RESEARCH PROTOCOL

The SAFER study:
Sleep Apnea and FEtal growth Restriction

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SYNOPSIS

Study Title	Sleep Apnea and Fetal Growth Restriction (SAFER Study)
Objective	To investigate the relationship between obstructive sleep apnea (OSA) and fetal growth restriction (FGR) and to assess the role of auto-titrated positive airway pressure (aPAP) as antenatal therapy in these patients.
Study Period	Planned enrollment duration: 2 years Planned study duration: 3 years
Number of Patients	400 potential patients screened, with 104 evaluable patients enrolled Participants will be enrolled at Washington University in St. Louis, Hadassah Hebrew University, and University of Rochester
Study Treatment	Autotitrated positive airway pressure (aPAP). Patients with FGR and a diagnosis of OSA will be randomized to this treatment.
Study Design	Prospective, multicenter, blinded, randomized control trial Stage 1. Prospective screening questionnaire in women with FGR to identify patients at high risk of OSA. Stage 2. Prospective observational study of women from Stage 1 (with FGR and high risk of OSA) using home sleep monitoring (HSM) to identify patients with a diagnosis of OSA. Stage 3. Randomized controlled trial in women from Stage 2 (with FGR and diagnosis of OSA) to compare aPAP vs. no aPAP in a 1:1 allocation ratio for their effects on fetal growth.
Inclusion and Exclusion Criteria	Inclusion: • Age ≥ 18 and ≤ 50 • FGR (defined as <10th percentile based on a routine 2nd trimester ultrasound) without a change to greater than the 15th percentile by time of written consent • Lower limit of gestational age at enrollment 22+0 weeks. • Upper limit of gestational age at enrollment: adequate time to complete Stages 1 and 2 and if appropriate to be randomized and receive intervention by no later than 32+0 weeks. • The absence of 2 minor or 1 major markers of aneuploidy Exclusion: • other known cause of FGR (including congenital anomalies or intrauterine infection) • reversed end-diastolic flow in the umbilical artery • preexisting diagnosis of OSA being treated with aPAP • chronic pulmonary disease (cystic fibrosis, moderate persistent asthma) • hemoglobinopathies (sickle cell anemia, thalassemia) • maternal craniofacial anomalies

	• premature rupture of membranes
Measurements	Stage 1. OSA risk assessment Stage 2. Apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). Stage 3. Primary: Birth weight. Secondary: Umbilical artery Doppler flows, APGAR at 1 and 5 min, mode of delivery.
Statistical Methodology	Our primary outcome (birth weight) in the RCT phase of this study (Stage 3) will be assessed by a 2 tailed t-test (parametric) or Wilcoxon rank-sum test (non-parametric) as appropriate for data distribution, using intention to treat as the grouping variable. We will use a mixed effect regression model to assess the effect of aPAP on the longitudinal association between estimated fetal weight and Doppler umbilical artery flows (ultrasound), while controlling for confounders

1. Background and Significance

1.1 Fetal Growth Restriction: Fetal growth restriction (FGR) affects 5-10% of pregnancies and is one of the leading causes of perinatal morbidity and mortality. [1] There are many potential causes of FGR, but in the absence of congenital anomalies or intrauterine infection, FGR is typically due to suboptimal uteroplacental perfusion. [2] Without intervention, FGR may progress to hypoxic ischemic neonatal encephalopathy [3] [4] and increases the risk of acute intrapartum fetal asphyxia. When the pregnancy is remote from term, interventional delivery exposes an already compromised fetus to additional complications of prematurity, in particular to neonatal brain injury from intraventricular hemorrhage.[4] [5] Both FGR and prematurity are independent risk factors for the development of cognitive delay, poor academic achievement, and adult diseases such as obesity, type 2 diabetes mellitus, coronary artery disease, and stroke.[2] [6] There is no intervention currently available to improve uteroplacental blood flow, so there is often no alternative to interventional delivery in these cases. [7] Hence, there is at present a clinical dilemma where both intervention and non-intervention may cause fetal brain injury.

