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SYSTEMATIC REVIEW

The effectiveness of continuous positive airway pressure for treating obstructive sleep apnoea in pregnancy: A systematic review

Rachael Nugent[1,2], **Amanda Wee**[1], **Lauren Kearney**[2,3] and **Caroline de Costa**[4]

[1]Department of Obstetrics and Gynaecology, Sunshine Coast Hospital and Health Service, James Cook University, Queensland, Birtinya, Australia

[2]The University of Queensland, Brisbane, Queensland, Australia

[3]Royal Brisbane and Womens Hospital, Queensland, Brisbane, Australia

[4]The Cairns Institute, James Cook University, Cairns, Queensland, Australia

Correspondence: Dr Rachael Nugent, Sunshine Coast University Hospital, Women and Families Service Group, James Cook University, Sunshine Coast, Queensland, Australia.
Email: rachael.nugent@health.qld.gov.au

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Background: Obstructive sleep apnoea (OSA) occurs in 15–20% of pregnant women living with obesity. As global obesity prevalence increases, OSA in pregnancy is concurrently increasing, yet remains under-diagnosed. The effects of treating OSA in pregnancy are under-investigated.

Aim: A systematic review was conducted to determine whether treating pregnant women with OSA using continuous positive airway pressure (CPAP) will improve maternal or fetal outcomes, compared with no treatment or delayed treatment.

Materials and Methods: Original studies in English published until May 2022 were included. Searches were conducted in Medline, PubMed, Scopus, the Cochrane Library and clinicaltrials.org. Maternal and neonatal outcome data were extracted, and quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (PROSPERO registration: CRD42019127754).

Results: Seven trials met inclusion criteria. Use of CPAP in pregnancy appears to be well tolerated with reasonable adherence. Use of CPAP in pregnancy may be associated with both a reduction in blood pressure and pre-eclampsia. Birthweight may be increased by maternal CPAP treatment, and preterm birth may be reduced by treatment with CPAP in pregnancy.

Conclusion: Treatment of OSA with CPAP in pregnancy may reduce hypertension and, preterm birth, and may increase neonatal birthweight. However, more rigorous definitive trial evidence is required to adequately assess the indication, efficacy, and applications of CPAP treatment in pregnancy.

KEYWORDS

continuous positive airway pressure, obstructive sleep apnoea, CPAP, OSA, pregnancy

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder characterised by repetitive episodes of nocturnal breathing cessation due to upper airway collapse, resulting in a decrease in oxygen saturation.[1] This condition has an estimated prevalence of 10.5% in early pregnancy increasing to approximately 30% in later pregnancy[2] and is associated with increased pregnancy complications for both mothers and babies.[3,4] For mothers, OSA in pregnancy is associated with increased rates of gestational hypertension, pre-eclampsia and gestational diabetes, and for the infant, is associated with lower birth weight, preterm delivery and neonatal intensive care unit admission.[4,5] Continuous positive airway pressure (CPAP) is an efficacious way to treat OSA in the general population without surgical intervention.[6] There are 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 life.

Obesity is the most common problem in obstetrics affecting both the mother and her offspring.[7] Obesity is strongly linked to OSA during pregnancy,[2] with OSA occurring in 15–20% of pregnant women diagnosed as obese.[2,3] Obesity is also a risk factor for the development of OSA, with disease prevalence increasing with increasing body mass index (BMI).

The standard treatment for obesity during pregnancy (and therefore the management of potential OSA) are lifestyle modifications, such as dietary change and exercise. This advice is recommended by peak body guidelines in the United States of America, the United Kingdom, Australia, and Canada.[8] While lifestyle modifications have demonstrated benefit in reducing gestational weight gain, they have a limited impact upon pregnancy outcomes.[9]

With globally increasing obesity rates, OSA in pregnancy is becoming more common, but is still under-diagnosed. Despite increasing prevalence and associated poor pregnancy outcomes, the effects of treating OSA in pregnancy remain under-investigated. Shared mechanistic pathways with pre-eclampsia and diabetes suggest that treatment of OSA may delay or diminish the significant maternal and fetal sequelae of these conditions; however, few studies have examined the effect of treatment of OSA. Therefore, this review summarises the existing literature on the treatment of OSA in pregnancy using CPAP.

MATERIALS AND METHODS

Search strategy and study selection

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement as the template for reporting the review.[10] Our study protocol was registered with the International prospective register of systematic reviews (PROSPERO) (registration number CRD42019127754). A systematic literature search was performed searching for citations on the use of CPAP in pregnancy in the following four databases up until May 2022: MEDLINE PubMed, Scopus, the Cochrane Library and ClinicalTrials.gov. Search terms were modelled on the PICO principle (patient, intervention, comparator, outcome). Search terms in PubMed included the MeSH terms for pregnancy and CPAP. Terms were combined using the Boolean operator, OR, within each category, and the Boolean operator, AND when combining between exposure and outcome.

