Research Protocol

CPAP for OSA & Outcomes in Pregnancy (COOP): A Pilot Trial

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**Introduction:**

Obstructive Sleep Apnoea (OSA) is a common disorder characterized by repetitive episodes of nocturnal breathing cessation due to upper airway collapse, resulting in a decrease in oxygen saturations1. This condition in pregnancy has an estimated prevalence of 10.5% in early pregnancy to approximately 30% in later pregnancy2 and is associated with increased pregnancy complications for both mothers and babies3,4. Continuous Positive Airway Pressure (CPAP) is the gold standard of treatment for OSA in the general population5. There is little data on the acceptability and effectiveness of CPAP in pregnancy and the impact that CPAP treatment of OSA during pregnancy has on maternal and fetal outcomes and maternal quality of life6.

We aim to conduct an initial pilot study comparing CPAP with standard treatment in a group of women with predisposing factors known to contribute to OSA during pregnancy.

**Background literature**

*Obesity and OSA*

Obesity affects increasing numbers of women in pregnancy, with approximately 50% of women who become pregnant either overweight or obese10. Obesity is strongly linked to OSA during pregnancy. The negative implications of OSA in pregnancy are well researched. For mothers, OSA in pregnancy is associated with increased rates of gestational hypertension and pre-eclampsia, and gestational diabetes, and for the infant, is associated with lower birth weight, preterm delivery and NICU admission4,5.

The standard treatment for Obesity during pregnancy (and therefore the management of potential OSA) are lifestyle modifications, such as dietary change and exercise. Whilst these modifications have demonstrated benefit to reducing gestational weight gain, they have a limited impact upon pregnancy outcomes (REF).

Minimal studies have been published to guide clinicians regarding effective strategies to manage obesity related conditions during pregnancy, such as OSA.

*Management of OSA during pregnancy*

There is little data on effect of treatment in pregnancy. A single RCT considering the difference between early and delayed treatment of women with OSA in pregnancy has been published (REF). This RCT of 36 women demonstrated that 2 weeks of CPAP treatment in the 3rd trimester was safe but did not result in improved glucose metabolism.

Other small trials have considered fetal movements following overnight treatment with CPAP, effect on maternal blood pressure and cardiac output. Two clinical studies were identified and are currently recruiting women for an RCT examining clinical outcomes. ‘Targeted CPAP Therapy for OSA in Pregnancy’ is an RCT comparing Sleep Study + CPAP in the experimental group against Standard Prenatal care and is recruiting up to 360 participants at the Naval Medical Centre in San Diego, California. The second study recruiting is the ‘Continuous Positive Airway Pressure (CPAP) for Sleep Apnea in Pregnancy (SLEEP)’ comparing Autotitrating CPAP with weekly contact, incentives for compliance and initial sleep hygiene counselling with initial sleep hygiene counselling alone. This study is an unmasked randomized controlled multi-centre clinical trial aiming to recruit 2700 women in the USA. These studies have similar inclusion criteria and examine similar outcomes measures but are still recruiting and are yet to publish. Our work will complement these studies, adding Australian data to what is known about the treatment of sleep apnoea in pregnancy.

It is essential that new approaches are sought to reduce the morbidity associated with obesity for women and their babies. This study investigates treatment of OSA in obese pregnant women as a new treatment option to minimize pregnancy risk.

**Research design**

**Aims:**

1. Inform feasibility and recruitability of a larger scale RCT to investigate maternal and foetal outcomes after treatment of moderate-severe OSA in pregnancy.

**Secondary objectives:**

1. Assess the acceptability and quality of life impact of sleep studies and CPAP treatment of OSA in pregnancy
2. Assess predictive utility of questionnaires, BMI, neck circumference in OSA in pregnancy
3. Assess the impact of diagnosis and treatment of OSA with CPAP in pregnancy on placental histology

**Method:**

Study type/design

This is a pilot study to assess the feasibility of conducting a full unblinded RCT comparing standard care, with the diagnosis and treatment of OSA in pregnancy using CPAP: designed to assess recruitability, feasibility and acceptability of the study for women.

Participants

In 2017, there were approximately 200 women who met eligibility criteria (see below) within SCHHS. All women eligible and consenting to participate will undertake a sleep study. For the purpose of the pilot 80 women will be recruited, and this will be sufficient to determine acceptability of the intervention to women, and determine recruitability for the project. Recruitment will continue for 24 months or until a sample size of 80 women is reached, whichever occurs first [see appendix A].