1.2 OSA in Pregnancy In the general, non-obstetric population, OSA is associated with increased incidence of hypertension, pulmonary hypertension, cardiac failure and cardiac death.[8] OSA in pregnancy has been associated with poor maternal-fetal outcomes, including low birth weight, preterm delivery, FGR, gestational hypertension/preeclampsia, gestational diabetes and higher rates of neonatal ICU admission.[9-16] Because very few pregnant women are referred for polysomnography (PSG), it is likely that OSA and other sleep disorders are under-diagnosed,[17] with the OSA-related symptoms of snoring, disrupted sleep, and fatigue being frequently considered as transient features of normal pregnancy.[18] Currently there it is no standard of care to screen pregnant patients for OSA nor is there a validated screening tool in this population [19]

1.3 OSA: Impact on Maternal and Neonatal Physiology & Outcomes: Recurrent apneic and hypopneic episodes are commonly associated with intermittent oxyhemoglobin desaturation. This recurrent hypoxia leads to oxidative stress, sympathetic activation, and inflammation that may be harmful to both the mother and her fetus,[20] and may be associated with poor outcomes.

This study aims to identify whether treating OSA with aPAP in patients with established FGR and OSA can improve intrauterine fetal growth. Positive findings will offer a new clinical therapeutic paradigm to treat FGR in OSA patients.

1.4 Preliminary Data

A pilot project was performed in order to determine whether pregnant patients with an AHI ≥ 5 had aPAP compliance rates similar to those of the non-pregnant population. Compliance was defined per Medicare guidelines as at least 4 hours usage/night for 70% of the nights studied. Nine patients met AHI criteria for aPAP administration. Two of those delivered their babies before they were given an aPAP device. Of the remaining 7, 6 were compliant with aPAP. There were no adverse events associated with either HSM or aPAP use.

2. Objectives

2.2. Study Goal

To assess the prevalence of OSA as an association with FGR; to identify patients with FGR and OSA and in these patients, to assess the role of auto-titrated positive airway pressure (aPAP) as an antenatal therapy to improve intrauterine fetal growth.

2.3 Potential Benefits of the Proposed Research to the Patients and Others

There is no known benefit to individual patients in this study. Society may benefit from a better understanding of treatment of obstructive sleep apnea during pregnancy.

3. Patient Selection

3.1 Inclusion Criteria

- Age ≥ 18 and ≤ 50
- FGR (defined as <10th percentile based on a routine 2nd trimester ultrasound) without a change to greater than the 15th percentile by time of written consent.
- Lower limit of gestational age at enrollment 22+0 weeks.
- Upper limit of gestational age at enrollment: adequate time to complete Stages 1 and 2 and if appropriate to be randomized and receive intervention by no later than 32+0 weeks. It may take as few as 3 days for inpatients or as long as 3-4 weeks for outpatients to complete stages 1 and 2 and receive aPAP if appropriate.
- The absence of 2 minor or 1 major markers of aneuploidy.

3.2 Exclusion Criteria

- Other known cause of FGR (including congenital anomalies or intrauterine infection)
- Reversed end-diastolic flow in the umbilical artery
- Preexisting diagnosis of OSA being treated with aPAP
- Chronic pulmonary disease (cystic fibrosis, moderate persistent asthma)
- Hemoglobinopathies (sickle cell anemia, thalassemia)
- Maternal craniofacial anomalies
- Premature rupture of membranes

3.3 Eligibility

Eligibility for stage 3 randomization is confirmed by a positive HSM for OSA defined as an AHI ≥ 5 and an oxygen desaturation index (ODI) ≥ 5, or an AHI ≥ 10 regardless of ODI.

3.4 Recruitment and Informed Consent

Potential patients with FGR will be identified through referral from OB or Epic EMR, myChart and VFH. Patients will typically be recruited by telephone and will be consented for the telephone

questions via telephone; however, they may also be recruited as inpatients or as outpatients in Barnes-Jewish Hospital.

Patients will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be requested to give written informed consent. A member of the study team provides all study descriptions, obtains informed consent, and answers all questions. Patients are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

3.5 Inclusion of Women

As this is a study of pregnancy, all of our patients will be women.

3.6 Inclusion of Minorities

All of our studies actively encourage the participation of minorities in the research. Our minority recruiting typically matches the demographic composition of the Washington University community from which patients will be recruited (78% white, 21% Black, <1 % Hispanic).

3.7 Inclusion of Children

We will ask the mothers at time of consent if we can collect standard of care Bayley Scores (neurological assessment) of their infants through the EMR, as well as performing an additional Bayley Score in selected patients at 18-24 months. This will appear as an optional check box on the consent form. We will not be performing this assessment in all patients but in a small subset in order to determine the sample size of a subsequent study whose primary endpoint will be neonatal neurological outcome.