Any type of observational study (cross-sectional, cohort, or case–control) or randomised controlled trial (RCT) published was included for review if they studied the use of CPAP in pregnancy comparing it to no treatment or delayed treatment and examined maternal or neonatal outcomes. English language articles only were included, and there was no date or publication status limitation imposed on the search. See Appendix S1 for the full search strategy employed in Medline, PubMed. Bibliographies of included studies were manually screened for relevant citations. Studies were excluded if they were conference abstracts, reviews, or case reports. Animal studies were excluded. All citations were combined, and duplicates excluded.

Two reviewers (RN, AW) independently screened titles, abstracts and full-text articles for inclusion/exclusion criteria. Disagreement between the two reviewers was resolved by consensus.

Data extraction and consensus

Data were extracted by RN using a pre-designed template, including study characteristics, intervention description, and maternal and neonatal outcomes (see Table 1). Study quality was reported using the Cochrane GRADE (Grading of Recommendations, Assessment, Development and Evaluations) checklist.

Data items and analysis

Maternal outcomes (hypertension, pre-eclampsia and adherence) and fetal outcomes (birthweight and preterm birth) were analysed. Outcomes were considered for quality review if they were reported in more than one study.

Studies were independently assessed for risk of bias[11] by RN and AW. Any disagreements were resolved by discussion, and if necessary, referred to a third reviewer (CdeC). The criteria for assessment included random sequence generation, allocation concealment, blinding of participants and outcome assessors, the handling of incomplete data, selective outcome reporting, and other possible sources of bias. An overall risk of bias was then assigned (Fig. 2).

Quality assessment

RN assessed the quality of the evidence for the reported outcomes using the GRADE approach, the findings of which were checked by AW. The GRADEpro Guideline Development Tool was used to create 'Summary of findings' (Table 2). The quality of evidence was

TABLE 1 Summary of the six studies examining the association between maternal CPAP and maternal and fetal outcomes

	Study characteristics			Exposure to CPAP		Reported outcomes		
Author	**Country, population**	**Participants, *n***	**Study design**	**Treatment indication**	**Timing; length of application**	**Maternal**	**Fetal**	**Main study finding**
Blyton et al, 2013[15]	Australia, hospital	10	Observational study of women with pre-eclampsia who underwent two sleep studies on and off treatment	Moderate to severe pre-eclampsia	Third trimester One night off, one night on	Total maternal sleep NREM stages 1&2, % sleep time NREM stages 3&4, % sleep time REM sleep % sleep time Maternal arousals per hour	Fetal movements Fetal hiccups	'The average number of hiccups and fetal movements during the night with CPAP was greater than during the night without CPAP'[18]
Blyton et al, 2004[12]	Australia, hospital	24 with PET; 15 controls	Randomised controlled trial	Severe pre-eclampsia	Third trimester One night off, one night on	Total maternal sleep REM and non-REM sleep Respiratory Disturbance Index Cardiac output Blood pressure† and heart rate Stroke volume Peripheral vascular resistance	Perinatal death Birth weigh‡	'Patients on CPAP had a reduction in cardiac output and in total peripheral resistance'[18] There was an association between increased CO and increased birthweight centile
Poyares et al, 2007[14]	Brazil, clinics with pre-existing HTN	16 women: 7 CPAP, 9 no CPAP	Randomised controlled trial	Pre-existing hypertension on medication and chronic snoring	<20 weeks	Vaginal delivery Postpartum visits Snoring as per bed partner BP† Adherence†	Birth weight† Apgar 1 min Preterm delivery†	
Chirakalwasan et al, 2018[13]	Thailand, clinics	18 treatment; 18 controls	Randomised controlled trial	GDM on MNT BMI ≥ 25 OSA diagnosed by REI ≥ 5	Second and third trimester Two weeks CPAP or waitlist control, then offered to all	Glucose metabolism CPAP average nightly use Adherence† Insulin use Total gestational weight gain Pre-eclampsia† Unplanned CS	Gestational age at delivery Birth weight† Preterm delivery† Apgar at 1 min Apgar at 5 min SGA LGA SGA or LGA	Two weeks of CPAP in females with GDM and OSA did not result in improved glucose levels, but insulin secretion improved in those adherent to CPAP. Continued CPAP was possibly associated with improved pregnancy outcomes

