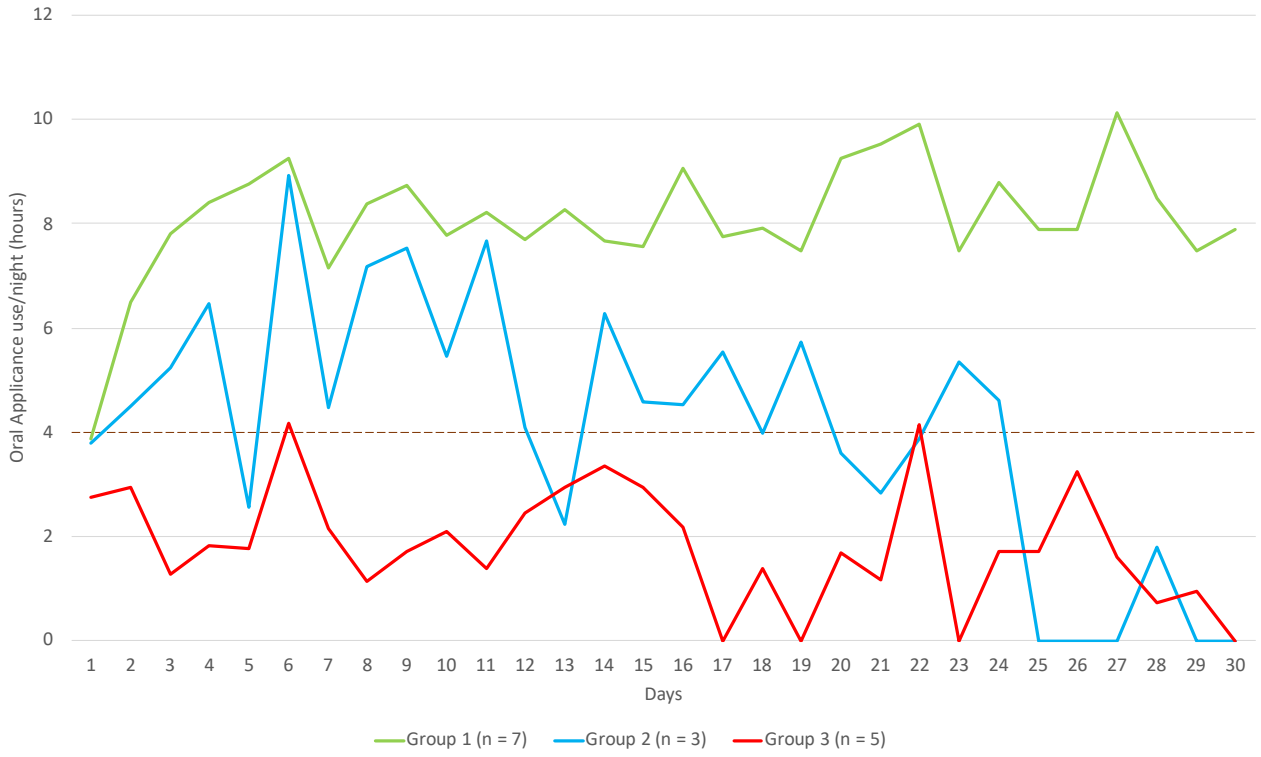


Figure 3. Adherence patterns in Mandibular Advancement Splint (MAS) cohort



Chapter 5: DISCUSSION

Objective 1: Examining whether pregnant individuals adhere to CPAP and if CPAP improves 24-hour glucose profiles using CGM.

This pilot study explored the use of CPAP in pregnant women with both SDB and GDM. The main outcome was CPAP adherence (feasibility outcome for a pilot trial), and the main health outcome was glucose control as measured by CGM. The objectively-measured average nightly use of CPAP in intention-to-treat analysis was ~3 hours. Among participants who completed the study protocol (per-protocol analysis; n= 16), the average nightly CPAP use increased to 3.9 hours. Intention-to-treat analysis for adherence to CPAP was performed by assigning an overall of 0h/night of adherence to the individuals who did not use CPAP at all. As a result, drop-outs may have contributed to the cohort's overall lower adherence rates. This is most likely due to their intolerance to CPAP, which is an issue that needs to be investigated in further qualitative studies. Interestingly, even with this modest level of CPAP adherence, the CGM results revealed lower overnight glucose levels in the CPAP group vs control, with significant differences in the early hours of the morning (3am-6am).

