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Referral practices and treatment of obstructive sleep apnea in pregnancies with obesity

Samantha Warhurst[1] | Ekavi Georgousopoulou[2] | Farah Sethna[3] | Hsin-Chia Huang[4]

[1]Department of Respiratory and Sleep Medicine, Canberra Health Services, Canberra, Australian Capital Territory, Australia

[2]Centre for Health and Medical Research, ACT Health Directorate, Canberra, Australian Capital Territory, Australia

[3]Department of Obstetrics and Gynaecology, Centenary Hospital for Women and Children, Canberra Health Services, Canberra, Australian Capital Territory, Australia

[4]Department of Respiratory and Sleep Medicine, Canberra Health Services and Medical School, College of Health and Medicine, Australian National University, Canberra, Australian Capital Territory, Australia

Correspondence
Hsin-Chia Huang, College of Health and Medicine, Australian National University, Canberra, ACT, Australia.
Email: carol.huang@act.gov.au

Abstract

Objective: Obstructive sleep apnea (OSA) affects maternal and neonatal health during pregnancy. This study aimed to identify characteristics and comorbidities associated with sleep clinic referral in high-risk pregnancies with Body Mass Index (BMI) ≥35 kg/m^2.

Method: Retrospective cohort study for individuals in a high-risk pregnancy clinic at a tertiary Australian hospital from 1 January to 31 December 2020 with BMI≥35 kg/m^2. The primary outcome measure was sleep clinic referral. Exposure data included multiple comorbidities and formal tools (Epworth Sleepiness Scale and STOP-BANG). Multivariable analysis was used to identify factors associated with referral. Descriptive data on barriers to diagnosis and treatment were collected.

Results: Of 161 pregnant individuals, 38.5% were screened using formal tools and 13.7% were referred to sleep clinic. Having STOP-BANG performed was associated with sleep clinic referral (Odds Ratio: 18.04, 95% Confidence Interval:4.5–71.7, $p < 0.001$). No clinical characteristics were associated with the likelihood of performing STOP-BANG. The COVID-19 pandemic was a treatment barrier for three individuals.

Conclusions: Current screening practices identify pregnant individuals with the highest pre-test probability of having OSA. Future research should evaluate real-world strategies to improve identification and management in this high-risk population.

KEYWORDS
COVID-19, obesity, obstructive sleep apnea, positive airway pressure, pregnancy, screening

Abbreviations: ACT, Australian Capital Territory; AHI, Apnea Hypopnea Index; BMI, Body Mass Index; COMS, Canberra Obesity Management Service; COVID-19, Novel Coronavirus; ESS, Epworth Sleepiness Scale; ODI, Oxygen Desaturation Index; OSA, Obstructive Sleep Apnea; PSG, Polysomnography.

The study was conducted at the Canberra Hospital, Canberra Health Services, ACT, Australia.

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1 | INTRODUCTION

Obstructive Sleep Apnea (OSA) is an important comorbidity of pregnancy as it is associated with increased maternal and neonatal morbidity. OSA in pregnancy is linked to gestational hypertension, pre-eclampsia and eclampsia as well as unplanned caesarean section, pulmonary embolism, gestational diabetes and cardiomyopathy.[1–5] Maternal OSA is also associated with preterm birth and small for gestational age infants.[2] There are also likely longitudinal effects; moderate OSA in high-risk pregnancies is associated with increased risk of developmental delay seen in children aged 6–36 months.[6]

The prevalence of OSA (defined as an Apnea Hypopnea Index [AHI] ≥5) in pregnant individuals with an elevated Body Mass Index (BMI) appears to be high. The prevalence of OSA was as high as 43.3% measured between 24 and 32 weeks of gestation for those with BMI ≥40 kg/m^2.[4] For those with elevated BMI, the pre-test probability of antenatal OSA is high and accurate identification and timely management is important to potentially prevent maternal and fetal complications.