TABLE 1 Continued

Author	Study characteristics			Exposure to CPAP		Reported outcomes		
	Country, population	Participants, *n*	Study design	Treatment indication	Timing; length of application	Maternal	Fetal	Main study finding
Edwards et al, 2000[16]	Australia, hospital	11 women	Observational single-arm study (two overnight sleep studies on and off CPAP)	Severe pre-eclampsia	Third trimester Overnight off then on	Total maternal sleep Non-REM stages 1&2 Non-REM stages 3&4 BP† Heart rate Uric acid	Nil	'Reduction of SBP (-18 mmHg) and diastolic BP (-19 mmHg) while on treatment'[18] Reduction in uric acid on the night treated with CPAP
Guilleminault et al, 2007[17]	USA, clinics	12 women	Prospective longitudinal uncontrolled study	High risk for pre-eclampsia	First trimester Until delivery	Total maternal sleep REM sleep Stages 3–4 non-REM Stage 2 non-REM BP† Pre-eclampsia† Miscarriage Adherence†	SCN/NICU admission Birthweight‡	All subjects with chronic hypertension maintained BP below 140/90 during pregnancy. Three out of 12 women had poor pregnancy outcomes
Stajić et al 2022[18]	Serbia, clinics	110	Prospective longitudinal controlled study	High-risk pregnancy ESS > 10 REI > 5 Significant night-time desaturation <90% Snoring Quantitative or qualitative pulse disorders	24 to 28 weeks gestation	Deepest nocturnal desaturation ESS Adherence† Gestational hypertension Mild pre-eclampsia† Moderate pre-eclampsia† Caesarean section	Birthweight† Gestational age at delivery† Apgar at 1 min Apgar at 5 min	CPAP therapy significantly reduced the incidence of severe forms of hypertensive syndrome (mild and moderate pre-eclampsia) in pregnant women with OSA

Note: BP, blood pressure; CO, cardiac output; CPAP, continuous positive airway pressure; CS, caesarean section; ESS, epworth sleepiness scale; GDM, gestational diabetes mellitus; HTN, hypertension; LGA, large for gestational age; MNT, medical nutrition therapy; NICU, neonatal intensive care unit; NREM, non rapid eye movement; OSA, obstructive sleep apnoea; REM, rapid eye movement; REI, respiratory event index; SCN, special care nursery; SGA, small for gestational age; SPB, systolic blood pressure; USA, United States of America.

†Outcomes included for quality assessment.

‡Outcome included for quality assessment, but incomplete data available.

TABLE 2 Summary of findings for maternal and neonatal outcomes

Maternal outcomes

Outcome	Studies	Findings	Rating	Quality assessment
Blood pressure[17]	Blyton et al 2004[12]	Overnight study only in *n* = 24 women diagnosed with severe pre-eclampsia, randomly assigned to receive CPAP or no treatment. BP was reduced in sleep compared to wakefulness when women were treated with CPAP. Overall MAP was reduced by 3 mmHg when comparing treatment to non-treatment group. (*P* = 0.005)	Study design: Risk of bias Inconsistency Indirectness Imprecision Publication bias Upgrading factors	Start low RCT × 2, PCS × 2 None detected (0) None(0) Serious (−1) None(0) Likely (−2) None (0) Very low-quality evidence
	Edwards et al 2000[16]	All women with chronic hypertension already on medication, none had an increase in BP over pregnancy. Significant compared to untreated group. *n* = 7/*n* = 9		
		Overnight study in women diagnosed with pre-eclampsia. *n* = 11 Demonstrated significant reduction in systolic and diastolic BP across all sleep phases (NREM 1&2, NREM 3&4, REM and total sleep) when comparing sleep without CPAP and sleep with CPAP in same subjects from night to night. The treatment group had an overall 10 mmHg lower systolic and diastolic blood pressure which were both statistically significant (*P* = 0.006 and *P* = 0.004 respectively)		
	Poyares et al 2007[14]	Reduction in medication required for CPAP women. Significant change in systolic BP (*P* = 0.001) and higher diastolic (*P* = 0.0003) BP at 32 weeks in control group. Suggests significant BP control in third trimester reducing medication requirement (methyldopa 750 mg in CPAP group vs 2000 mg in control group).		
	Guilleminault et al 2007[17]	Sample size of seven women with history of chronic hypertension maintained BP < 140/90 during pregnancy. Mean SBP 128 ± 3 mmHg, Mean DBP 86 ± 2.2 mmHg at the ninth month obstetric exam. No medication adjustment was required, not necessary from the third month until delivery. No significant BP increase over time in these women.		
Pre-eclampsia	Chirakalwasan et al 2018[13]	No difference in pre-eclampsia between CPAP and waitlist control, no difference between ≤2 weeks CPAP and >2 weeks CPAP	Study design: RCT and PCS Risk of bias Inconsistency Indirectness Imprecision Publication bias Protective factors	Start moderate Serious (−1) Serious (−1) Serious (−1) Serious (−1) Serious (−1) None Very low-quality evidence
	Guilleminault et al 2007[17]	Two out of 12 women in 'high risk' group of PCS developed pre-eclampsia		
	Stajić et al 2022[18]	Patients with OSA treated conservatively had significantly more mild and moderate pre-eclampsia (24% vs 8% *P* = 0.02)		
Adherence	Chirakalwasan et al 2018[13]	Variable compliance, with an average rate of adherence of 46.7% (or seven out of 15 women who used the device).	Study design: Risk of bias Inconsistency Indirectness Imprecision Publication bias Upgrading factors	Start moderate RCT × 2, PCS × 2 None detected (0) Serious (−1) None (0) None (0) None detected (0) None (0) Low-quality evidence
	Poyares et al 2007[14]	Brazilian study with *n* = 7 women randomised to the CPAP treatment group and used the machine for a mean of 6 h per night, 7 days a week.[14]		
	Guilleminault et al 2007[17]	A USA prospective cohort study which includes 12 women who have risk factors for pre-eclampsia treated with CPAP from early pregnancy. All women using nasal CPAP nightly with a mean usage of 5.4 ± 0.6 h, seven nights a week from early pregnancy until the end of pregnancy.[17]		
	Stajić et al 2022[18]	Serbian study with *n* = 41 women with OSA treated conservatively (medicaments for various indications, psychological, postural therapy), and *n* = 50 women with OSA were offered the same and treated with CPAP. Median compliance to CPAP use was 6.1 ± 1.0 h per night for four weeks from 24 to 28 weeks.		