Following recruitment, all women will complete the questionnaires (see below) and undertake a sleep study with baseline measurements. Following this, randomisation will occur to standard care OR the intervention arm +/- CPAP). Block randomization will be by a computer generated random number list prepared by an investigator with no clinical involvement in the trial. The study will not be blinded, due the nature of the intervention, however the placental histological examiner (pathologist) can be blinded for this component of the study.

All women referred to antenatal clinic will be assessed for eligibility, and if eligible will be informed of the study during their visit to antenatal clinic and invited to participate.

Eligibility:

* Women with a BMI ≥ 35
* ≥ 18 years of age
* Singleton gestation
* <24 weeks at booking visit/recruitment
* low risk first trimester screen and a normal morphology ultrasound (if done prior to recruitment)

Exclusion criteria:

* known sleep disordered breathing with mechanical therapy
* patient declines randomisation
* multiple gestation
* fetal anomalies or high risk first trimester screen
* women with coronary artery disease or congestive heart failure or cardiomyopathy
* inability to read or understand the consent

Measurements

Baseline data for all participants – demographic data, BMI, Quality of Life (QoL) questionnaire at entry, and the STOP-BANG sleep apnoea diagnostic tool, measurement of neck circumference, and baseline urine protein-creatinine ratio, FBC, U&E, LFTs (routine investigation for care of women with BMI >35 pathway)

Clinical outcome data – A composite outcome assessing placental disease (gestational hypertension, pre-eclampsia, eclampsia, low birth weight/small for gestational age, preterm birth less than 34 weeks and less than 37 weeks, stillbirth).

Additional clinical outcomes will include: number of pregnancy related hospital admissions; postpartum length of stay; co-morbidities (hypertension, gestational diabetes, pre-existing diabetes); gestational weight gain; onset of labour; mode of birth (vaginal birth, vacuum, forceps, elective or emergency caesarean section); estimated blood loss; blood transfusion, ICU admission, maternal death, histological placental examination; gestation at birth; birthweight; admission of neonate to special care nursery; neonatal length of stay, neonatal death, neonatal respiratory support

QoL data: This data will be collected via a questionnaire administered at study entry and at 36 – 38 weeks gestation or immediately before delivery if preterm delivery is electively planned. Women in the investigation/treatment arm will be invited to complete an acceptability questionnaire after their initial sleep study and at 36 – 38 weeks gestation.

Interventions/Procedures/ Study Plan

After a patient is considered eligible for the study (inclusion and exclusion criteria as previously described), they will be invited to participate. It is voluntary and if patients decline to participate, or if they decided to take part and withdraw later on, their usual health care within our healthcare system and their relationship with their healthcare providers will not be negatively impacted. Information about a patient’s participation in the project may be recorded in their health records. Women participating in the study will be provided with a voucher to cover the costs of parking due to any extra hospital visits that may be required for the purposes of the study.

Once recruited at their booking in appointment, patients will be invited to take part in the baseline data collection and sleep study. All participants will be asked to complete questionnaires about:

* General demographics (once only) and measurements (for example, neck circumference and weight)
* Quality of Life Questionnaire (at recruitment and 36-38 weeks)
* Sleep Apnoea diagnostic tools (once only)
* Sleep study

For those with an AHI ≥ 15 they will then be randomised to the intervention or standard care arm. Women with an AHI < 15 will follow a standard care pathway (as per Queensland Health guidelines). If the participant is in the intervention arm, the following will be additional requirements:

* If the sleep study indicates moderate to severe sleep apnoea (AHI ≥15), the participant will be asked to use a CPAP device for the remainder of the pregnancy. This includes comprehensive fitting and advice regarding the use of the device.
* Data will be collected regarding duration of use in pregnancy (depending of gestational age at commencement of treatment and birth), and also from the device itself regarding adherence overnight.

All participants will be given a Participant Information and Consent Form to sign and given a copy to keep.

There are no additional costs to the patient when participating in this project, nor will they be paid to participate. The participants will however, be reimbursed for parking expenses incurred as part of the participation in the study.

As part of the study, all participants will consented to have the placenta sent to the pathology department within our hospital. This will provide further insight as to whether CPAP has had an impact on potential placental disease. All bio-specimens will be destroyed as per usual hospital processes once testing is complete.

Endpoints

* Recruitability

If 80 women can be recruited over 24 months, this represents a recruitment rate of 20%. Inability to recruit to this level would make a larger scale RCT project unfeasible given that many interventional studies will recruit at approximately 30 – 50%.

* Acceptability

Women will undertake a QoL survey at study entry and at 34 – 36 weeks gestation. Women in the Intervention arm will additionally be surveyed regarding the acceptability of investigation with sleep study, and treatment with CPAP if indicated.