It is unclear how OSA is currently screened in real-world high risk obstetric clinics and there are currently no guideline recommendations despite the knowledge that OSA is a significant risk to both mother and infant. A survey of obstetric anesthesiologists found that 82.7% did not have departmental guidelines for the assessment and management of OSA in pregnancy.[7] Referral rates increase with a streamlined referral pipeline, but completion rates for sleep studies are still suboptimal, even when individuals are seen in a specialist obstetric sleep clinic.[8] Evidence supporting use of traditional screening tools (e.g., STOP-BANG[9]) in pregnancy is inconsistent, especially for individuals with BMI ≥35 kg/m^2.[10–12] These traditional tools incorporate characteristics irrelevant to most pregnant individuals for example, male gender and age over 50 in STOP-BANG. Other screening tools have been developed specifically for pregnancy, for example, Facco and colleagues' tool, which utilizes frequent snoring, chronic hypertension, age and BMI in its calculation.[13]

There is little published on the barriers to OSA diagnosis and treatment in pregnancy. Positive airway pressure (PAP) therapy is the mainstay of treatment and is associated with decreased diastolic blood pressure and risk of pre-eclampsia in high risk pregnancies.[14] Previously, low suspicion for OSA, inconvenience, and concerns about testing and treatment equipment have been documented as barriers to OSA testing.[8] COVID-19 lockdowns and OSA diagnosis late in pregnancy may also be barriers to initiation and continuation of OSA treatment.

1.1 | Aims and hypotheses

This study aimed to identify the individual characteristics and comorbidities associated with referral to sleep clinic, for pregnancies seen in the Bariatric, Multidisciplinary Clinic (BuMP clinic) at an Australian tertiary hospital using a retrospective cohort study. As part of this clinic, it is anticipated that most pregnant individuals will be screened for sleepiness and OSA, using ESS and STOP-BANG, respectively, as well as general questioning around sleep and somnolence. It is not clear how formal screening tools are used in making referral decisions and whether clinicians also utilize information such as demographics, symptoms and relevant comorbidities (e.g., hypertension, previous pre-eclampsia, BMI).

Secondarily, this study aimed to identify the barriers to OSA diagnosis and treatment in individuals from the 'BuMP clinic' who attended the sleep clinic. This was collected descriptively from patient records.

2 | METHOD

2.1 | Study setting, design and exclusion criteria

This study collected retrospective data from medical records of all pregnant individuals seen in 'BuMP Clinic' for high-risk pregnancies with BMI ≥35 kg/m^2 who gave birth between 1 January 2020 and 31 December 2020. The BuMP clinic is an obstetrician-led service in a tertiary hospital in Canberra, Australia, which serves approximately 650,000 people.[15] Individuals in the BuMP clinic are also seen by midwives, diabetes educators and endocrinologists. There are no sleep physicians directly involved in the clinic. As a publicly funded service, patients receive medical consultations and polysomnography with no out-of-pocket costs, but were required to fund their own therapy if OSA was diagnosed.

Individuals were excluded if they gave birth at another hospital. If a participant had more than one pregnancy during the study period, only the first was included.

2.2 | Data collection

Manual file audit and automatic data extraction from the Birthing Outcomes System (BOS) were used to collect data on multiple demographic characteristics and comorbidities by the first author. The primary outcome measure was referral to a sleep clinic (Yes/No). Other variables are shown in Table 1 and included patient demographics, cardiometabolic and respiratory comorbidities, data on screening outcomes (Epworth Sleepiness Scale[16] and STOP-BANG score) and pregnancy characteristics. For individuals referred to the sleep clinic, data were collected on whether they attended and then completed polysomnography (PSG). If PSG was completed, the Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), gestation of both diagnosis and treatment (in weeks) and attendance at follow-up post-partum were recorded.

2.3 | Statistical analysis

Normality was tested graphically via histograms. Continuous variables were presented as mean (standard deviation) or median (1st,

TABLE 1 Individual characteristics by referral to sleep clinic using univariate analysis ($N = 161$).