TABLE 2 Continued

Maternal outcomes				
Outcome	**Studies**	**Findings**	**Rating**	**Quality assessment**
Birthweight	Chirakalwasan et al 2018[13]	Birthweights not significantly different in women with GDM: CPAP for two weeks vs weight-listed controls. No significant difference in birthweight between >2 weeks and CPAP ≤ 2 weeks (3099 g ± 509 vs 3196 ± 608, *P* = 0.605) in post-hoc analysis.	Study design: RCT x 2 Risk of bias Inconsistency Indirectness Imprecision Publication bias Upgrading factors	Start high Serious (−1) Serious (−1) None (0) Serious (−1) Not detected (0) None (0) Very low-quality evidence
	Poyares et al 2007[14]	Birthweights not significantly different between CPAP treated (*n* = 7) mean weight 2928.8 ± 796.9 g and controls (*n* = 9) 2860 ± 757.9 g in a Brazilian population with hypertension in early pregnancy.		
	Stajić et al 2022[18]	Birthweight was significantly lower in the OSA group without CPAP treatment (3448.9 + 405 vs 3207.6 + 522.9, *P* = 0.02)		
Prematurity	Chirakalwasan et al 2018[13]	Secondary analysis of one study suggested a reduction in preterm delivery in women CPAP > 2 weeks compared ≤2 weeks (*n* = 23 vs *n* = 13).The intention-to-treat analysis of the same data suggested no difference in premature birth between the CPAP treatment and non-treatment groups.	Study design: RCT 2, PCS 1 Risk of bias Inconsistency Indirectness Imprecision Publication bias Upgrading factors	Start moderate None (0) Serious (−1) None (0) Serious (−1) Serious (−1) None (0) Very low-quality evidence
	Poyares et al 2007[14]	Brazilian RCT of women with hypertension treated from the first trimester. One out of nine untreated controls vs zero out of eight women in CPAP treatment arm delivered before term.		
	Stajić et al 2022[18]	The prevalence of preterm labour in the OSA group treated with CPAP was 4%, in the OSA group with conservative treatment 20% *P* = 0.03. Pregnant women with OSA conservatively treated (no CPAP) had significantly earlier delivery 38.1 ± 1.6 vs 39.2 ± 1.7 GW *P* = 0.01.		

assessed using five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) for each outcome.

RESULTS

General characteristics of included studies

Seven studies met inclusion criteria (see Fig. 1). The characteristics of these studies are summarised in Table 1. Three of the studies were RCTs,[12–14] and the remainder were small-scale interventional studies of which three were cohort studies and one was a non-RCT.[15–18] Demographic and intervention diversity was significant, with studies varying in participants, interventions and outcomes studied and significant methodological heterogeneity. Meta-analysis was not able to be undertaken due to heterogeneity in the study outcomes. For example, treatment for a variety of indications (from diagnosed sleep apnoea with an Apnoea/Hypopnoea Index (AHI) >3 to displaying several risk factors for the development of pre-eclampsia); and length of treatment application varied from considering single parameters such as blood pressure (BP) during a one-off treatment overnight, to persistently using CPAP from early pregnancy until delivery at term.

Definition of exposure and outcome

Indication for CPAP ranged between studies from risk factors for pre-eclampsia, to severe pre-eclampsia requiring hospital admission, to OSA confirmed on polysomnography (PSG) with an AHI >3. The application of the intervention ranged from overnight in the third trimester in several studies, to nightly CPAP from early pregnancy to CPAP from the diagnosis of gestational diabetes mellitus (GDM) in the third trimester, to a four-week block of CPAP between 24 and 28 weeks.