4. Study Design

This is a collaborative, multi-site, blinded randomized control trial with three participating sites: Washington University (Coordinating Site), Hadassah Hebrew University, and University of Rochester. We need to enroll 104 evaluable patients in Stage 3 and this will require enrolling 200-350 patients in Stage 2 – between all centers over the 3 year period of the study. We estimate that the patient load will be spread evenly between centers.
In addition, Washington University will collect the following for a subset of patients: a piece of the placental tissue for analysis, and Bayley Score neurological assessment at 18-24 months. The Hadassah Hebrew University will conduct the fetal heart monitor test in a subset of patients.

The study period is anticipated to take 3 years.

4.1 Randomization is by computer generated 1:1 randomization, in randomized blocks of 2, or 4 patients and stratified by study site, and within each site is stratified by AHI. Randomization for Stage 3 occurs only after completion of Stage 2 with a positive HSM.

4.2 Blinding: Ultrasound assessments are made by a technician blinded to patient randomization status. Clinical decision-making is performed by treating obstetricians who are also blinded to patient randomization status.

4.3 Minimization of Bias

There will be no specific ethnic background for enrollment. Regarding gender bias, we are assessing pregnant women only. We will attempt to enroll all patients who meet eligibility criteria until our study size target is achieved.

5. Study Procedures

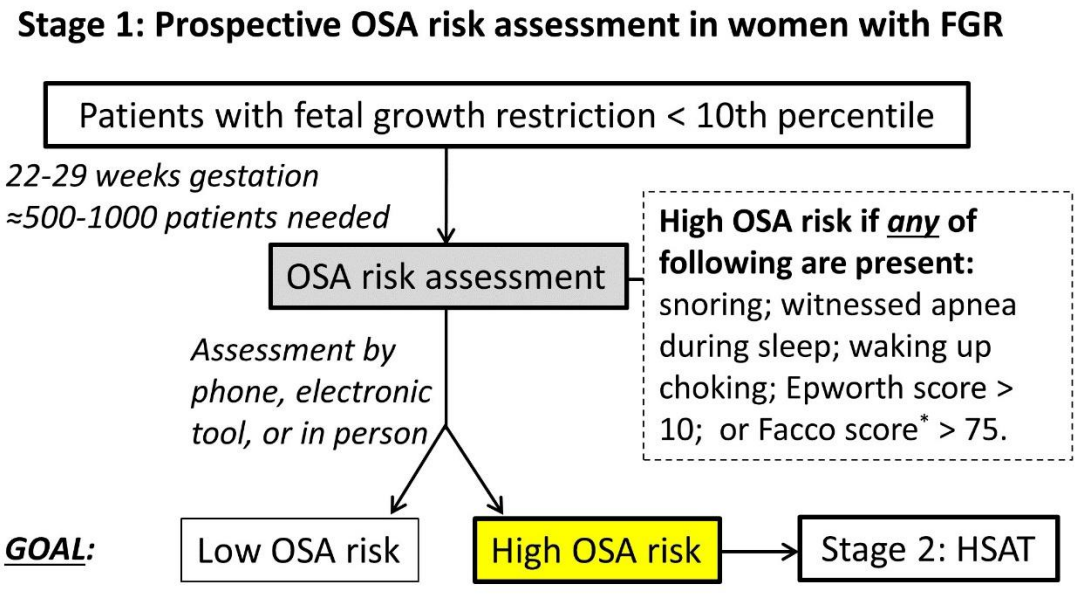
5.1 Pre-Study Period

Patients receive standard care and no additional tests are administered.

5.2 Stage 1

Potential patients with FGR will be identified through referral from OB or Epic EMR,myChart and VFH. Those who meet inclusion and exclusion criteria will be approached for consent either by telephone, in the outpatient clinics, or as inpatients by a member of the research team. Determination of OSA risk is defined by the presence of any of the following signs or symptoms: snoring, history of witnessed apnea (including self-reported waking or gasping), and excessive sleepiness as defined by an Epworth Sleepiness Scale score >10, or a Facco score >75 (Figure 1). Patients with evidence of OSA risk will be invited to proceed to Stage 2.