	Referred to sleep clinic ($n = 22$)	Not referred to sleep clinic ($n = 139$)	Significance[a] (p)
Age at delivery, years, mean (SD)	30.32 (5.44)	30.35 (5.10)	0.720
Booking BMI, kg/m^2, mean (SD)	44.32 (5.60)	43.69 (6.36)	0.650
ESS performed, *n* (%)	22 (100%)	40 (28.8%)	**<0.001**
STOP-BANG performed, *n* (%)	19 (86.4%)	43 (30.9%)	**<0.001**
ESS, median (1st–3rd quartile range)	11 (8–15)	3 (2–4)	**<0.001**
STOP-BANG, median (1st–3rd quartile range)	3 (2–4)	2 (1–2)	**<0.001**
Country of birth			
Australia, *n* (%)	21 (95.5%)	128 (92.1%)	0.425
Overseas, *n* (%)	1 (4.5%)	11 (7.9%)	
Indigenous[b], yes *n* (%)	4 (28.6%)	10 (7.2%)	0.089
Number of miscarriages			
Nil, *n* (%)	10 (45.5%)	84 (60.4%)	**0.003**
One, *n* (%)	5 (22.7%)	33 (23.7%)	
Two or more, *n* (%)	7 (31.8%)	22 (15.8%)	
Hypertension			
Prior to pregnancy, *n* (%)	2 (9.1%)	18 (12.9%)	0.610
Prior to 20 weeks, *n* (%)	1 (4.5%)	9 (6.5%)	0.728
After 20 weeks, *n* (%)	5 (22.7%)	22 (15.8%)	0.421
History of pre-eclampsia, yes *n* (%)	1 (4.5%)	5 (3.6%)	0.827
History of diabetes (non-gestational), yes *n* (%)	2 (9.1%)	0 (0%)	**<0.001**
Gestational diabetes			
Previous pregnancy, *n* (%)	5 (22.7%)	17 (12.2%)	0.183
Current pregnancy, *n* (%)	12 (54.5%)	62 (44.6%)	0.385
Previous diagnosis of sleep apnea, yes *n* (%)	0 (0%)	2 (1.4%)	0.571
History of asthma, yes *n* (%)	6 (27.3%)	32 (23.0%)	0.663
History of smoking			
Prior to pregnancy, *n* (%)	7 (31.8%)	27 (19.4%)	0.186
During current pregnancy, *n* (%)	3 (13.6%)	18 (12.9%)	0.929

Note: Bold values are statistically significant.

Abbreviation: ESS, Epworth Sleepiness Scale.

[a]Alpha set at 0.05.

[b]Aboriginal and/or Torres Strait Islander.

3rd quartile) when normality was not met. Categorical variables were presented as frequencies and relative frequencies. To compare continuous variables between the Referred and Not Referred groups, *t*-tests were used when normal distribution was met. Mann-Whitney *U* Test was used to compare continuous variables when distribution was not normal. Chi-square was used to determine the relationship between categorical variables and referral status.

A nested multivariable logistic regression model was performed to determine variables independently associated with referral to a sleep clinic (referral vs. non referral). The variables were added in blocks of clinical relevance and significance, with the first model including age (in years) and booking BMI (in kg/m^2), the second model included age, booking BMI, having STOP-BANG performed and indigenous status and the third model included variables from the first two models as well as history of ≥2 miscarriages, hypertension after 20 weeks, current smoker status, gestational diabetes in current pregnancy and history of asthma. The STOP-BANG score was not used in the model as it utilizes other variables included in the multivariable model (BMI, age and history of hypertension).

Statistical significance was set at alpha = 0.05. Analysis was performed using IBM® SPSS® Statistics Version 28.[17]

2.4 | Barriers to diagnosis and treatment

Barriers to diagnosis (i.e., completion of sleep study) were documented for individuals who attended sleep clinics using descriptive information from clinical records. For those who completed polysomnographic testing, barriers to initiation and maintenance of treatment were also documented descriptively.

The Australian Capital Territory (ACT) Health Human Research Ethics Committee provided a waiver for this research (ACT Reference 2022.LRE.00109) to proceed as a quality assurance activity.

3 | RESULTS

3.1 | Factors associated with referral to sleep clinic

During 2020, 161 individuals were seen in the BuMP clinic with BMI ≥35 kg/m^2, and 22 of those individuals (13.7%) were referred to the sleep clinic. All were singleton pregnancies. Two individuals (1.2%) had pre-pregnancy OSA documented in clinic notes. It was intended that all individuals should have both STOP-BANG and ESS performed, but this was only performed for 58 individuals (36%). The STOP-BANG was performed for 62 individuals (38.5%), ESS was also performed for 62 individuals (38.5%), but some patients only had one or the other tool administered.

Table 1 shows the demographic and clinical characteristics collected and differences between the individuals referred and not referred to the sleep clinic using univariate analysis. Individuals referred to the sleep clinic were more likely to have ESS and STOP-BANG performed and their scores in these tools were significantly higher. They were also more likely to have a history of non-gestational diabetes and a history of more miscarriages.

Having a STOP-BANG performed was the only variable significantly associated with referral to sleep clinic in a nested multivariable logistic regression model (see Table 2).