There have been previous large cardiovascular trials in SDB involving non-pregnant populations, and these have exhibited similar adherence rates to what we reported. For instance, the SAVE trial examining if CPAP could prevent cardiovascular events in OSA reported a mean adherence of 3.3 hours/night [259]. Similarly, the ISAAC trial reported a mean adherence of 2.8 hours/night [260]. As such, the results from our pilot study suggest that pregnancy does not inherently lower adherence rates compared to the general population. The ITT analysis showed a sleep duration of 3 hours/night, which is below the conventional threshold of 4 hours.

Despite this, the intervention was still effective in reducing glucose levels, even in the ITT analysis.

By leveraging CGM, this study demonstrated novel findings on the longitudinal and temporal effects of CPAP on gestational glycemic control. While our analysis revealed no statistically significant differences in mean 24-hour glucose levels between groups, the CPAP group showed improved glycemic control during the early morning period (3am-6am) and at noon. Both groups had comparable insulin requirements, which suggests the CPAP group's decrease in glucose levels is not a direct consequence of insulin action.

Throughout pregnancy, insulin resistance exhibits a gradual rise. This culminates in a decline of insulin sensitivity to approximately 50% of its normal expected value by the third trimester [261]. Several factors are believed to contribute to this decline in insulin sensitivity during pregnancy, including rising levels of hormones like estrogen, progesterone, and human placental lactogen (hPL) [261]. This would explain why post-treatment (~35 weeks gestational age) glucose levels were higher than pre-treatment (29 weeks) levels in the control group (Figure 2B). Our findings suggest that CPAP therapy might offer some protection against the increase in blood glucose levels (and potentially insulin resistance) that typically occurs during pregnancy, particularly in the early morning hours. Conversely, leaving both SDB and GDM untreated could worsen this physiological process.

Our study is consistent with findings in the nonpregnant population. A study investigating the effects of CPAP on a group of mostly obese type 2 diabetics found that sleeping, nocturnal and mean 24-hour glucose levels were reduced and sleeping interstitial glucose levels were less variable during CPAP treatment [262]. Another prospective study using

CGM showed that patients with severe SDB and type 2 diabetes exhibited a significant reduction of nocturnal glucose variability and improved overnight glucose control when using CPAP therapy [263].

Based on our findings, SDB may be a novel reversible risk factor for GDM by contributing to poor nighttime glucose control in pregnancy [24, 35, 36, 47, 264], independent of obesity. One study in pregnant participants with SDB and GDM found that two weeks of consistent use of CPAP resulted in an improved insulin secretion, but not in glucose control [37]. This study did not use CGM however, so nighttime glucose levels were not assessed. Additionally, the SDB severity in this study was mild, and so was the hyperglycemia, which could explain the insignificant change in glucose levels [37]. Future studies to examine whether the benefit of CPAP varied by SDB severity (i.e. AHI, ODI, hypoxic burden) would be beneficial in elucidating who would derive the greatest benefit from treatment in pregnancy. We are unfortunately limited in our ability to perform this analysis due to the small sample size of our CPAP group.

Our study's observation of a nighttime, rather than daytime, decrease in glucose levels in the CPAP vs. control groups might be explained by CPAP mitigating the increase in glucose specifically caused by individual SDB events [262]. Since our findings indicate that early morning hours (3-6am) were most susceptible to reductions in glucose in the CPAP group, REM-related SDB may be a more clinically relevant subgroup to explore in future studies.

Multiple studies have shown that obese pregnant women have higher nocturnal glucose levels than non-obese controls [265, 266], but these studies did not screen for SDB, so the possibility that a significant portion of the study population might have had undiagnosed and untreated SDB is plausible. A different study showed SDB patients without diabetes had

increased nocturnal glucose levels when they stopped using CPAP, however levels normalized shortly after awakening in the morning, suggesting compensation by normal insulin secretion [267].