Maternal outcomes

Blood pressure

Four studies examined the impact of treatment with CPAP on maternal BP.[12,14,16,17] Two of these studies were conducted on women overnight in the third trimester and examined the effect of BP on women admitted with pre-eclampsia, compared to no treatment. Blyton et al[12] randomised 24 women diagnosed with pre-eclampsia to subsequent nights of polysomnography monitoring, and either treatment or no treatment with CPAP. This group found that when pre-eclamptic women were treated with nocturnal nasal CPAP, BP was reduced during sleep compared with wakefulness. It also concluded that in pre-eclamptic women

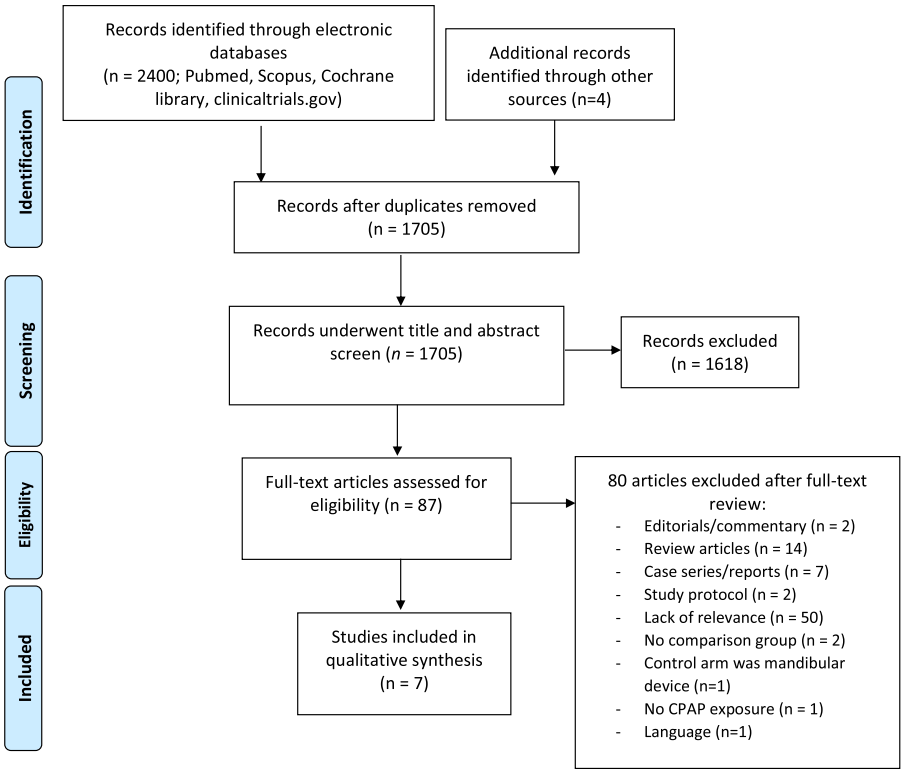

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

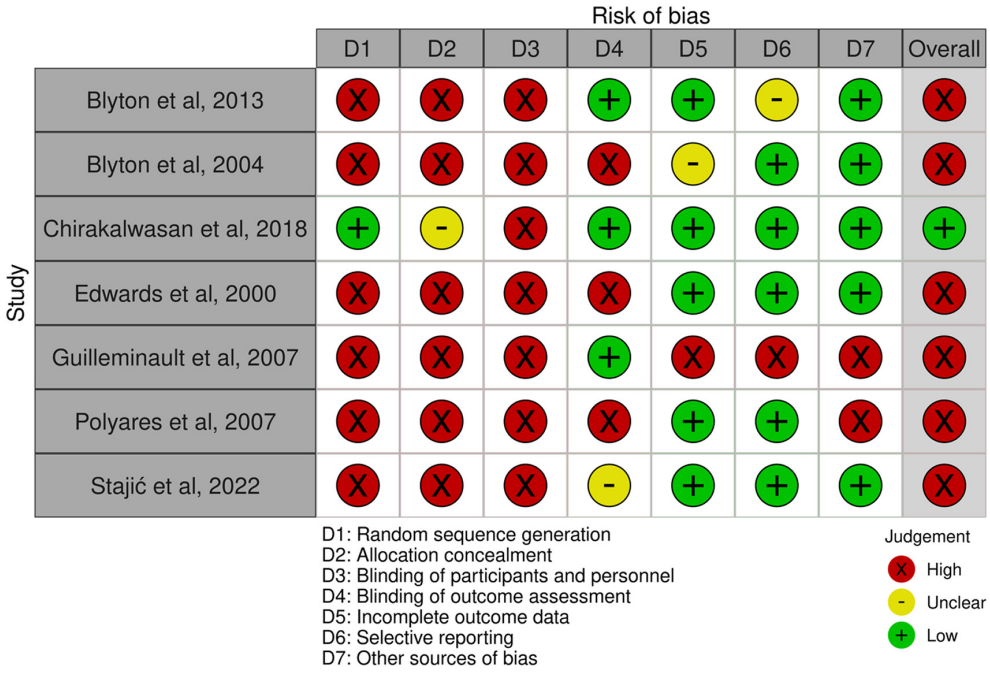

FIGURE 2 [28]Risk of bias assessment.

overnight treatment with CPAP reduces mean arterial pressure by 3 mmHg when compared with no treatment with CPAP ($P = 0.005$).