3.2 | Factors associated with completion of STOP-BANG screening for OSA

Given the significant effect of STOP-BANG completion on an individual's referral to a sleep clinic, we investigated patient or clinical characteristics that might determine whether a clinician is more likely to complete this tool. No variables predicted the completion of a STOP-BANG in a nested multivariable regression model (Table 3).

3.3 | Results for individuals who completed polysomnography (PSG)

Of those referred to the sleep clinic, 18 individuals (81.8%) attended and 14 (63.6%) completed PSG. Results can be seen in Table 4. Of those who completed PSG, 12 individuals (85.7%) had an Apnea-Hypopnea Index (AHI) ≥ 5 consistent with a diagnosis of OSA. Three individuals (25%) had mild OSA (AHI 5–14.9), three had moderate OSA (AHI 15–29.9) and six individuals had severe OSA (AHI ≥30). For the 12 individuals diagnosed with OSA (i.e. AHI ≥5), median ESS was 13.5 (1st to 3rd Quartile Range 8–15) and median STOP-BANG was 4 (1st to 3rd Quartile Range 2.75–5).

3.4 | Barriers to diagnosis and treatment of OSA in those who attended sleep clinic

For 16 of the 18 individuals who attended the sleep clinic, PSG was recommended because of a clinical history consistent with OSA. Two individuals declined the offer of PSG. For 10 of 12 individuals diagnosed with OSA, the treating clinician recommended CPAP therapy. For the two individuals in whom CPAP therapy was not recommended, the clinicians cited low severity of disease and lack of symptoms in their reasoning. Three individuals had virtual sleep clinic consultations due to COVID-19 lockdown, with emailed CPAP

TABLE 2 Nested multivariable model showing individual demographics and clinical characteristics associated with referral to sleep clinic.

	Model 1		Model 2		Model 3	
Variable	**OR (95% CI)**	***p*[a]**	**OR (95% CI)**	***p*[a]**	**OR (95% CI)**	***p*[a]**
Age at delivery (years)	1.002 (0.916–1.095)	0.973	0.996 (0.901–1.101)	0.934	0.993 (0.895–1.103)	0.902
BMI (kg/m^2)	1.016 (0.947–1.089)	0.661	1.005 (0.918–1.099)	0.917	0.996 (0.906–1.094)	0.932
Indigenous status			4.278 (0.887–20.636)	0.070	4.012 (0.794–20.259)	0.093
STOP-BANG performed			15.847 (4.251–59.066)	**<0.001**	18.038 (4.536–71.727)	**<0.001**
History of asthma					0.805 (0.240–2.700)	0.725
Hypertension after 20 weeks					2.397 (0.653–8.803)	0.188
Gestational diabetes current pregnancy					0.937 (0.319–2.752)	0.906
Two or more previous miscarriages					2.348 (0.675–8.168)	0.179
Smoking during this pregnancy					1.155 (0.225–5.935)	0.863

Note: Bold values are statistically significant.

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a]Alpha set at 0.05.

TABLE 3 Nested multivariable model showing individual demographics and clinical characteristics associated with completion of STOP-BANG tool.

	Model 1		Model 2		Model 3	
Variable	**OR (95% CI)**	***p*[a]**	**OR (95% CI)**	***p*[a]**	**OR (95% CI)**	***p*[a]**
Age at delivery (years)	1.034 (0.970–1.101)	0.306	1.033 (0.969–1.102)	0.318	1.031 (0.965–1.102)	0.369
BMI (kg/m^2)	1.018 (0.968–1.072)	0.486	1.018 (0.968–1.072)	0.486	1.016 (0.964–1.071)	0.544
Indigenous status			0.964 (0.300–3.091)	0.950	0.966 (0.295–3.167)	0.954
History of asthma					1.568 (0.730–3.369)	0.248
Hypertension before 20 weeks					0.703 (0.168–2.933)	0.629
History of pre-eclampsia					1.580 (0.296–8.431)	0.593
Gestational diabetes previous pregnancy					1.313 (0.512–3.362)	0.571
Two or more previous miscarriages					1.262 (0.538–2.962)	0.593
Smoking during this pregnancy					1.068 (0.401–2.847)	0.895

Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

[a]Alpha set at 0.05.

TABLE 4 Sleep study results for individuals who completed polysomnography.