Figure 1:



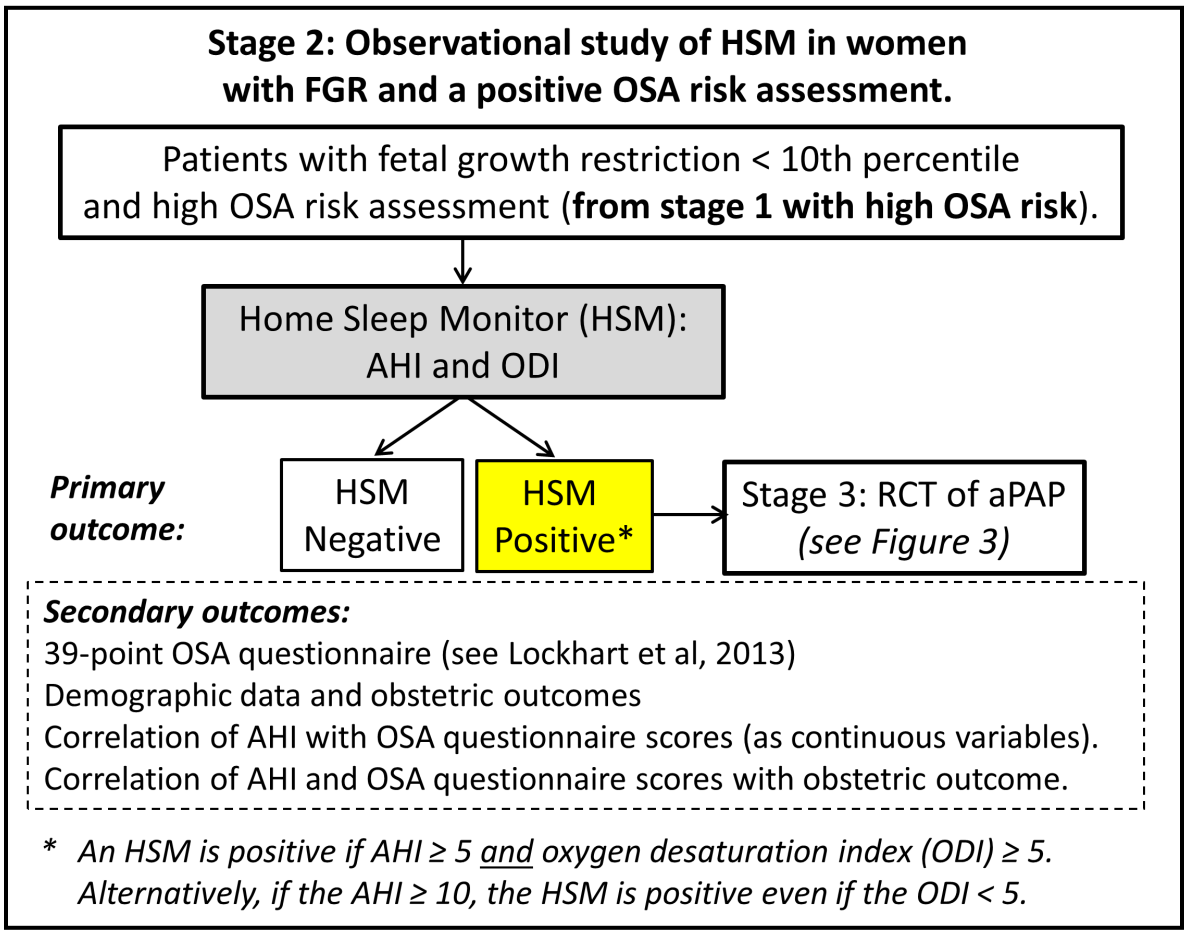
5.3 Stage 2

Patients with FGR < 10th percentile with high OSA risk assessment from Stage 1. These patients will undergo home sleep monotoring (HSM) within the gestational age range of 22 to 28 weeks + 6 days. HSM will be performed with an FDA approved type III home sleep monitor (ResMed Apnea Link Air). Per American Academy of Sleep Medicine (AASM) guidelines, a type III HSM includes air flow, respiratory effort, and oximetry. Airflow will be measured using a nasal cannula and pressure transducer. Respiratory effort will be measured using Respiratory Inductance Plethysmography (RIP) belts that will go around the chest. Oximetry will be measured by pulse oximetry from the finger. Each study participant will be instructed by a member of the study team to use the device for two consecutive nights, however, a single night of use is acceptable if the recorded data is adequate to determine an AHI and ODI. The HSM studies will be reviewed and scored by a registered polysomnographic technologist per standard scoring rules, using recommended (3% desaturation) criteria for hypopneas and oxygen desaturations. If the data from the first night of HSM use is inadequate to determine an AHI and an ODI, then the data from the second night will be assessed. A positive HSM for OSA is defined as an AHI ≥ 5 and an oxygen desaturation index (ODI) ≥ 5, or an AHI ≥ 10 regardless of ODI. Patients with a positive HSM will proceed to Stage 3. The binary result of a positive or negative HSM is noted at the time of the study. The AHI and ODI data, (together with the time course of nocturnal oxygen saturation and apneic/hypopneic episodes) will be saved as a digital file and not accessed until after delivery. While unanticipated in women of childbearing age, it is possible that significant arrhythmias or critical hypoxemias will be detected on HSM. Therefore, participants with ventricular tachycardia lasting >30 seconds, asystole for >5 seconds, other high-risk arrhythmia (site PI discretion), any SaO2 desaturation to <50%, or any SaO2 desaturation <70% lasting >2minutes continuously, will be excluded from the study and expeditiously referred to their primary care providers and obstetricians for further evaluation. Variables derived from HSAT will include AHI, ODI, SaO2 nadir, and time with SaO2 <90%.