In one study with GDM participants, even slightly elevated nocturnal glucose levels (~ 6.0 vs. 5.5 mmol/L) were associated with an increased risk of delivering large-for-gestational (LGA) age infants [268]. In this study, daytime glucose levels and time in range did not differ between the groups. This suggests that even a relatively modest difference of 0.5 mmol/L in nighttime glucose levels was a significant factor influencing the outcomes observed in the study. In a study using CGM, it was demonstrated that even subtle differences in glucose in pregnancy can affect neonatal clinical outcomes, such as LGA, neonatal hypoglycaemia, admittance to NICU, and infant length of hospital stay [269]. SDB was once again not assessed in these studies, however. Our study showed CPAP-related reductions by ~0.7mmol/L, which therefore provides a compelling rationale for future, adequately powered studies to definitively determine whether CPAP intervention can reduce the incidence of LGA infants in the context of GDM. LGA births are a great concern, as they are associated with an increased risk of complications for both mother and infant [270]. These complications can include birth difficulties, hypoglycemia in the newborn, and even fetal death [271, 272]. Consequently, preventing LGA births is a crucial objective in managing GDM.

Our results suggest that fetuses of individuals with GDM and untreated SDB may be exposed to higher glucose levels at night, compared to those whose mothers received CPAP therapy. Our findings support our previous work, which identified a link between the severity of SDB and elevated blood glucose levels, particularly at night and in the early morning, among

women with GDM [35]. Similarly, another study using CGM demonstrated that increasing severity of SDB (measured by AHI and ODI) was related to higher 24-hour glucose levels in pregnant SDB patients without GDM [273]. The HAPO study, which recruited a large multinational, racially and ethnically diverse cohort, showed that an increase in maternal glucose during pregnancy increases the likelihood of adverse pregnancy outcomes, such as LGA, cesarean section, fetal insulin levels and neonatal fat content [274]. As such, if SDB is left untreated in GDM and glucose levels are left unchecked, this can increase the risk of these perinatal complications related to the fetus' exposure to maternal hyperglycemia. Obesity is the main risk factor for SDB [275], and since many babies are born LGA from obese mothers who do not have GDM [276], undiagnosed and untreated SDB becomes especially relevant. Therefore, SDB represents a potential, yet often overlooked, contributor to macrosomia.

Our study's findings hold potential implications for the understanding of the developmental programming of health and disease theory, which states that perinatal exposures, encompassing even the pre-pregnancy period, are increasingly recognized as potential contributors to the etiology of diverse chronic health conditions, including diabetes mellitus, CVD, and asthma [209].

Emerging evidence reveals an association between chronically elevated blood glucose levels in mothers with GDM and epigenetic modifications in their offspring, specifically alterations in DNA methylation patterns [277]. Houde et al. showed that subtle variations in maternal glucose levels, even below GDM thresholds, have been shown to exert an influence on the offspring's epigenome [278]. This study specifically identified an association between maternal hyperglycemia, even within the normal range, and altered DNA methylation patterns

in the placenta and cord blood. Notably, these changes occurred at three specific gene loci: BRD2, LRP1B, and CACNA1D, all of which are considered strong candidates for influencing the development of obesity and cardio-metabolic diseases [278]. Therefore, if CPAP therapy could lower circulating glucose levels among patients with GDM and SDB, it could potentially serve as a preventative measure against the development of obesity and diabetes later in life in the offspring.

A strength of our study is the CGM, which allowed for dynamic monitoring of glucose levels. Because participants checked their glucose levels using capillary blood glucose monitoring four times a day, the CGMs were calibrated. Further, CGM values were verified for valid calibrations using the mean absolute difference (MAD), as we have previously published [35].

However, our study is not without limitations. Because this is a pilot study, our sample size was small and was not powered for glucose control, but rather for the primary objective of verifying objective CPAP adherence. Our analysis was therefore limited and unable to explore the full extent of changes in CGM values after CPAP use, in relation to CPAP adherence. Stratifying by adherence is an important question, however these analyses would be significantly underpowered. We are currently undertaking a comprehensive on-treatment analysis, which is taking into consideration the time of CPAP usage in relation to CGM measurement (~15,000 post-treatment CGM values for the CPAP arm alone). These ongoing post-hoc analyses will further examine the relationship between CPAP adherence and CGM glucose control in exploratory analyses, since we have corresponding hourly CPAP adherence data for the 72-hour CGM per participant.

While our primary focus was on nocturnal blood glucose due to its relevance to SDB, exploring potential differences in other clinically important thresholds could also yield valuable insights. We are currently undertaking additional analyses using over 60,000 measurements of CGM values (pre- and post- from both treatment arms) to ascertain clinically meaningful thresholds such as time in range, % time above and % time below.