Sleep study result	Median	1st to 3rd quartile range
AHI (n = 14)	25.8	8.3–47.4
ODI (n = 13)	15.5	3.8–42.2
Gestation of OSA diagnosis (n = 14)	25.0	23.5–29.0
Gestation of OSA treatment commencement (n = 9)	27.0	25.0–29.0

Abbreviations: AHI, Apnea-Hypopnea Index; ODI, Oxygen Desaturation Index.

scripts. They did not have any follow-up so it was unclear if this treatment was initiated or tolerated. One patient was unable to commence treatment due to late gestation of diagnosis (36 weeks) and development of pre-eclampsia. Another patient did not complete PSG and OSA treatment until post-partum due to late gestation of referral. The remaining five individuals did not have significant barriers to OSA treatment.

Of the 14 individuals who attended a sleep clinic antenatally, nine (64%s) were followed up post-partum. The individuals who did not attend follow-up either did not have treatment (n = 2) or had their CPAP prescriptions emailed without further follow-up organized (n = 3).

4 | DISCUSSION

This retrospective study found that obstetricians working at this tertiary hospital in Australia are referring a small proportion (13.7%) of individuals seen in a high-risk pregnancy clinic for specialized sleep assessment. These clinicians are primarily using formal tools (STOP-BANG or ESS) as criterion for sleep clinic referral, performed in 38.5% of individuals. Although it is expected that screening was performed for all individuals in the clinic, this was not the case in practice. There were no demographic or clinical characteristics that affected the clinicians' decision to refer to a sleep clinic or to complete a formal screening tool. The decision to formally screen for OSA was possibly clinician- or gestation dependent but these data was not documented.

This study also descriptively documented barriers to diagnosis and treatment of OSA for the small number of individuals who attended sleep clinics and completed PSG. Two individuals were referred to the sleep clinic at a late gestation, which affected their diagnosis and optimal management. Impacts of the COVID-19 pandemic were noted; it likely played a role in accessing services with virtual CPAP prescription and no post-partum follow-up for three individuals. This is consistent with other research showing that the diagnosis and management of OSA was more challenging during the COVID-19 pandemic[18]; laboratories in Australia were not completely closed down, but management changed significantly with virtual clinic consultations and reduction in polysomnography services. Implementation and troubleshooting of PAP therapy was challenging as it is considered to be a potentially aerosol-generating procedure. The COVID-19 pandemic likely impacted negatively on referral rates to sleep clinics, rates of polysomnography testing and initiation of OSA treatment in high-risk pregnancies.

There is no gold-standard screening tool for OSA in pregnant populations, but some studies have attempted to develop pregnancy-specific tools, to improve the sensitivity and specificity of OSA screening. Facco and colleagues[13] proposed a screening tool based on age, BMI, chronic hypertension and frequent snoring. The score is calculated using the formula [(15 if frequent snoring) + (15 if chronic hypertension) + age + BMI]. If pregnant individuals have a score of

75 or above, they likely have OSA, with a sensitivity of 86% and specificity of 74%. Although, data on frequent snoring was not available for our retrospective population (STOP-BANG asks regarding loud snoring), 80/161 (49.7%) individuals included in our study had a score of 75 or above, indicating they likely have OSA based on their age, BMI and presence of chronic hypertension. This number would likely have been higher with the inclusion of snoring data.

Furthermore, individuals who were ultimately diagnosed with OSA in the current study had high median ESS and STOP-BANG scores (13.5 and 4, respectively), suggesting that only those with the highest pre-test probability of having OSA were identified. There is likely a significant amount of undetected OSA in this group of pregnant individuals with BMI ≥35 kg/m^2.

In further exploration of this argument, data from the current study was compared to unpublished data from the Canberra Obesity Management Service (COMS),[19] where patients are systematically screened for OSA and referred to sleep clinic as appropriate. During a 12-month period (July 2018-June 2019), 82 non-pregnant women were seen in the COMS aged 17–45, with mean BMI of 51.1 kg/m^2. (Standard Deviation 9.7) and all were screened for OSA. Thirty-one (37.8%) were referred for sleep study and 27 of these (87.0%) completed PSG. All those who completed PSG were diagnosed with OSA. Although COMS population's mean BMI was higher than that of our high-risk pregnant population and the COMS population was studied pre-covid, the referral rates to sleep clinic were substantially higher (37.8% in OMS compared with 13.7% in the high-risk pregnancy clinic). This is likely attributable to universal screening in the COMS population. Similarly, in a United Kingdom-based bariatric clinic (both males and females) with universal screening for OSA and a mean BMI of 48.7 kg/m^2, there was a very high prevalence of OSA of 73%.[20] Therefore, it appears that the screening performed in 'BuMP' clinic's population is likely only to identify those with the highest pre-test probability of having OSA.

