Title: Auto-PAP Therapy For Improved Fetal Growth

Statement of issues to be addressed/target population: The target population is pregnant women with sleep-disordered breathing (SDB). SDB affects up to 35% of 3rd trimester pregnant women in the general population[1, 2] and up to 85% of those with hypertensive pregnancies[3, 4]. It is associated with fetal growth restriction (FGR),[5-7] a serious condition that affects approximately 10% of fetuses and is a significant disease burden not only for mothers but also for the long-term health of the child. *The purpose of this proposal is to prospectively demonstrate that fetal growth trajectories are altered by maternal SDB such that estimated fetal weight measures will slow across the last trimester in women with SDB, a pattern that will not be observed in women treated with APAP therapy*. Moreover, we will provide evidence that SDB induces placental hypoxia and vasculopathic inflammation, mechanisms by which SDB could cause poor fetal outcomes. Findings will demonstrate that APAP therapy, a non-invasive and non-pharmacological intervention, will have clinical utility as a novel therapy to address fetal growth problems.

Description: goals, measurable objectives, action plans, and capacity to carry out the study:
Goal: The primary goal is to provide evidence that in women with SDB fetal growth trajectory is impaired, defined as fetal weight falling across standard centile curves, but that fetal growth is not impaired in women treated with APAP therapy. In addition, we will show that placental tissue of women with SDB has evidence of hypoxia and inflammation, which will not be found in women treated with APAP therapy. These data will demonstrate that APAP therapy can minimize serious morbidity in pregnant women.

Background: Fetal growth restriction is associated with increased perinatal morbidity and mortality including preterm birth, admission to the NICU, stillbirth, and long-term morbidities such as neurodevelopmental impairment and cardiovascular dysfunction.[8-11] In the majority of cases, FGR is the result of placental insufficiency, usually caused by dysfunction of feto-placental perfusion with subsequent hypoxia and acidosis in the fetal circulation. It presents a major challenge in perinatal healthcare. The birth of a growth-restricted infant brings considerable emotional and economic costs to families and has implications for public-sector services, such as health insurance, educational, and other social support systems.[12, 13] *There currently are no effective clinical interventions that improve intrauterine growth.*

Maternal sleep disruption, specifically SDB, has emerged as a predictor of poor maternal outcomes. Symptoms of SDB affect up to 15% of women at conception,[2, 14] up to 35% of women in the 3rd trimester,[1 2] and up to 85% of women with hypertensive disorders of pregnancy.[4, 15] Objectively-diagnosed SDB has been found in 8% of all pregnant women by mid-gestation,[16] 15% of obese pregnant women,[14] and approximately half of hypertensive pregnancy women.[4, 15] There is now a wealth of literature that demonstrates independent associations between maternal SDB and gestational hypertension, preeclampsia, and gestational diabetes.[2, 17-20] Maternal SDB has also been associated with FGR,[6, 19] including a large study by our group.[7] In some exciting and novel preliminary data we have demonstrated that APAP use in pregnancy is associated with improved infant birth weight: infants born to women who used APAP during pregnancy (n=18), compared to infants born to women with SDB who did not use APAP (n=17), have larger birth weight (3036±833g vs. 2485±1050g, p=0.08) even after accounting for duration of PAP use. In addition, we have preliminary data to show that APAP in pregnancy is associated with longer gestation; women who used APAP (n=18) continued their pregnancies for a mean of 2.5±3.4 weeks longer than those who did not use PAP (n=17; 37.7±2.8 weeks vs. 35.1±4.1 weeks, p=0.03*). This is a clinically significant duration that will have long-term impact on infant health.* Moreover, in a retrospective study we have data to show that fetuses of women with SDB have a fall in growth across the centiles, a pattern that was not present in women using APAP therapy.[21] In a small pilot study it has recently been reported that SDB in women with preeclampsia is associated with reduced fetal movement, which was partially reversed with APAP therapy.[22] Taken together, these preliminary findings suggest that APAP treatment of pregnant women with SDB is a window of opportunity to provide an urgently-needed clinical intervention that will improve fetal growth trajectory and thus have a positive impact on not only short-term pregnancy outcomes but also on longer-term morbidity.

