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Is sleep-disordered breathing associated with miscarriages? An emerging hypothesis ☆

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ABSTRACT

Sleep-disordered breathing (SDB) is a common disorder that has numerous medical consequences including cardiovascular morbidity. The clinical presentation in women is frequently vague, leading to its under-recognition in this population. Sleep is known to influence several female hormonal cycles including estrogen, progesterone, prolactin, luteinizing hormone (LH), and follicle stimulating hormone (FSH); consequently, sleep disruption may have adverse effects on female health including pregnancy. Miscarriage, defined as the loss of a pregnancy in the first trimester, occurs in one in four pregnancies; in up to half of cases, the cause may be unknown. Risk factors for miscarriage include increased age, increased weight, and a history of polycystic ovarian syndrome, all of which are also risk factors for SDB. Since SDB is frequently accompanied by sleep fragmentation and intermittent hypoxemia, we speculate that these factors may contribute to miscarriage risk. If this is the case, then treatment of SDB may be a possible intervention for subsequent pregnancies.

Background

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing (SDB) characterized by collapse of the upper airway in sleep, resulting in sleep fragmentation and hypoxemia. SDB events include apneas, hypopneas, and "respiratory effort related arousals" (RERAs, a form of hypopnea without significant hypoxemia). These events can lead to numerous medical and psychiatric consequences, possibly mediated through mechanisms such as sleep deprivation, sleep fragmentation, and intermittent hypoxemia. Although various treatments can be considered, SDB is most often treated with continuous positive airway pressure (CPAP) therapy, which consists of a mask worn at night that delivers room air at a specified pressure to keep the airway open.

SDB in women

Depending upon how OSA is defined, studies suggest that it may affect 5–11% of premenopausal women [1,2]. OSA is frequently under-diagnosed in this population, particularly in younger women and those who have not developed medical complications [1]. Part of the challenge of diagnosis is that the clinical presentation may differ significantly from symptoms that are routinely seen in men, such as loud snoring and excessive daytime sleepiness. Women complain more frequently of insomnia, depression and excessive daytime fatigue [3–5].

Additionally, a type of SDB called "upper airway resistance syndrome" (UARS) is twice as likely to be found in women when compared to men. UARS is a milder form of SDB in which sleep is fragmented primarily by arousals associated with RERAs, in the absence of significant hypoxemia [6]. Whether UARS is located on a spectrum of SDB severity that ranges between primary snoring and OSA, or exists as a separate clinical entity, is matter of significant debate [7,8]. While men are diagnosed with OSA at a rate 2–3 times that of women, the gender distribution of UARS is 1:1 [6,8]. The diagnosis of UARS requires use of a polysomnogram with electroencephalogram (EEG) leads to measure cortical arousals associated with respiratory events in the absence of oxygen desaturation. Patients with UARS present more frequently with insomnia, headaches, chronic pain, dizziness or fatigue [11]. Unlike OSA, in which patients are frequently overweight or obese [9], women with UARS are frequently slim, with a normal neck circumference and blood pressure [8]. As a result, they are more likely to come to the attention of psychiatrists than internists, which may further complicate the recognition and proper treatment of this syndrome [8].

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SDB, female hormones, and fertility

Sleep itself is thought to have a significant influence on female hormones, including estrogen, progesterone, prolactin, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Sleep deprivation adversely affects estrogen [10]. Sleep interruptions adversely affect LH pulsatile secretion, and consequently could affect pregnancy [11]. Other changes in sleep architecture, such as those induced by shift work, have been shown to alter menstrual cycles and exacerbate fertility problems [12]. According to Baker and Driver, "modified circadian rhythms of temperature and hormone secretions in the menstrual cycle are hypothesised to be important in maintaining a stable intrauterine environment for implantation and embryonic development." [12].