To improve OSA screening and treatment in high-risk pregnancies, multiple changes are recommended to overcome the various barriers observed in clinical practice (see Figure 1). The first and most obvious solution is improved or universal screening in high-risk pregnancy clinics and implementing a streamlined referral pipeline or multidisciplinary clinics.[8] Ideally, guidelines for OSA screening in pregnancy would come from formal obstetric or midwifery associations Members of the high-risk antenatal care team (i.e., obstetricians, midwives, anesthesiologists) need further education on OSA diagnosis and management, its link with complications of pregnancy and associated increased maternal/neonatal morbidity. Research on recognition of OSA in Obstetric physicians is limited[21] but a recent survey of Obstetrics-interested anesthesiologists found that approximately 21% of respondents routinely screen for OSA in pregnancy and 35.4% only screen if patients are deemed at-risk, most commonly using the STOP-BANG tool.[7] Respondents commonly considered OSA in pregnant individuals with obesity and essential hypertension, but were less likely to consider OSA in individuals with pre-eclampsia and gestational diabetes.[7] Furthermore, the optimal timing of screening needs to be considered. This is likely between 12 and 18 weeks to allow enough time for meaningful treatment,[22] but later screening should still be performed, especially for women at high risk or with significant related comorbidities for example, signs of right heart failure. Early gestational screening for OSA in individuals with chronic hypertension is also beneficial.[23] Unfortunately, gestation of OSA screening was also not recorded in our study.

Another consideration in improving the identification of OSA in high-risk pregnancies is the screening method. As discussed, there is no clinical gold-standard for screening of OSA in pregnancy and this area would benefit from further research. In Australia, the STOP-BANG and ESS are commonly used due to inclusion in the Medicare Benefits Schedule that is, patients can qualify for funded PSG prior to sleep physician assessment. However, as demonstrated in many previous studies, the sensitivity and specificity of these tools for OSA in high risk pregnancies with BMI ≥35 kg/m^2 can be poor.[11,12] The use of other pregnancy-specific tools should be considered as the use of BMI as a continuous rather than categorical variable appears to improve screening sensitivity in pregnant populations.[13]

Finally, even with improved screening, there are barriers to diagnosis and treatment that need to be addressed. Those identified as high-risk of OSA during screening need timely access to sleep services. Support for socioeconomic disadvantage needs to be considered for access to PSG and PAP therapy. Further research is also needed on the effectiveness of PAP and other treatments and their impact on pregnancy complications.

This study adds to a very limited body of evidence on the practice of obstetric physicians when it comes to referring individuals with high-risk pregnancies for sleep clinic review. It identifies a significant gap in clinical practice that not only requires further research but would benefit from more specific guidelines from obstetric and midwifery professional bodies. This study was limited by its retrospective design and some data were incomplete. For example, data on ethnicity were not easily available and this likely impacts the effect of BMI on pregnancy-related complications such as OSA.[24] The study represents the practice at one tertiary hospital in Australia, so results may vary depending on how pregnancy and sleep services are delivered in other centers and countries. The data collection period was also during the COVID-19 pandemic, when interactions with the health system were altered.[25] Given the small number of individuals who were diagnosed and treated for OSA, this study may not have captured all the important barriers to clinical practice in this area.

There is still much to be done when it comes to identifying OSA in high-risk pregnancies, in day-to-day clinical practice. Obstetricians in this Australian center are referring a small proportion of individuals seen in high-risk pregnancy clinics for specialist sleep physician review and are primarily using formal screening tools as a basis for this referral. It is likely that referral rates will be much