Edwards et al[16] examined the effect of a single night's treatment with CPAP in 11 pre-eclamptic women in a prospective cohort study. This study demonstrated statistically significant reduction in systolic and diastolic BP (10 mmHg, each $P = 0.006$ and $P = 0.004$ respectively) across all sleep phases when comparing sleep without CPAP and sleep with CPAP in the same participants from night to night.

The effect of sustained use of CPAP in pregnancy on BP values has been assessed in two RCTs. Poyares et al[14] recruited women in Brazil with existing medicated hypertension and snoring in

early pregnancy. Women were randomised to routine care (n = 9) or routine care with CPAP (n = 7). The authors found a significant decrease in systolic and diastolic BP over the course of the pregnancy when compared to the non-CPAP group. Additionally, women treated with CPAP on average had a methyldopa dose of 750 mg compared to the no CPAP women on 2000 mg of methyldopa on average. Despite the higher dose of methyldopa in the non-CPAP patients, BP was significantly higher in the non-CPAP patients at 32 and 35 weeks gestation (P = 0.0003).

Guilleminault et al's[17] prospective cohort of seven women with a history of chronic hypertension found women treated with CPAP from early pregnancy, maintained BP <140/90 during pregnancy. The mean systolic BP was 128 ± 3 mmHg and mean diastolic BP was 86 ± 2.2 mmHg at the nine-month obstetric examination. No medication adjustment was required from the third month of gestation until delivery, and no significant BP increase over time was observed. Overall, the literature demonstrates CPAP is associated with both short-term[12,16] (overnight) and longer-term,[14,17] (over the duration of the pregnancy) reduction in BP. It may also be associated with a reduction of medication dosage required to control BP in women with chronic hypertension in the third trimester. The quality of this evidence is very low due to indirectness and publication bias (Table 2).

Pre-eclampsia

Three studies considered the impact of CPAP treatment on the incidence of pre-eclampsia. Chirakalwasan et al's[13] RCT recruited women with a GDM diagnosis in Thailand, (n = 36). A secondary prospective cohort study recruited women with a risk factor for pre-eclampsia such as previous pre-eclampsia, obesity or chronic hypertension in the USA (n = 12). Stajić et al's[18] prospective cohort study recruited women in Serbia with high-risk pregnancies and an Epworth Sleepiness Scale score of ≥10 (n = 110). There was significant clinical heterogeneity between the three studies, both in terms of participants recruited, and application of intervention.

The Thai trial[13] completed an intention-to-treat and per-protocol analysis comparing women who underwent treatment of OSA with CPAP in pregnancy in women with diagnosed GDM. There was no significant difference in rates of pre-eclampsia in either analysis, although the study was not adequately powered to look at this outcome. The RCT initially randomised to immediate CPAP or waitlist control, with CPAP offered to the control group after two weeks as a waitlist control for ethical reasons. The study then compared the outcomes of women who underwent ≤2 weeks of CPAP with those who had >2 weeks of CPAP. There was no significant difference in rates of pre-eclampsia between the two groups. Guillemniault's prospective cohort study recruited 12 women with risk factors for pre-eclampsia such as chronic hypertension, obesity or previous pre-eclampsia and observed two women developed pre-eclampsia. Stajić's study recruited 110 women into three groups: pregnant women with OSA starting CPAP treatment for four weeks between 24 and 28 gestational weeks, women with OSA treated conservatively, and women without OSA treated as a control group. Women with OSA treated with CPAP (n = 50) had significantly lower rates of mild and moderate pre-eclampsia than women with OSA who were conservatively managed (n = 41).[18]

Treating OSA in pregnancy with CPAP may reduce the incidence of pre-eclampsia. The quality of this evidence is very low due to selection bias, inconsistency, indirectness, imprecision and publication bias. See Table 2 for details of quality assessment.

Adherence

Four studies examined maternal adherence to CPAP treatment.[13,14,17] Reasonable CPAP adherence was considered ≥4 h per night for 70% of nights.[13] Eighty-four women overall were examined for adherence data across two RCTs (n = 15, n = 7) and two prospective cohort studies (n = 12, n = 50). Adherence findings were mixed. Chirakalwasan et al's[13] study found variable compliance, with an average rate of adherence of 46.7% (or seven out of 15 women who used the device). This may have been related to the degree of symptoms experienced by women, as generally this study found higher rates of adherence in women experiencing worse symptoms of daytime somnolence.

The alternative RCT from Brazil[14] found the seven women randomised to the CPAP treatment group used the machine for a mean of six hours per night, seven days a week. This group demonstrated very good treatment compliance, suggesting acceptability to the women treated. One prospective cohort study, which included 12 women treated with CPAP from early pregnancy, also suggested good adherence with all women using nasal CPAP nightly with a mean usage of 5.4 ± 0.6 h, seven nights a week from early pregnancy until the end of pregnancy.[17] A larger Serbian study recruited 50 women for treatment with CPAP between 24 and 28 weeks, and showed median compliance to CPAP use was 6.1 + 1.0 (4.5–8.5) h per night.[18]

This data suggest that CPAP adherence may be variable, with some populations experiencing extremely good compliance, and some experiencing variable compliance. The quality of this evidence is low due to inconsistency (Table 2).