In addition, patients will receive a OSA questionnaire consisting of six OSA screening tools (Berlin, American Society of Anesthesiologists checklist, STOP, STOP-BANG [STOP plus body mass index (BMI), age, neck circumference, and gender], Flemons Index, and Epworth Sleepiness Scale). The survey includes demographic information, medical comorbidities, and evaluations by the examiner (BMI, neck circumference, oral examination, and presence of craniofacial abnormalities).

Participants who complete Stage 2 will receive a $25 Target gift card.

Figure 2



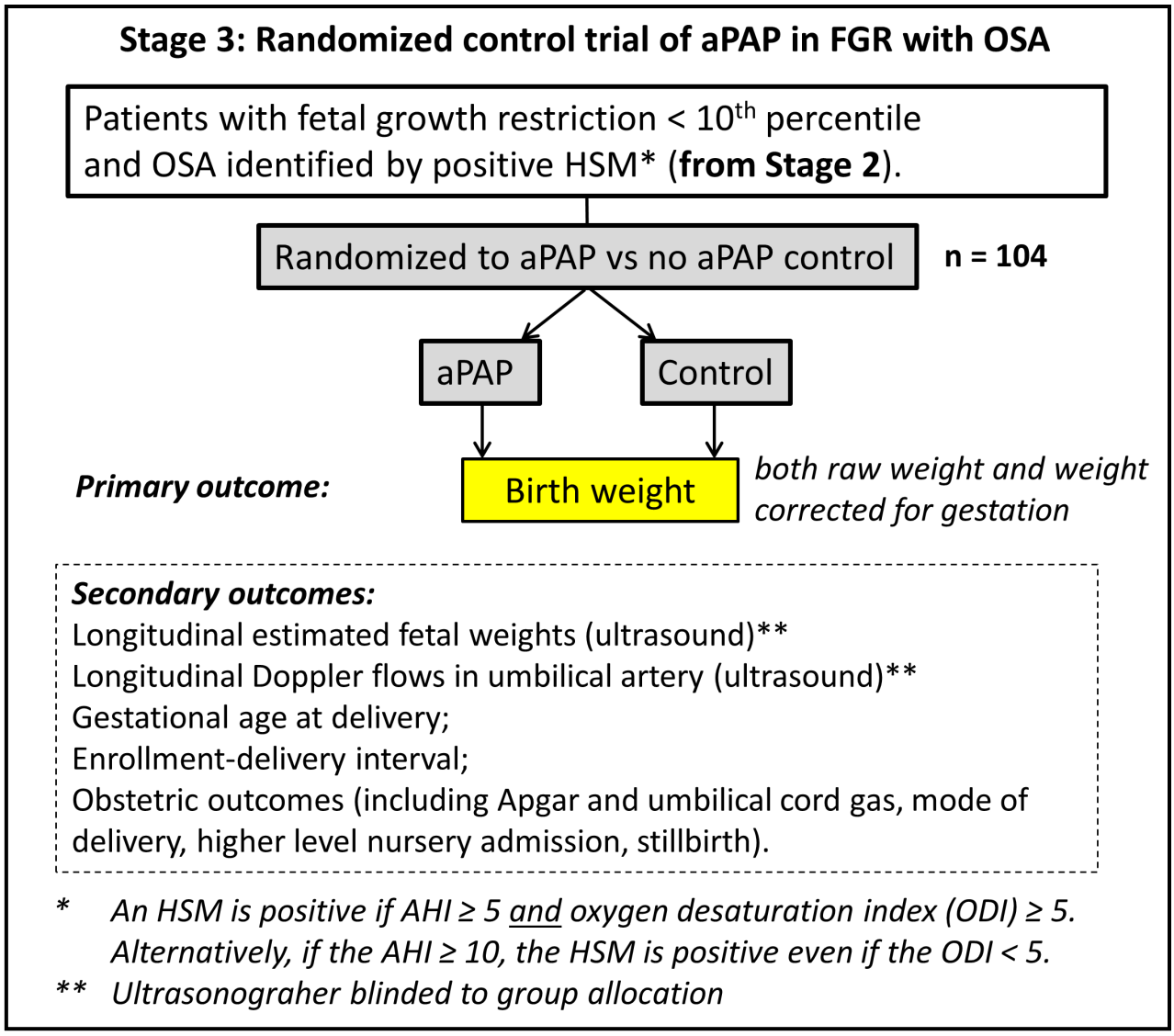
5.4 Stage 3

Patients with a positive HSM from Stage 2 will be randomized to either standard care (no aPAP) or aPAP (ResMed Airsense 10). Women in the aPAP group will be asked to wear the aPAP device every night until delivery. They will be able to choose either a full face mask, nasal mask or nasal pillow mask, depending on their comfort; patients will be able to change their mask style during the study in order to improve comfort and compliance. They will be instructed how to use the device and demonstrate understanding. If required, additional instruction will be provided by a member of the research team. Data from the device, including compliance with therapy, will be transmitted and reviewed by the research team. We measure compliance with aPAP, defined as ≥ 4hrs per night for ≥ 70% of nights per week. Data will be stored on ResMed's secure, cloud-based patient management system (https://airview.resmed.com/login), and downloaded to a secure WU network.

All patients in Stage 3 will be referred to their PCP for possible referral to a sleep physician after delivery.

Patients who complete Stage 3 will receive a $25 Target gift card.

Figure 3:



5.5 Potential Risks

The potential risks in this study involve the potential mild discomfort from the HSM and aPAP mask and the psychological effects of being involved in any study. We do not anticipate risks related to privacy invasion or socio-economic status.

Patients may experience a loss of confidentiality, e.g. others may become aware of patients' participation in this study because of use of study related devices.

5.6 Procedures to Minimize Potential Risks