Additionally, while participants maintained nutrition journals, this data was not analyzed, leaving our results unable to account for glucose fluctuations related to dietary intake. The feasibility of a larger-scale trial may be constrained by the poor adherence observed in this cohort, with a notable dropout rate of approximately 24%. To ensure the intervention's efficacy for a broader population of women, it is crucial to address adherence challenges before proceeding with a larger trial.

Objective 2: Evaluating objective night-to-night adherence patterns to SDB treatment (CPAP or MAS)

This is the first description of night-to-night adherence patterns to CPAP and MAS in the pregnant population. Adherence rates hovered between 32-47% for the CPAP studies and 47% of participants in the MAS study were adherent. Three distinct patterns of adherence were revealed in the GDM and HDP patient populations: 1) consistent usage, 2) improved usage after initial adaptation period, and 3) inconsistent usage. MAS adherence mirrored CPAP, with consistent and inconsistent users. However, a subgroup started well but treatment adherence slowly declined later.

Interestingly, CPAP pattern 2 suggest a potential adaptation period during the first few days of treatment. However, this is in contrast to data from the non-pregnant population, which showed that adherence in the first four days of treatment usually indicates the patient's level of adherence for the entire course of treatment [54].

The major challenge of CPAP treatment is achieving adequate adherence but defining a threshold for adequate adherence remains controversial in the field. In 1993, Kribbs et al. defined "regular use" as using CPAP at least 4 hours/night for 70% of the days monitored [244]. Following the successful introduction of PAP therapy for OSA, the Centers for Medicare and Medicaid Services (CMS) authorized coverage for thousands of units due to its demonstrated effectiveness [279]. Data from 2009 indicates that CPAP therapy incurred total costs of $213 million, with CMS authorizing coverage for 2.6 million associated services [279, 280]. The number of patients being prescribed CPAP increased, however many of them had difficulty adapting to the novel therapy, which resulted in the urgent need to establish adherence criteria for valid coverage [279]. The CMS adopted Kribbs et al.'s definition (4 hours/night for 70% of nights) which has been the prevailing norm for coverage policies and evaluation of CPAP adherence ever since [279]. This has been controversial, especially in the United States, where if Medicare patients do not meet this minimum adherence threshold, their PAP may be confiscated, which limits the opportunity for some patients to receive treatment [281]. One RCT found that even if patients are sub-optimally adherent to PAP (<4 hours/night), they still found a decrease in daytime sleepiness and improved quality of life compared to the sham-PAP group [282]. This adherence cutoff has sparked significant debate in the field [283]. As such, evaluating

these adherence patterns involves greater complexity, particularly in vulnerable populations such as pregnant individuals.

One study in the general population found early data on adherence to MAS that suggests potentially better adherence compared to CPAP [234]. In this study, analysis of the intention-to-treat polysomnography data revealed significant improvements in all SDB metrics for both treatment groups [234]. However, the magnitude of improvement was greater for CPAP compared to MAS therapy. When examining health outcomes, however, results were similar after 1 month of optimal MAS and CPAP treatment in patients with moderate-severe SDB [234]. This may be explained by the less optimal adherence of CPAP being compensated by a greater efficacy relative to MAS, resulting in similar effectiveness between groups [234]. Further research is needed to investigate whether the same health outcomes in pregnancy improve equally with either CPAP or MAS.

In our descriptive study, the consistent users for MAS averaged a higher usage time (~8 hours/night) than those in the CPAP cohorts (~6 hours/night). Thus, similar to the general population, MAS demonstrates higher adherence than CPAP in pregnancy, and is therefore better tolerated as a treatment option. As such, when treating the pregnant population, MAS may represent an alternative treatment option for those unable to tolerate CPAP therapy. Future protocols may benefit from reassessment of SDB severity later in pregnancy, not only for re-titration of MAS but also for reassessing efficacy, especially considering increases in AHI as pregnancy advances [7]. This might explain why some patients stopped using it after initial consistent use, having noticed recurrence of symptoms due to decreased efficacy of MAS.