Neonatal outcomes

Birthweight

RCT evidence alone suggests no significant difference in child birthweight between women allocated to the CPAP treatment arm compared to women allocated to usual care.[13,14] Child birthweights were not significantly different in women with GDM: CPAP for two weeks vs weight-listed controls. Also, there was no significant difference in birthweight between CPAP >2 weeks and CPAP ≤2 weeks (3099 g ± 509 vs 3196 ± 608, P = 0.605) in post-hoc analysis.

Birthweights were not significantly different between babies of women treated with CPAP and untreated controls in a Brazilian study of women with hypertension in early pregnancy.[14]

The treated population (n = 7) had a mean birthweight of 2928.8 ± 796.9 g and untreated controls (n = 9) 2860 ± 757.9 g. Conflicting data have emerged from a larger prospective cohort study examining women with high-risk pregnancy and high Epworth Sleepiness Scale with OSA who self-assigned to treatment with CPAP (n = 50) or conservative management (n = 41). In this Serbian study, neonatal birthweight was significantly higher in women with OSA treated with CPAP compared with women with OSA managed conservatively, by over 200 g.[18] Overall quality of this evidence was very low due to selection bias, inconsistency, and imprecision.

Prematurity

Two RCTs and one prospective cohort study have examined the outcome of preterm birth in women treated with CPAP.[13,14,18] Secondary analysis of a Thai study found women with GDM suggested a reduction in preterm delivery in women with CPAP >2 weeks compared ≤2 weeks (n = 23 vs n = 13).[13] This was a post-hoc analysis. The intention-to-treat analysis suggested no difference in premature birth between the treatment and non-treatment groups. It is likely that adherence may play a role in the reduction of preterm birth. A Brazilian study examining CPAP in women with pre-existing hypertension and snoring found one out of nine controls vs zero out of eight women on treatment delivered before term. While the results are overall positive, the sample size was small and not powered to detect a clinically significant difference.

A larger Serbian cohort study found a significant reduction in the prevalence of preterm labour in the OSA group treated with CPAP (4%), compared to the OSA group treated conservatively (20%).

Use of CPAP in pregnancy may be associated with reduced preterm birth in populations at risk of pre-eclampsia such as women diagnosed with GDM or pre-existing hypertension.

Risk of bias across studies

Following assessment of individual studies for risk of bias (see Fig. 2), an assessment of the quality of the evidence for each outcome measure was undertaken. In grading the quality of the evidence, the following domains were considered: study design, risk of bias across studies, inconsistency, indirectness, imprecision, and publication bias. Upgrading factors such as a large effect size, dose response relationship or no plausible confounding were considered. All outcomes were awarded a low or very low quality of evidence rating.

Only a small number of studies were suitable for inclusion in this systematic review. All reported positive outcomes or managed in post-hoc analysis to ensure the analysis of their data to suggest some positive finding, raising concerns regarding publication bias. Standardisation of reporting data sets including tabled reporting of maternal characteristics such as maternal age, BMI and parity as well as outcome measures would allow more meaningful assessment of the range of small-scale trials and observational studies which have been conducted. Larger-scale RCTs are required.

DISCUSSION

Women diagnosed with OSA in pregnancy experience increased rates of gestational hypertension, pre-eclampsia, gestational diabetes and delivery of a low birthweight infant.[4] OSA and gestational hypertension share common inflammatory pathways including increased weight gain, fluid retention, and elevated BP.[19] The mechanism through which pre-eclampsia is exacerbated by OSA is thought to be by induction of hypoxia in the human placenta which leads to the production of inflammatory cytokines.[20] In non-pregnant populations, the use of CPAP to treat OSA has been associated with a reduction in hypertensive disease.[21]

There has also been suggestion that because OSA and metabolic syndrome and/or type 2 diabetes frequently co-exist, there can potentially be metabolic and haemodynamic interaction.[21] There is evidence that regular snoring and OSA are independently associated with alterations in glucose metabolism.[29] Thus, OSA might be a risk factor for the development of type 2 diabetes. Possible causes might be intermittent hypoxia and sleep fragmentation, which are typical OSA features. The different associations of OSA and type 2 diabetes need further investigation[30] and especially in the pregnant population.

While the relationship between OSA and poorer pregnancy outcomes has been demonstrated,[22] there is limited evidence describing the impact for maternal and fetal outcomes when treating OSA in pregnancy with CPAP.

Regarding maternal outcomes, the use of CPAP in pregnancy appears to reduce BP overnight[12,16] and throughout the pregnancy when consistently used.[13,14] One of the studies suggested an overall 10 mmHg lower reading in both systolic and diastolic measurements in the treatment group.[16] Women treated with CPAP for a prolonged period appear to have reduced medication needs compared with their untreated counterparts[14] and a more stable medication requirement over pregnancy has been described.[17] In accordance with this clinical reduction in BP in the third trimester with CPAP treatment, rates of pre-eclampsia in treated women may be reduced, although data is conflicting[13,17,18] (very low-quality evidence).