Studies are conducted under the supervision of the PI and the co-investigators. The investigators are trained and experienced in performing human subjects' research. The investigators are physicians with extensive experience in their specialties. Inclusion and exclusion criteria, and the clinical protocol are designed to ensure that risks are absolutely minimal. Patients are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

With regard to confidentiality; 1) All subjects will be assigned a study ID number, 2) Samples will be kept confidentially. 3) Data will be stored under lock and key (office, file cabinet) and only the investigators and research team will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 5) Study data will not be entered in subjects' medical records.

5.7 Remuneration

In order to compensate patients for their time, patients in Stages 2 and 3 will be remunerated with $25 gift cards after return of the HSM (Stage 2) and after return of the aPAP (Stage 3) in patients randomized to the aPAP group, with a further $25 if they have met aPAP compliance criteria; to a maximum of $75.

5.8 Subject Retention

In addition to remuneration, we will make effort aimed at retention. Patients will be contacted by coordinators and reminded to return the devices, and those on aPAP will be contacted to discuss their compliance and to see if they require another mask fitting or meeting with a member of the research team.

6. Observations and Measurements

6.1 Primary Outcome Measures

6.1.1 Stage 1

Identification of high OSA ***risk*** as defined in Figure 1.

6.1.2 Stage 2:

Identification of OSA ***diagnosis*** as defined in Figure 2.

6.1.3 Stage 3:

Birth weight as defined in Figure 3.

6.2 Secondary Outcome Measures

6.2.1 Stage 1:
Demographic data and obstetric outcome

6.2.2 Stage 2:
OSA questionnaire; demographic data and obstetric outcomes; correlation of AHI with OSA questionnaire scores (as continuous variables); correlation of AHI and OSA questionnaire scores with obstetric outcome.

6.2.3 Stage 3:
Longitudinal estimated fetal weights (ultrasound); longitudinal Doppler flows in umbilical artery (ultrasound); gestational age at delivery; enrollment-delivery interval; obstetric outcomes (including Apgar and umbilical cord gas, mode of delivery, higher level nursery admission, stillbirth); aPAP compliance data (dichotomous per criteria above), aPAP usage per night, aPAP nights used, pressures delivered by aPAP, residual AHI measured by aPAP.