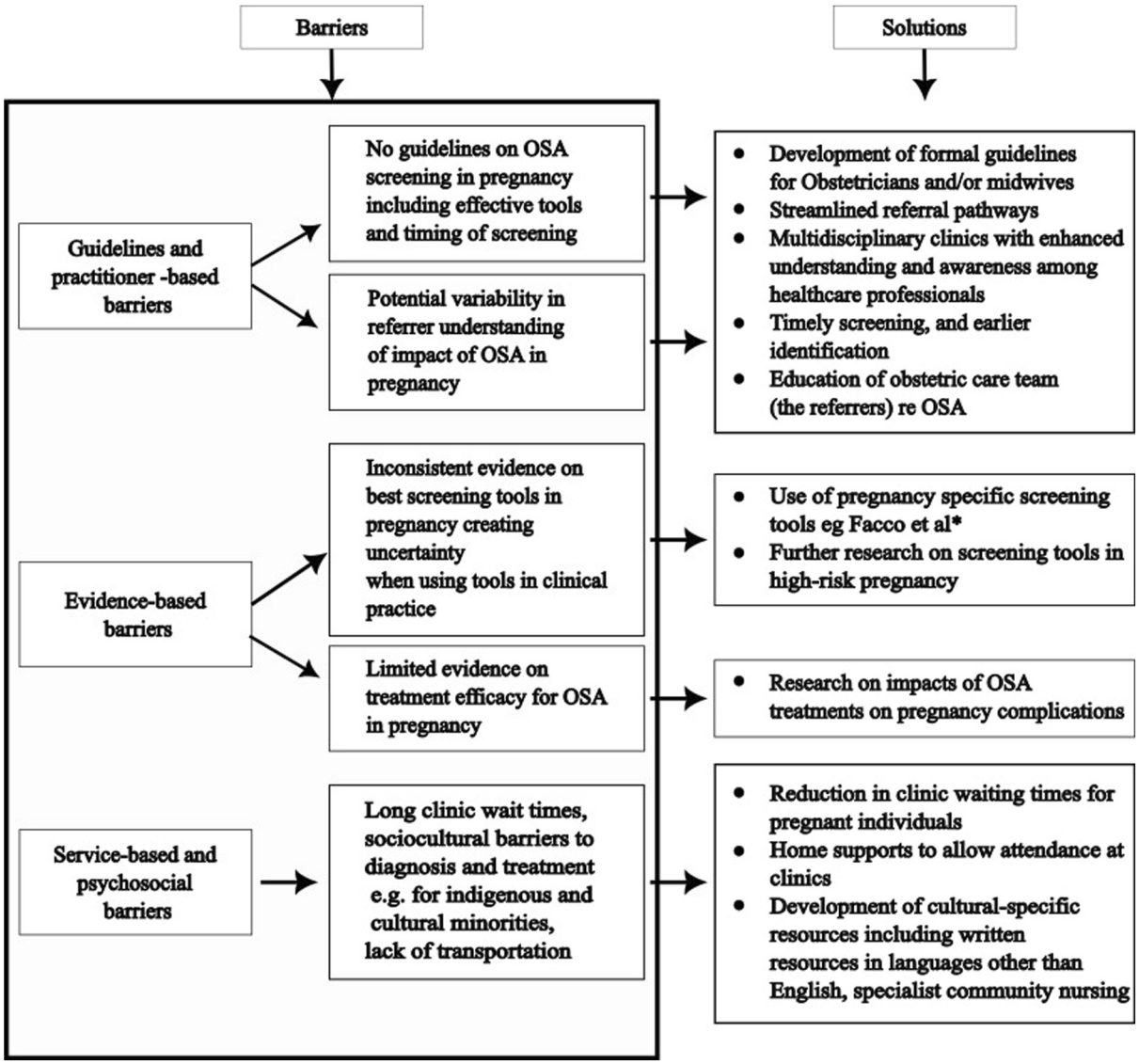

FIGURE 1 Barriers to OSA diagnosis and treatment in high-risk pregnancies and potential solutions for addressing these.

higher with systematic screening using either standard or pregnancy-specific screening tools.[13] Referral rates are probably similar in other tertiary institutions, especially in the absence of formal multidisciplinary clinics or streamlined referral pathways.

This study documents the real-life challenges of OSA identification and management in high-risk pregnancies and the need for more rigorous and effective screening pathways. Future research should evaluate the effectiveness of strategies for improving clinical practice in managing OSA in high-risk pregnancies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Dr Hsin-Chia Huang has received speaker's honoraria from Astra Zeneca for Respiratory Medicine Meetings unrelated to this manuscript. No other financial or non-financial disclosures for any author.

ORCID

Samantha Warhurst https://orcid.org/0000-0002-0008-5652

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