Placental dysfunction is central to many complications of pregnancy, including preeclampsia, FGR, and stillbirth.[23] Disruption of the normal tightly-regulated developmental cascade that occurs during gestation can lead to abnormal placentation, which may manifest by functional and structural alterations such as changes in blood flow and changes in placental shape, texture, and patterns of injury.[24] One of the major insults that impacts placental function is hypoxia, a major regulator of angiogenesis and thus placental vascular development. Chronic hypoxic stress or cycles of intermittent hypoxia during gestation result in an inadequate supply of oxygen

to the fetus. Animal models have shown that rodents exposed to intermittent hypoxia deliver growth-restricted pups,[25-27] and that these pups have long-term metabolic consequences similar to those seen in humans born with FGR.[25, 28] Emerging data suggest that placentas from women with SDB have markers of hypoxia and angiogenesis.[29, 30] Our preliminary data shows that the feto-placental weight ratio, a common metric of the balance between fetal and placental growth, decreases with increasing severity of SDB (see Figure). Furthermore, we have found that women with SDB have markers of hypoxia such as chorangiosis and increased nucleated red blood cells at a 2-fold higher frequency than women without SDB. Despite the critical role of the placenta, studies investigating uteroplacental function and structure in maternal SDB are lacking. We will provide pathologic evidence that SDB induces placental hypoxia and vasculopathic inflammation, patterns of injury that are not observed in women treated with APAP, providing highly novel mechanistic insight into mechanisms by which SDB could cause poor fetal outcomes.

	AHI<5 (n=23)	AHI>5 (n=14)	AHI>15 (n=6)	AHI>30 (n=4)
Feto-placental weight ratio	6.3±1.5	6.1±1.3	5.8±1.0	5.3±0.3

Measurable objectives: 1) To conduct serial fetal growth measures via ultrasound every 4 weeks from 28 weeks' gestation to 36 weeks' gestation to demonstrate that growth falls across centiles (defined as ≥30% fall in centile in women with SDB but not in those using APAP; 2) To obtain placental tissue and perform histologic examination using a rigorous, methodical pathologic review adapted from Salafia & Popek[31] to demonstrate that placentas of women with SDB show significantly more hypoxic injury and inflammation that placentas of women using APAP therapy.

Action Plan: *Recruitment:* Pregnant women will be recruited from both clinical sleep referrals and obstetric clinics as in our previous studies.[2, 4, 5, 32] Those who report snoring at least 3 nights/week will be invited to undergo a home sleep study. This approach will ensure that the majority of eligible women will be identified early in pregnancy, which will allow ample sample size to recruit from and sufficient time to initiate treatment in those enrolled and randomized to APAP. Inclusion criteria: ≤24 weeks gestation, singleton pregnancy, and objective evidence of SDB, defined as an AHI≥5[33] or a respiratory disturbance index (RDI)≥5. Exclusion criteria: unable to give informed consent, smoking, alcohol or drug use, current PAP treatment, and multiple gestation pregnancies. Women with severe SDB (AHI≥30) or severe daytime sleepiness (ESS>15) will not be randomized and instead triaged to clinical care. However, while these women will receive clinical treatment for SDB we will still follow them in an observational manner through the rest of the protocol (see below). No data exist to support or refute the hypothesis that among women with SDB, those with low AHI's may suffer less impact. Published data from small series indicate that very mild SDB during pregnancy could have profound impact on pregnancy outcomes.[22, 34-36] Furthermore, the vast majority of pregnant women with SDB have mild-to-moderate disease. Women with AHI≥5 or RDI≥5 will be randomized to no-APAP therapy or APAP therapy using the **biased coin minimization technique,[37] a CONSORT-approved method for assignment of treatment groups in RCTs**.[38] The first subject is truly random; for subsequent subjects the treatment allocation that minimizes the imbalance of selected factors between groups is identified and subjects are assigned to the treatment or non-treatment group, with higher probability being given to assignment to the group that results in the least imbalance between groups. This maintains randomness in the assignment with the advantage of making small groups closely similar for subject characteristics at all stages of the trial. Minimization is the only acceptable alternative to true randomization and may be superior.[39] We will use minimization to assign to the two study groups based on the following variables: blood pressure groups (hypertensive vs. not hypertensive), diabetes (diabetic vs. non-diabetic), BMI (normal vs. overweight/obese), education (high school or less vs. post-high school), and SDB severity (AHI 5-14.9 (RDI 5-14.9) vs. AHI 15-29.9 (RDI 15 and above)). Women with an AHI≥30 or a daytime sleepiness score ≥16 on the Epworth Sleepiness Scale[40] will not be randomized and will be referred for clinical APAP care. However, these women will still undergo the 3rd trimester assessments (see below).