* Compliance data collected from the machines will be analysed to assess treatment compliance (adherence to protocol). Treatment time of >5hours per night is considered compliant.
* Clinical outcome data will be used to determine prevalence estimates. The pilot will help to define the prevalence of sleep apnoea in the eligible population at SCHHS and the prevalence of the primary composite outcome of placental disease. The prevalence of the composite outcome will be used to inform the sample size for the larger study.

Analysis

Data will be entered into a secure, password-protected web-based, electronic case-report format. Data will be coded for patient confidentiality and kept in a password protected file.

Data will be analysed using an intention to treat analysis.

Relevance and proportions of variables surveyed will be reported. Group comparisons comparing equivalency of control and interventions will be conducted with chi-squared test for categorical measures and analysis of variance or Kruskal-Wallis test for continuous measures as appropriate assessing for normality and equality of variances.

Questionnaire results will be entered into a purpose-built Microsoft Excel database for data cleaning and preparation for statistical analysis. Statistician support will be accessed to assist with data analysis.

Funding

The project is being funded through an early career research grant, awarded by the Study, Education, Research and Training Fund within the SCHHS. No member of the research team will receive personal financial benefit from patients being involved in the project (other than their ordinary wages).

Resource requirements

Aspects of this study has been funded by the Study, Education, Research and Training Fund: these include

* Hardware: CPAP masks. CPAP machines
* Parking vouchers for patients
* Sleep technician (data collection: conduct and interpretation of sleep studies, fitting of CPAP masks)
* Research Nurse (recruitment and data collection of baseline characteristics)

Additional resources that may be required and will be provided by the researchers in their own time include:

* Assessment of patient records to assess for eligibility
* Data analysis
* Write-up of reports, dissemination of findings

Resources that will provided by in kind contribution of the health service include

* 3 monthly safety and monitoring meetings
* Overnight use of sleep laboratory for sleep test and fitting of masks/CPAP trial.

Supervision

The trial will be overseen by Dr Rebekah Shakhovskoy and Dr Rachael Nugent, who will chair 3 monthly meetings of the steering group. Members of the steering group shall include Dr Shiv Erigadoo, Dr Elise Gilbertson, Dr Lauren Kearney.

This trial will be completed as part of the PhD thesis for Dr Rachael Nugent under the supervision of Prof Caroline de Costa and Prof Robyn McDermott, both of James Cook University. Their supervision will include oversight of protocol design, analysis of results and write up and dissemination of findings.

Dissemination of findings:

The project will be presented locally at our multidisciplinary meetings within Women’s and Families Services in SCHHS, and will be presented at the annual research day.

The findings will be written up and published in a peer reviewed journal (Obstetrics and Gynaecology and/or Sleep journal), and presented at national and/or international conferences.

Benefits to community

If the project is deemed recruitable and acceptable to patients, the pilot will likely continue with a larger scale RCT project and publish in international journals to contribute to the current literature as there is a paucity of data with regards to treating OSA in pregnancy.

## Follow-up

Allocated to intervention

* CPAP
* Ongoing usual cares
* Repeat QoL questionnaire at 36 – 38 weeks gestation

 Usual postpartum care

 If OSA diagnosed in pregnancy, medical review at 12 weeks post partum

## Randomisation

Allocated to usual care

* Repeat QoL questionnaire at 36 – 38 weeks gestation

Allocated to control group

* Ongoing usual cares
* Repeat QoL questionnaire at 36 – 38 weeks gestation

AHI ≥ 15

Excluded

* Not meeting inclusion criteria
* Known SDB treated mechanically
* Patient declines randomisation
* Abnormal CFTS or morph USS
* Known CAD/CCF/cardiomyopathy
* Inability to read and understand consent
* Declined to participate

Demographics

Bloods – FBC, UEC, LFTs

Urine protein-creatinine ratio

neck circumference, weight, BMI

Sleep apnoea diagnostic tool

QoL and Sleep questionnaire

Sleep Study

## Data collection

## Enrolment

Assessment for eligibility

* ≥ 18 years old
* Singleton
* BMI ≥ 35
* < 24 weeks at recruitment
* Primary outcomes – gestational hypertension, pre-eclampsia, eclampsia, low birth weight, pre-term birth ≤ 34 and ≤ 37 weeks gestation and stillbirth
* Secondary outcomes – Number of pregnancy related hospital admissions, post-partum length of stay, hypertension, gestational or pre-existing diabetes, gestational weight gain, onset of labour, mode of birth, estimated blood loss, blood transfusion, ICU admission, maternal death, histological placental examination, gestation at birth, birth weight, admission of neonate to special care nursery, neonatal length of stay, neonatal respiratory support, neonatal death.

## Outcomes

AHI <15

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