6.3 List of Protected Health Information Collected for Study
Name, date of birth, estimated due date, date of services (ultrasounds, office visits), mailing address, phone number, electronic mail address

6.4 Sources of Materials

6.4.1 EMR
Name, date of birth, gestational age, expected due date, medical history, Bayley Score

6.4.2 Specimens
In a small sample of 10 patients in each group, we will collect placentas (unwanted human tissue) at the time of cesarean delivery. Placentas of patients are typically sent to pathology in patients with fetal growth restriction per usual clinical protocol. In patients who specified in the consent form that they agree to placental specimen analysis, a member of the Washington University research team will obtain four small $1cm^3$ pathology specimens - two from each side of the placenta in the central zone and prepared accordingly for analysis.

We will assess markers of placental hypoxic injury. In addition we will use RNAseq as a tool to discover novel genes that may be differentially expressed in fetal growth restriction with OSA. We will also assess candidate genes quantitatively using reverse transcription quantitative polymerase chain reaction (qPCR) ; including ESX1, SRSF11 and HIF1a.

6.4.3 Bayley Score

A small sample of patients will have their babies assessed neurologically after birth. Global assessment of neurodevelopment across three key domains (cognition, language, and motor function) will be assessed by administering the Bayley Scales of Infant Development – Third Edition (BSID-III), which has high reliability and validity. Children will be assessed at 18-24 months because the results are more reliable at this age compared to earlier assessments.

6.4.4 Site Data Entry Timeline Expectation

- Participant registration in RedCap will be completed within 3 business days of consent.
- HSM data will be uploaded to the WUSTL Box within 3 business days of return of device to a member of the research team.
- HSM data will be reviewed and scored within 7 business days of upload to WUSTL Box.
- HSM results will be entered in to RedCap within 2 days of review and scoring.

7. Statistical Methods

Data will be assessed for normality by visual inspection of the histogram of each outcome variable and by Kolmogorov-Smirnov test. Normally distributed data will be presented as mean (standard deviation); otherwise, we will use non-parametric statistics to present the data as median (interquartile range). Our primary outcome (birth weight) in the RCT phase of this study (Stage 3) will be assessed by a 2 tailed t-test (parametric) or Wilcoxon rank-sum test (non-parametric) as appropriate, using *intention to treat analysis* based on the randomized grouping allocation. Similar tests will also be applied to other secondary outcome variables which are continuous (gestational age at delivery; enrollment-delivery interval; birth weight corrected for gestational age; Apgar and umbilical cord gas). For categorical outcomes (mode of delivery; higher level nursery admission; stillbirth; compliance with aPAP), we will apply chi-square (parametric) or Fisher's exact test (non-parametric) as appropriate for comparison across groups. Additionally, we will use a mixed effect regression model to assess the effect of aPAP on the longitudinal association between estimated fetal weight and Doppler umbilical artery flows (ultrasound), while controlling for confounders (Stage 3). In these analyses, we will model the intercept as the random component to account for any omitted variable. We will also use similar mixed effect regression model to assess the temporal correlation between nocturnal apneic/hypopneic episodes and nocturnal FHR abnormalities (Stage 1). By standard convention, statistical significance will be based on a two-tailed p value <0.05 to determine the significance of association. All statistical testing proposed will be conducted using SAS® version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

7.1 Sample Size

In high risk obstetric populations, the risk of OSA is as high as 35%. [21] We are adding the additional step in stage 1 of screening this high risk population for known clinical manifestations of OSA and only performing HSM in these high risk patients. We therefore estimate there will be a positive HSM in 30-50% of these screened patients. Consequently, we will need to assess HSM in between 200-350 patients in stage 2 in order to achieve our sample size of 104 evaluable patients for

Stage 3.

In stage 3, 104 patients with a positive HSM will need to be randomized to aPAP or control in order to have 90% power to detect a 150g difference in birthweight with aPAP. This is based on a baseline birthweight of 2535 ± 234g among infants with FGR in our population (based on unpublished delivery data at Barnes-Jewish Hospital), an alpha of 0.05, anticipated 5% loss to follow up and a 2-tailed t-test.

7.2 Premature Discontinuation

If a patient withdraws from the study after randomization but before initiation of aPAP, the patient will be replaced in order to provide the required number of evaluable patients. The replacement patient will be randomized to avoid enrollment bias. Patients will be withdrawn if the investigator decides that discontinuation is in the best interest of the patient, or the patient requests withdrawal from the study. The reasons for withdrawal are listed in the investigator log.