Polysomnography and APAP: Ambulatory polysomnography will be used to determine SDB status at baseline. We have previously validated home-based polysomnography in pregnant women.[32] Following the nocturnal study, data will be down-loaded and analyzed using criteria of the American Academy of Sleep Medicine.[33] Women with SDB will be randomized to APAP therapy; use of auto-titrating machines allows delivery of the lowest effective pressure without need for multiple in-laboratory re-titrations as pregnancy progresses. Women will use APAP for the remainder of their pregnancies and will be closely followed by the study team. This will include remote monitoring of adherence, a major strength of our prior work. Ambulatory polysomnography will be repeated at 32-weeks with the addition of nocturnal fetal monitoring. Any woman in the non-APAP group who

no longer has SDB in the 3rd trimester will not be included in the final analysis. In our experience it is uncommon, although not impossible, for a women with SDB early in pregnancy to no longer have SDB in the 3rd trimester. Typically the severity of SDB worsens as pregnancy progresses. Nonetheless, to ensure that all non-APAP women still have SDB in the 3rd trimester it is important to repeat the sleep study in the 3rd trimester.

Fetal Assessment: *Fetal growth*: Women will undergo traditional Doppler ultrasounds three times during the 3rd trimester (28, 32, and 36 weeks) for estimated fetal weight which will be adjusted for key, non-pathological maternal variables known to affect fetal growth, using the US dataset of the GROW software.[41] Such customization is superior to population-based fetal weight standards as it generates an in utero growth standard that is customized for each fetus, to adjust for relevant maternal characteristics that may impact fetal growth. Thus the growth is optimized to obtain the growth potential of the fetus in the absence of pathology such as smoking, preeclampsia, or diabetes. Birth weight and gestational age will be abstracted from medical records. Birth weight will be converted into an adjusted birth centile using the GROW software.[41] The purpose is to calculate the 'term optimal weight' as an ideal standard, against which the actual weight can be assessed. We have successfully used this software in a previous large cohort study.[5] During a second home sleep study in the 3rd trimester women will undergo in-home continuous portable fetal monitoring using the Monica DK, a small Holter-type device (Nottingham, UK), which has been validated against cardiotocography.[42-44] Patterns of fetal movement will be assessed at the same three time-points in the third trimester as the ultrasounds.

Placental Pathology**:** At the time of delivery, 3 full-thickness placental disc samples will be obtained and processed in routine fashion. Gross placental pathology will be performed including placental weight, and feto-placental weight ratio. Histologic examination will be conducted using a rigorous, methodical pathologic review adapted from Salafia & Popek[31] and developed with the intention of identifying underlying pathophysiologic processes. These factors include acute and chronic inflammation, uteroplacental vascular pathology and villous lesions, and intraplacental vascular pathology. This examination was piloted[45] and refined in our preliminary analysis of placental tissue. Samples of placental tissue will also be banked for future research.