Additional limited studies evaluating the effects of SDB on women show that this condition may alter menstrual cycles [13] and prolactin pulse frequency [14,15]. Lower levels of estradiol, progesterone and 17-hydroxyprogesterone are also seen [16]. Sexual function is impaired in women with SDB [17]; as a result, several investigators have speculated that this may affect fertility [15,18]. It is already known that several other conditions adversely affect fertility, including obesity [19,20] and polycystic ovarian syndrome [21,22] (PCOS). Interestingly, both of these conditions are strongly associated with OSA, with up to 70% of PCOS patients showing evidence of SDB [23,24]. The nature of the relationship between all of these factors and fertility, however, is unknown [18].

HYPOTHESIS: spontaneous abortions (miscarriages) and SDB

Miscarriage or spontaneous abortion involves the extemporaneous loss of a pregnancy, usually within the first 3 months of conception. The estimated frequency of spontaneous abortion is between 12% and 24% [25] of all clinically-identified pregnancies. Several factors have been shown to be associated with a higher risk of spontaneous abortion, including extremes of age, smoking history, increased body mass index and previous miscarriage [20,26,27]. Recurrent miscarriage, defined as three or more consecutive miscarriages, has been associated with several factors, including chromosomal abnormalities, coagulopathies, immunologic conditions, and uterine deficiencies; however, in half of cases the cause is not known [20].

SDB in pregnancy and associated complications

OSA in pregnancy is becoming recognized as a significant risk factor for pregnancy complications [28–30]. This topic has received several reviews recently [18,29,31–33]. Several maternal complications have been associated with untreated or unrecognized OSA in pregnant women, including gestational hypertension, pulmonary hypertension with associated right-sided heart failure, increased need for caesarean section, and impaired glucose control [18,29,33,34]. Fetal outcomes have also been adversely affected by maternal OSA, as evidenced by lower Apgar scores and small-for-gestational-age births in some reports [35,36]; however, other investigators have not seen such findings [37]. In some cases, CPAP therapy was initiated when SDB was identified and was associated with improved maternal and fetal outcomes [38,39]. In a case report by Brain and colleagues, a female patient with spina bifida and ileo-urinary conduit experienced 2 miscarriages before severe SDB was diagnosed. Her Apnea Hypopnea Index (AHI, the frequency of apneas and hypopneas per hour of sleep) was 29.2/hr, with oxygen saturation dropping to 40%. After CPAP therapy was initiated, she became pregnant within 3 months and subsequently had a successful delivery [35].

The link between obesity, spontaneous abortion, and stillbirth is the subject of more intense research [20,40]. While obesity has been previously reported as a risk factor for spontaneous abortion, SDB has not. Fung has speculated that OSA may act as an intermediary factor, i.e., mediating the relationship between weight and spontaneous abortion [41]. How sleep might be involved is unclear at this time, but several possibilities exist.

The precise effect of SDB on female hormones is unclear, although there is mounting evidence for a significant influence. Guilleminault and colleagues [13] noted that almost half of women with UARS have amenorrhea or dysmenorrhea; when comorbid SDB was treated by nasal CPAP, these menstrual irregularities vanished. Studies have also shown negative effects of SDB on prolactin, although the majority of these investigations focussed on men [15]. Conception, implantation, and fetal development are dependent on a complex interplay between estrogen, progesterone, plus other hormones such as LH and FSH. Consequently, adverse effects of OSA on the amounts or secretion patterns of these hormones may have adverse effects on pregnancy.

OSA has also been strongly linked with obesity. A recent review by Metwally and colleagues [26], found several studies that linked obesity with first trimester miscarriage, but not all studies are consistent. Other mechanisms by which SDB could potentially have adverse effects on pregnancy (possibly mediated via obesity) include increased risk of preeclampsia, gestational diabetes, and effects on the hypothalamic pituitary axis. The influence of SDB on these disorders has been the subject of several recent reviews [18,33], including an elegant summary of possible mechanisms by Iczi and colleagues [42]. A recent study by Louis and colleagues [28] demonstrated significant adverse pregnancy outcomes in 57 women with OSA, when compared with either normal-weight or obese controls. Sequelae included higher rates of preterm birth, preeclampsia and maternal morbidity, but a history of spontaneous abortions was not evaluated.