Beyond an observed increase in total sleep time during the sleep study night for GDM patients and a later stage of pregnancy for HDP patients, no other patient characteristics, including demographics or baseline SDB severity, were associated with consistent or inconsistent CPAP/MAS use. Future studies with larger, more diverse populations are warranted to explore potential factors influencing adherence to SDB treatment during pregnancy. In these larger cohorts, it would be interesting to see if baseline factors differentiating adherent vs. non-adherent patients previously identified in others CPAP studies, such as level of education and occupation [244], remain significant when comparing MAS patients.

While this study offers the first objective assessment of night-to-night adherence patterns in both CPAP and MAS users during pregnancy, it is important to acknowledge some key limitations. Our analysis is limited by the relatively small sample size. Additionally, the study design was not powered to statistically compare adherence patterns between CPAP and MAS users. Therefore, our findings should be considered preliminary and require confirmation in future studies with larger participant groups. Furthermore, the absence of qualitative data in this study limits our understanding of the reasons behind the observed usage patterns.

Lastly, the CPAP adherence data was collected from individuals with either GDM or HDP, comorbidities that could potentially negatively affect adherence by adding an additional burden to the already frequent medical visits and treatments for those conditions. However, investigating adherence in GDM and HDP is especially important because the strongest existing evidence linking SDB to negative pregnancy outcomes is concentrated in these two conditions [24].

The importance of night-to-night adherence is underscored by its ability to provide important information on adaptation and barriers to therapy in pregnancy. Early identification of inconsistent treatment use, followed by timely interventions like CPAP mask/pressure adjustments or MAS protrusion modifications, could be the key to improving adherence. Future studies should incorporate qualitative research to explore the motivations behind these usage patterns. This deeper understanding will guide the development of innovative, patient-centered interventions to enhance adherence and ultimately improve SDB treatment efficacy.

Chapter 6: CONCLUSION

While SDB is linked to a 2-3 fold increase in GDM risk [24], the impact of CPAP treatment on blood glucose control during pregnancy remains unknown. This highlights a critical gap in our current knowledge for treatment of this comorbid condition. Our results indicate that pregnant individuals overall have difficulty adhering to CPAP, yet despite the modest adherence observed, those randomized to CPAP in a pilot RCT had lower glucose levels than control after treatment, with significant differences in the early hours of the morning (by ~0.7 mmol/L). Recent research has suggested that an increase in circulating glucose during pregnancy of even as low as 0.5 mmol/L could increase the risk of adverse fetal health outcomes, such as large-for-gestational age infants [268]. Additionally, more research is needed to determine what thresholds of usage are related to outcomes in pregnancy.

Our study suggests that SDB may be a novel and treatable risk factor for GDM by contributing to impaired overnight glucose control in pregnancy [24, 35, 36, 47, 264], independent of BMI. As such, SDB may also be an undetected reversible risk factor for fetal exposure to elevated maternal glucose levels. To solidify our findings and evaluate the potential impact of CPAP on pregnancy outcomes in women with GDM, larger studies are warranted. These future studies should implement strategies to enhance overall adherence to SDB therapy in this specific population.

CPAP is the established gold standard treatment for SDB. However, its acceptability and tolerability among pregnant women with SDB remain uncertain. Our descriptive study investigated and revealed longitudinal patterns of night-to-night adherence, which were previously unexplored in this population. Four distinct patterns were observed: 1) consistent

users (CPAP or MAS), 2) improved usage after initial adaptation period (CPAP), 3) initial usage with subsequent decrease in adherence (MAS), or 4) inconsistent users (CPAP or MAS). More qualitative research is needed to understand these patterns of adherence and put forth potential treatment interventions geared towards improving adherence. These solutions should be patient-oriented, which will ultimately improve the effectiveness of treatment of SDB.

This thesis has successfully addressed both objectives. In the pilot RCT using continuous glucose monitoring, we showed that CPAP is adhered to less than 50% of the time in pregnant individuals, and despite this poor adherence, it improves 24-hour glucose profiles vs. control (Objective 1). The following descriptive study evaluated longitudinal night-to-night adherence patterns to CPAP or MAS in pregnant individuals, thereby characterizing adherence to SDB treatment in this patient population (Objective 2). However, future larger cohort studies are needed to validate our preliminary findings regarding glucose control. Additionally, qualitative research is needed to understand CPAP or MAS adherence and determine optimal interventional strategies to improve adherence in pregnancy.