Potential Problems and Alternative Strategies: Although our preliminary data solidly support the hypotheses there is the possibility that no differences will be found for fetal growth trajectory. In the unlikely even that this occurs, we will examine fetal heart rate variables and subjective measures of fetal movement for any subtle signs of fetal compromise that may not translate to large enough insults to significantly affect fetal growth measures but which may aid in the understanding of fetal wellbeing. Another potential problem is that insufficient women with SDB will be identified. However, given the large pool of women (approximately 4500/year) we do not foresee problems with recruitment. Although infrequent, it is possible that women with SDB in early pregnancy may not meet the threshold later in pregnancy. To minimize this (as well as drop out for other reasons), we will over-enroll women to allow our final sample size to be sufficient for analysis (at least 27 women per group). Women could decline to undergo home monitoring; this is not likely to occur, since >50% of high and low-risk women approached for home monitoring have enrolled in our protocols. An additional potential problem is the use and adherence to APAP. However, we have previously demonstrated our ability to maintain adherence in 80% of pregnant women in a longitudinal study of APAP therapy in hypertensive pregnancies, of which about half did not even meet present criteria for SDB (K23HL095739); of those with SDB, we were able to maintain adherence in >90%. Our success was due to the ability to build a strong rapport along with frequent contact. The current study will only randomize women with SDB and thus, we believe that we are in a strong position to retain sufficient women on APAP. A further possibility exists in that no differences in gross placental pathology will be found. However, histological differences may still be present. If markers of hypoxia are not found, we will use the banked placental tissue to investigate the presence of angiogenic factors and receptors e.g., vascular endothelial growth factor, placental growth factor, and soluble fms-like tyrosine kinase 1. We will also investigate neutrophil extracellular traps as we have previously described[45] or epigenetic changes.

Sample Size and Power Calculation: To estimate the sample size required to detect a clinically important difference between groups we calculated the difference in birth weight between newborns of women with SDB who used APAP vs. those who did not use APAP, using a linear regression model which accounted for length of APAP use. From preliminary data of n=18 APAP users and n=17 non-PAP users, the APAP users delivered infants who were 551grams (over 1 pound) larger than non-APAP users. Assuming a mean birth weight of 2485g for the SDB group and 3036g for the APAP group with a standard deviation of 625g, a sample size of n=27 per group has 90% power to detect a difference with α=0.05. Even with a sample size of n=21 per group, we would

still have >80% power to detect this difference. We are therefore confident that our milestones will be obtained if we enroll n=30 women per group. There is ample power to detect a clinically significant endpoint.

Statement of how patients will be recruited and retained:
Recruitment: Pregnant women will be recruited from obstetric clinics as described above. Our wealth of experience in conducting sleep-related protocols with pregnant women has allowed efficient, targeted screening in order to identify those at highest risk of SDB, and reserving objective confirmatory testing to those likely to provide the highest yield of SDB diagnoses. Our preliminary data demonstrate that report of habitual snoring (snoring ≥3 nights per week) is an excellent marker for the presence of objectively confirmed SDB. In a group of n=67 pregnant women (mean gestational age 28.2±7.8 weeks) who underwent polysomnography, mean AHI was significantly higher in habitually snoring pregnant women compared to non-snoring pregnant women (17.3 vs. 3.3; p<0.01). We found that habitual snoring has good sensitivity (0.80), specificity (0.77), positive (0.70) and negative (0.90) predictive value for identifying women with confirmed SDB. Our approach thus minimizes the need for widespread objective testing. Furthermore, we have successfully treated pregnant women with APAP**.** Of n=51 pregnant women with SDB who were offered PAP (K23 HL095739) we enrolled n=45 women (88% of invited).

Retention: We are one of a handful of centers that has conducted longitudinal sleep protocols in pregnant women and the PI was the first investigator to receive funding to study the impact of APAP therapy in pregnancy. We have been able to retain >90% of women with SDB on APAP therapy of >4 hours/night until delivery and therefore have demonstrated ability to promote excellent adherence to APAP therapy in pregnancy. An experienced team with APAP adherence in pregnant women is critical for the success of this proposal. Our team has been working together for several years to maximize retention and adherence of pregnant women in APAP-therapy protocols. The close relationships forged with study subjects together with APAP education, initial daily contact, and use of web-based software for real-time monitoring of APAP adherence have been major strengths to our success. Real time monitoring allows for same-day identification of problems and thus subsequent targeted intervention; the ability to intervene and address concerns early is key for maximum adherence.