Among women with SDB, those with OSA experience intermittent hypoxemia which can lead to inflammation, oxidative stress and excess sympathetic activation. The increased oxidative stress may also contribute to endothelial dysfunction and the presence of increased pro-inflammatory cytokines such as TNF-alpha, IL-6, and C-reactive protein, all of which have been linked to adverse pregnancy outcomes [42]. Additionally, OSA has been linked to decreased levels of adiponectin and alterations in leptin levels; both of these peptides have been linked to impaired glucose control. All of the above factors have been shown to be related to the development of gestational diabetes and preeclampsia, both of which are well-known to be associated with pregnancy loss [42–44]. Whether it is sleep fragmentation, sleep deprivation, chronic intermittent hypoxemia, or a combination of these factors that predisposes to the above adverse events is unknown.

Given that spontaneous abortion may occur in up to one in four pregnancies, and given that SDB adversely affects pregnancy and hormones known to be involved in fertility, we speculate that a possible contributing factor to spontaneous abortion may be unrecognized SDB. Several other authors [18,41] have also speculated that such a relationship might exist, but as yet there is very little data to support or refute this theory. One possible reason is that SDB is challenging to recognize in pre-menopausal women.

Evaluation and empirical data

Since there is limited data to address this hypothesis, we performed a retrospective chart review to see whether SDB in pre-menopausal women would be associated with a higher likelihood of spontaneous abortion (miscarriage) compared to women without SDB.

Subjects

This study was approved by the Institute of Mental Health Research (IMHR) Research Ethics Board in Ottawa, Canada. Our sample consisted of a retrospective review of sequential Clinic charts of 147 premenopausal women, each with a history of at least one pregnancy, who had been referred to our Sleep Disorders Clinic for an evaluation of sleep complaints between 2007 and 2012.

At their intake interview with a board-certified sleep specialist, each provided a pregnancy history, including total number of pregnancies and number of miscarriages (if any). Any reports of elective abortions or stillbirths (pregnancy loss after 20 weeks gestation) were removed from the data, since it could not be clarified whether elective abortions were related to personal choice or possibly to a pregnancy that would have progressed to miscarriage without intervention. Demographic data were also obtained. Since studies [2] suggest that perimenopause/postmenopause is established by the age of 50 years, a cut-off age of 50 or less at the time of consultation was chosen as an inclusion criterion. One reason for this choice was that menopause is known to dramatically change the severity of sleep-disordered breathing [45]. Another inclusion criterion was completion of a level-1 polysomnogram in accordance with the American Academy of Sleep Medicine guidelines [46]. In most cases, the indication for polysomnography was suspicion of SDB.

Methods

Stages of sleep

These were scored from EEG derivations F3-M2, C3-M2, and O1-M2 based on the "10–20" electrode placement method. Respiratory events were recorded with an oral–nasal pressure transducer, an oral–nasal thermistor, and respiratory inductance plethysmography; these channels were then scored according to the guidelines of the American Academy of Sleep Medicine [46]. Trans-cutaneous oxygen saturation was measured by an illuminated oximeter probe on a finger. The severity of SDB was summarized by the apnea hypopnea index (AHI) and the respiratory disturbance index (RDI). AHI is defined as the total number of apneas plus hypopneas in the night, divided by total hours of sleep, while RDI is the total number of all respiratory events (apneas, hypopneas, and RERAs) divided by total hours of sleep. Obstructive apneas were defined as a 10 s pause in breathing with at least a 90% drop in baseline breathing amplitude for 90% of the event; hypopneas as a >30% reduction in airflow for at least 10 s, with a >4% drop in oxygen saturation from pre-event baseline, with 90% of the event's duration meeting the amplitude reduction criterion. If the sequence of breaths did not meet either apnea or hypopnea criteria, a RERA was scored; typically, this involved flattening of the nasal pressure waveform associated with an EEG arousal. All data were scored by registered polysomnography technologists who had been certified by the Board of Registered Polysomnographic Technologists.