8. Regulatory and Reporting Requirements

8.1 Adverse Experiences

The likelihood of adverse events in this study is low as the devices that will be used in the study (HSM and aPAP) are ones that have been used in the general and obstetric population for years. The participants will, however, be monitored for adverse experiences using HSM and aPAP. The possible adverse events with this study from using the HSM device are mild discomfort from wearing the nasal cannula, finger pulse oximeter and respiratory effort belt. The possible adverse events from using the aPAP device and mask are skin irritation, dry nose and mouth, dry eyes, difficulty falling asleep, headache, claustrophobia and rarely a mild sense of fullness in the chest.

The investigator will closely monitor patients for evidence of adverse events. All adverse events related to the devices will be reported according to all regulatory guidelines and followed until satisfactory resolution.

8.1.1 Adverse Event Definition

Any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

8.1.2 Attribution (relatedness), Expectedness, and Seriousness

The definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

8.2 Serious Adverse Event

8.2.1 Serious Adverse Event Definition

Any adverse device experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

8.3 Unexpected Adverse Experience

8.3.1 Definition

Any adverse device experience, the specificity or severity of which is not consistent with the current device documentation.

8.4 Life-Threatening Adverse Experience

8.4.1 Definition

Any adverse device experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

8.5 Unanticipated Problems

8.5.1 Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.6 Noncompliance

Failure to follow any applicable regulation or institutional policies that govern human patients research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

8.7 Serious Noncompliance

Noncompliance that materially increases risks, that results in substantial harm to patients or others, or that materially compromises the rights or welfare of participants.

8.8 Protocol Exceptions

A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

8.9 Data Collection Procedures for Adverse Events

Participating sites are responsible for gathering and documenting data pertinent to adverse events occurring at their sites and for collecting adverse event information from each treating physician, including but not limited to:

- Description of the event, including onset and duration
- Correspondence regarding the event
- Classification of the event (severity, relationship, expectedness, seriousness)

8.10 Reporting Procedures for Adverse Events

- **Serious Adverse Events**: Must be reported to the local IRB and Coordinating Center via e-mail as soon as possible, within 24 hours of the occurrence of the event or notification to the investigator or research team of the event.
- **All other Adverse Events**: Must be reported to the local IRB and the Coordinating Center promptly via REDCap AE form within 5 working days of the occurrence of the event or notification to the investigator or research team of the event.
- **Noncompliance**: Must be reported to the local IRB and the Coordinating Center via REDCap within 10 working days of the occurrence of the event or notification to the investigator or research team of the event.

All adverse events will be collect from the time of informed consent through the last assessment.

Any adverse events that are considered related to the trial, will also be reported to IRBs at other participating sites and to the chairperson of the DSMB.

9. Data and Safety Monitoring

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of the home

sleep monitor and its comfortability. Based on these considerations, the monitoring plan involves engaging a colleague from the Department of Anesthesiology who is not involved in the study to serve in a monitoring capacity. Based on the small size and relatively low risks nature of the protocol, only a third person (the colleague), rather than a full Data Safety Monitoring Board will be used. The colleague will be an anesthesiologist knowledgeable in the risks associated with obstructive sleep apnea. This individual will review the annual summary of adverse events. In addition, this colleague will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

9.1 Data Management

The Division of Biostatistics Informatics Core at Washington University will be used as a central location for data processing and management. Washington University belongs to a consortium of institutional partners that work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Division of Biostatistics Informatics Core. The iterative development and testing process result in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Division of Biostatistics at Washington University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Washington University guidelines. REDCap currently supports >500 academic/non-profit consortium partners on six continents and 38,800 research end-users.62

Compliance will be monitored via output from the aPAP device on a daily basis via an internal modem. Data will be sent via a HIPAA compliant ResMed AirView™ secured server. Data will be available to the study coordinator and investigator during subject engagement in real time.

10. Clinical Site Monitoring

Site monitoring will be conducted to ensure that human participant protection, study procedures, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol.

Washington University will perform one remote site audit at each clinical center during the study unless significant problems with data collection, recording or management are found.

Monitoring visits will include, but are not limited to, a review of the following:

- Regulatory files
- Informed consent forms
- Subject eligibility checklist or other inclusion/exclusion documentation
- Source documentation

11. Human Patients Research

The study will be conducted under appropriate approvals. The Washington University Institutional Review Board will be the IRB of record for protocol and consent form approvals. The study will be conducted under the supervision of the PI, a Board-Certified and GCP-certified anesthesiologist. All participating sites will obtain appropriate Institutional review board approvals prior to the study being initiated at each site.

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