Impact Statement: The societal burden, medically, emotionally, and financially, of poor pregnancy outcomes is immense. Despite multiple strategies to reduce the incidence of FGR, prematurity, and stillbirth, figures demonstrate that little improvement has been made in recent years.[33] There are currently no effective interventions that improve fetal growth yet our exciting preliminary data suggest that APAP therapy could indeed be such a novel target for early intervention in women with SDB. The latter is a significant population that is currently under-diagnosed. *In our opinion, the proposed research is innovative because it will target maternal sleep as modifiable risk factor for fetal growth, using an RCT design, which has never been used in this population.* This will generate a substantial new rationale for the clinical use of a non-invasive, non-pharmacological intervention that is safe in pregnancy. The benefits of APAP therapy to two vulnerable individuals will be clearly demonstrated, paving the way for a novel application of a standard therapy that may ultimately have significant public health impact with beneficial ramifications on healthcare spending.

Timetable: The time required for training staff and launch of the protocol is minimal (<1 month) due to our extensive experience in conducting APAP trials in pregnant women, together with our existing collaborations with Maternal-Fetal Medicine and Pathology. This then allows maximal time to run the protocol and enroll n=4 women per month to ensure that all women are randomized by month 17. This will allow for intervention, 3rd trimester ultrasounds, and collection of all placental tissue by month 23, prior to analysis for grant submissions (month 24).

EVALUATION: Plans for evaluation, how success will be measured and how progress/results will be documented: Successful milestones will be considered as follows: a) ≥95% of women have good quality home sleep tests with ≥4 hours sleep time; b) serial fetal growth measures are obtained on ≥95% of participants; c) for women randomized to APAP, ≥85% of women will use APAP ≥4 hours per night, ≥4 nights/week, and d) placental tissue is obtained on ≥95% of women. The PI and coordinator will meet twice per week to discuss progress and troubleshoot difficulties. The whole team will meet monthly. The main outcome will be longitudinal fetal growth trajectory and the secondary outcome will be placental histology. ***Analytic approach:*** A multi-level model will be the primary analysis method used to assess fetal growth measures over time and between groups. The model will account for the repeated collection of these measures over time Nonlinear time trends will also be

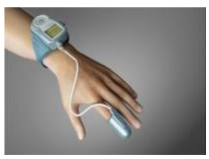
investigated as it is hypothesized that the slope for fetal growth over time will not be as steep in the third trimester, especially for women with SDB. The model will take the general form: $y_{ij} = \beta_1 + \beta_2 x_{2ij} + \beta_{3ij} + \ldots + \beta_p x_{pij} + \phi_{0j} + \varepsilon_{ij}$ where y_{ij} is the fetal growth measure at visit i for participant j and ϕ_{0j} is the participant specific random intercept. β_1 through β_p are the fixed effect parameters estimated by the model and ε_{ij} is the time varying residual. The β coefficients associated with group membership are of primary interest. In addition to the random intercept per participant, random slopes will also be investigated for inclusion into the final model. For analysis of placental histology a Chi-square goodness of fit test will first be used to test for mean differences in the binary placental histology measurements between groups and a multivariable logistic regression will be used to assess group differences while controlling for potentially confounding polysomnographic variables (e.g., oxygen saturation nadir or AHI). We expect that the presence of SDB will slow fetal growth across the third trimester (>30% fall in centiles), a phenomenon not present with use of APAP therapy. Furthermore, we expect to demonstrate decreased feto-placental weight ratio, increased chorangiosis (hypoxia), and increased vasculopathic inflammation in SDB placentas, phenomena not observed with use of APAP therapy. These data will show that maternal SDB exerts an effect on the fetus that is at least partially reversible with APAP therapy.