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Appendix 1: Other work: Maternal sleep-disordered breathing in pregnancy and risk of adverse health outcomes in mothers and children: A follow-up study of the 3D pregnancy and birth cohort

Background

Maternal sleep-disordered breathing occurs in 17-45% of women by the third trimester of pregnancy, depending on the level of the study, scoring criteria and comorbidities [6]. In pregnancy, SDB is associated with gestational hypertension and gestational diabetes [24].

It is not well understood if SDB in pregnancy: 1) is associated with greater risk of SDB and adverse health outcomes in offspring, or 2) is associated with an increased risk of persistent SDB after delivery and adverse health outcomes in the mother. Gestational animal models have shown that sleep fragmentation and intermittent hypoxia, which are the two hallmarks of SDB, increase the risk for catch-up growth in the offspring, which in turn increases the risk of developing obesity later in life [225]. Accordingly, glucose levels were higher in exposed offspring, showing worse glucose metabolism [226].

Rationale and hypotheses

As such, the goal of this longitudinal study is to determine whether maternal SDB is associated with adverse child health outcomes, such as obesity, cardiometabolic disease and worse cognitive outcomes, and to determine if childhood SDB is a potential mediator for these adverse health effects.

Objective for current pilot study

The objective of the current pilot study is to determine the feasibility of performing simultaneous home-based measurements in both mother and child (Level 2 Sleep studies in children, Level 3 studies in mothers, 24-hour ambulatory blood pressure monitoring (ABPM) and actigraphy in both). The results from this pilot study will help fine-tune the protocol for the future larger study.

Objectives for future larger study

The objectives of the future larger study are to determine whether maternal SDB during pregnancy adversely affects the following health outcomes, assessed 9-11 years after delivery.

Our primary objective is to determine whether children born to mothers who had SDB during pregnancy, compared to children born to mothers who did not have SDB, are at increased risk of the following adverse outcomes: obesity (from BMI z-scores/DEXA scans), cardiometabolic risk (24-hours ABPM, fasting lipids, C-reactive protein, HOMA-IR), neurocognitive and behavioural measurements, and presence of childhood SDB measured by polysomnography Level 2.

Our secondary objective is to determine whether women who had SDB during pregnancy, compared to women who did not have SDB, are at increased risk of the following adverse outcomes: Persistent SDB in the mother (9-11 years after delivery) using simplified portable sleep studies (Level 3), increased blood pressure, impaired quality of life, and worse depression scores.

Methods

Participants

Mothers and children from the 3D (Design, Develop, Discover) cohort were recruited 9-11 years after delivery. This birth cohort had around 2400 participants, out of which 1000 are currently being followed-up on, from which we are recruiting for our study. While the large cohort study will include 392 participants, this smaller pilot study includes 43 participants. The exposed group is a random sample of women with SDB during pregnancy (i.e. women who self-reported loud snoring more than once a week during the third trimester). The unexposed group is a random sample of women without SDB during pregnancy, so women who reported never snoring in the third trimester.

Outcomes

This pilot study includes one single home visit to minimize participant burden. All children took a level 2 polysomnography test in their homes, which includes simultaneous recordings of sleep state, nasal respiration, cardiac rhythm, muscle activity, gas exchange, and snoring. Oxygenation metrics and sleep stages were measured too. Mothers underwent a level 3 HSAT (without EEG). Additionally, 24-hour ABPM which measures day and night blood pressure, was performed for both mothers and children. 7-day actigraphy was done as well. Anthropometric measurements were taken by the research assistant in the participants' home: height, weight, waist, neck, and head circumference measurements were recorded. During this home visit is when the research assistant administered questionnaires, which included the Epworth Sleepiness Scale, the Hospital Anxiety and Depression Scale, the Insomnia Severity Index and others.

Results

The pilot study has been completed, 43 mother-child dyads have been recruited and have performed the home sleep apnea test. The results of the pilot study suggest excellent feasibility, with oximeter, nasal cannula, abdominal RIP (respiratory inductance plethysmography), and thoracic RIP signal qualities being very satisfactory, for both mothers and children. 97.6% of mothers and children completed the ABPM, 100% of mothers and children completed the actigraphy, and 100% of mothers and 93% of children completed the home sleep test.

Conclusion

Home-based simultaneous sleep study and outcome measurements are feasible in both mothers and children. Participant burden is minimized while maintaining adequate signal

quality. The larger phase of the study will reveal any associations between maternal SDB in pregnancy and long-term maternal and child health outcomes.