Sleep disordered breathing in pregnancy was associated with low birthweight infants[4] in a 2014 metanalysis by Pamidi et al. Birthweight was therefore selected as a reported outcome and was reported in three studies.[13,14,18] Two further studies reported birthweight in centiles[12,17] but these data were incomplete. While two smaller studies reported no significant difference in birthweight for women treated with CPAP in pregnancy,[13,14] a larger Serbian cohort study found a significant increase in birthweight for women with OSA treated with CPAP vs their conservatively managed comparators.[18]

This was very low-quality evidence based on three small intervention trials with limited numbers. The percentile birthweight data reported in the observational studies were incomplete and \ therefore could not be assessed. Further investigation is required with large prospective RCTs to determine the impact of treatment with CPAP in rates of pre-eclampsia and growth restriction.

Participants generally had good adherence (low-quality evidence), suggesting acceptability of the intervention in pregnancy. 'Good adherence' was defined as more than 4 h/night on CPAP for more than 70% of the time.[13] No serious side effects or complications were reported in any study. Guilleminault[23] has previously reported on 12 pregnant women with sleep disordered breathing. Women in this study commonly complained of 'morning nasal congestion' and bed partners reported snoring.[23] Use of CPAP appears to be safe in pregnancy, based on the small number of reported studies available. An observational cohort study demonstrated that CPAP was not sufficient to prevent pregnancy-related adverse clinical outcomes[17] with a second trimester pregnancy loss, a preterm birth secondary to pre-eclampsia at 31 weeks via caesarean and an additional preterm birth at 30 weeks secondary to pre-eclampsia reported in three of the 12 participants. Women were recruited if they had additional risk factors for pre-eclampsia in early pregnancy such as obesity, pre-existing hypertension, or previous pregnancy affected by pre-eclampsia.

This systematic review of the literature assessing maternal and neonatal outcomes for treatment with CPAP during pregnancy yielded seven studies, three of which were RCTs. Heterogeneity of study design, participants, treatment application and reporting of results was sufficient to preclude meta-analysis. Standardised outcome reporting in studies in obstetrics is required to improve the quality of the evidence and allow the pooling of similar studies to enable more powerful assessment of intervention effects on maternal and neonatal outcomes.

An online search of clinicaltrials.gov has revealed there are two RCTs that have completed their study and are in the process of publishing their findings. One was done in the USA with 193 patients, the other was done in Thailand with 340 patients. There is currently one multicentre RCT in the process of recruiting in the USA and they are aiming to recruit 1500 patients which would be the largest RCT looking at CPAP for sleep apnoea in pregnancy. The data from these studies will add much to what is known about the efficacy and safety of CPAP for sleep apnoea in pregnancy.

A recent study compared four national guidelines for the management of obesity during pregnancy.[24] This work analysed the guidance of the American College of Obstetrics and Gynecology[25] (ACOG), the Royal College of Obstetrics and Gynaecology[26] (RCOG), the Australian and New Zealand College of Obstetrics and Gynaecology[27] (RANZCOG) and the Society for Obstetrics and Gynaecology of Canada[8] (SOGC). ACOG recognises that OSA is increased in obese women in pregnancy and recommends screening with referral to specialists as needed.[25] No further management recommendations were made regarding the treatment of OSA in the obese population in pregnancy. RANZCOG[27] and SOGC[8] guidelines acknowledge that rates of OSA are increased in the obese population and that exercise may help control symptoms. Further recommendations regarding screening, diagnosis or treatment are absent. The RCOG guideline for the management of obesity in pregnancy does not comment on OSA.[26] Further robust data on OSA in pregnancy and its treatment with CPAP are required.

There are several important limitations to this systematic review. A high risk of bias was considered in most studies across several domains. The small number of available studies which in turn had small numbers of participants increased the likelihood of indirectness bias. Imprecision bias may be problematic due to large confidence intervals and small effect sizes. Positive publication bias is likely reflected in the overrepresented positive findings in the literature. There was a high degree of heterogeneity among studies regarding the recruited population, the application and timing of the therapy in pregnancy and therefore caution must be exercised in generalisation of the results.

We have reviewed the available data for impact of CPAP in pregnancy on maternal and neonatal outcomes and very low-quality evidence suggests that CPAP may reduce BP and pre-eclampsia, reduce prematurity and increase birthweight. Although OSA is recognised as a risk factor for worsening maternal and neonatal health, there is limited high-quality evidence to support its efficacy as a treatment for OSA in pregnancy, and to show significant impact on maternal and neonatal outcomes. Large prospective randomised trials are required to investigate optimal indication for CPAP in pregnancy, and to improve precision of estimated effects on selected outcome measures. Standardised reporting of outcome measures in obstetric studies is required to facilitate pooling and meta-analysis of results.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1