Expected results and dissemination: The societal burden, medically, emotionally, and financially, of poor pregnancy outcomes is immense. Despite multiple strategies to reduce the incidence of FGR, prematurity, and stillbirth, little improvement has been made in recent years.[33] Identification of novel targets for early intervention that will yield significant real-world benefit is crucial. The proposed research is innovative because it will target maternal sleep as a modifiable risk factor for fetal growth. This will be the first study to prospectively assess the impact of APAP therapy on fetal growth. We will demonstrate that fetal growth trajectory falls across centiles in women with SDB during pregnancy and that APAP therapy prevents poor growth. We will also provide mechanistic data via placental pathology to support that APAP therapy minimizes hypoxic injury to the placenta. Our innovative approach requires a fusion of multidisciplinary investigators from Sleep Medicine, Maternal-Fetal Medicine, and Pathology; this represents a substantive departure from current methods of fetal surveillance. Our preliminary data strongly support a timely need for the proposed study, findings from which will be disseminated at national and international conferences and in international high-impact journals. Our findings will promote a considerable new rationale for the clinical use of APAP therapy as a novel tool in obstetric practice.

Covid19 amendment March 2020:

Due to Covid19 research operations involving face-to-face interaction were suspended. Research ultrasound visits were cancelled for all women except those on active APAP therapy. We are able to continue with some of the follow ups remotely such as questionnaire adminstration. However, subsequently we were no longer able to have access to offices and were thus unable to mail out home sleep test devices. In order to avoid missing a critical measure central to the project, we are requesting that disposable devices are mailed to participants – directly from the manufacturer - who would otherwise miss their third trimester home sleep test. We currently have approximately 4 women who are due to have their third trimester home sleep test in the upcoming month.

These devices are the newer models of the devices that we currently use for this project (see below). The WatchPAT device is a home sleep test that we typically give to women and they self-administer it at home. It is a wrist-worn device with a finger probe and snore/position sensor. The new version of the WatchPAT ("WatchPAT One") is the disposable version. The algorithm is the same as the current WatchPAT and the probes are the same. The difference is that the data are not stored directly on the device (which typically requires physical collection and downloading via USB to a laptop). The WatchPAT One utilizes a smartphone and a secure cloud. Thus, no physical contact with a person is required. Indeed, Itamar Medical Inc. provides a shipping service and participants simply put the device in the trash the following morning. The sleep data will be captured in the cloud (coded IDs on a server only for the study team). This is the methodology that will be adopted in new studies going forward, but we currently have no other option (other than lose a vital data point) than to utilize it sooner due to Covid19.

Current device: 

Newest version (WatchPAT One): 

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Amendments:

Add team member (OBGYN) approved 4/2/18

Add research assistant (BL) approved 4/12/18

Clarify the inclusion criteria to include women with a respiratory disturbance index of at least 15 events per hour even in the absence of an AHI of at least 5. This is an alternative definition of sleep disordered breathing.

Approved 7/3/18

Change the threshold for SDB identification to RDI of 5 in line with other studies in pregnancy. Also to clarify that gestational age threshold is <=20 weeks for inclusion (not just <20 weeks). Approved 9/20/18

Expanding the gestational age to include up to 24 weeks (was previously 20 weeks). We have been having difficulties with recruitment and in consultation with maternal-fetal medicine the most efficient upper limit for gestational age was agreed to be 24 weeks. Approved 1/16/19

We are adding study staff LH and SR to the study and removing MN and KN. Approved 6/26/19

Addition of AM, OB research coordinator. Approved 7/19/19

We are adding JM as a study coordinator approved 7/24/19

Retain women triaged to clinical care w/ severe sleep apnea. Approved 8/26/19

Add SH (sleep physician) to the study team approved 10/7/19

Removing LH (coordinator) approved 2/19/20

Time-sensitive: mail-out home sleep devices during Covid19 shutdown; follow up questionnaires by phone; cancelation of ultrasounds for non-intervention women. Approved 4/10/20

Some of the data and samples (placental tissue) from this study will be shared with the University of Manchester in the UK for study HUM00133250.

Study team members that are no longer working on this project have been removed. Approved 4/20/20