Statistical design

The dependent variable in our study was the *number of miscarriages* as reported on the date of sleep clinic consultation. We wished to see if any of the independent variables: Body Mass Index (BMI), Apnea Hypopnea Index (AHI), neck circumference, or oxygen saturation while asleep were significant predictors of the number of miscarriages in the past. Inspection of the data showed that a large number of the women in the sample had not experienced a miscarriage (87 out of 147 subjects), whereas many had suffered more than one. Inspection also showed that while frequency distributions of both BMI and AHI were grossly skewed, they approached a normal distribution after transformation with base-10 logarithm.

While "counts" data such as miscarriages are usually studied by log-linear analysis or Poisson regression, there is a compelling opinion in the statistical literature [47–49] that such methods are inappropriate for data with a high number of zeroes, such as ours. A class of methods called "*zero-inflated Poisson regression*" does deal properly with such data; it effectively reduces Type-II error (i.e., failing to find significance when it is actually present) when compared to simple Poisson regression. One such method is called "Hurdle Regression" [50]. We used the R-Statistical System, version 2.12, and the "hurdle" routine from the R-package "pscl" [51]. This produced two tables, one based on a Poisson multiple regression that used a log-link function for subjects with miscarriages in the range of 1 to *n*, (Table 1), plus another regression table based on a binomial distribution and using a *logit*-link function for those subjects with zero miscarriages compared to subjects with any number of miscarriages (Table 2).

Results

Both AHI and BMI were shown to be significant independent predictors of the number of miscarriages, if there was one or more (Poisson regression, Table 1). Oxygen saturation showed a non-significant trend in the same direction, while neck circumference was not a significant predictor. There was also a trend for interaction between AHI and BMI in affecting miscarriage risk (interaction not shown, but visible in Fig. 1, association with miscarriage risk seen in Fig. 1). When analyzed in a binary fashion (Table 2), there was a non-significant trend for AHI to predict miscarriage but no other effects.

Discussion

These results support the hypothesis that while both SDB and excess weight are associated with a history of spontaneous abortion, the effect of SDB might be the greater one. There are several limitations to our study. (1) A correlational study cannot demonstrate a causal relationship; this would require a prospective study.

Table 1
Poisson regression predicting dependent variable "number of miscarriages".

	Estimate	s. e.	*z*-value	*P*
(Intercept)	13.98971	17.45228	0.802	0.42279
BMI	8.81231	2.74473	3.211	0.00132**
AHI	−0.95321	0.32050	−2.974	0.00294**
Neck_Circ	−0.05449	0.21486	−0.254	0.79981
MinO2sat	−13.40465	8.99219	−1.491	0.13604

Independent variables entered into the "truncated Poisson regression with log-link" were base-10 logarithms of: Body Mass Index (BMI), Apnea Hypopnea Index (AHI), and minimum trans-cutaneous oxygen saturation while asleep (MinO2sat). Neck circumference was entered as cm. Significance shown as: ** = $p < 0.005$.

Table 2
Zero-hurdle regression. Prediction of presence or absence of miscarriage.

	Estimate	s.e.	*z*-value	*P*
(Intercept)	−3.28512	22.09021	−0.149	0.8818
BMI	−1.11530	3.09094	−0.361	0.7182
AHI	0.65884	0.34217	1.925	0.0542#
Neck_Circ	−0.07042	0.25455	−0.277	0.7821
MinO2sat	2.75917	10.81338	0.255	0.7986

The independent variables entered into "zero-hurdle regression with *logit*- link" were base-10 logarithms of: Body Mass Index (BMI), Apnea Hypopnea Index (AHI), and minimum trans-cutaneous oxygen saturation during the sleep study (MinO2-sat). Neck circumference was entered as cm. Only AHI approached significance: "#" = $p < 0.1$.

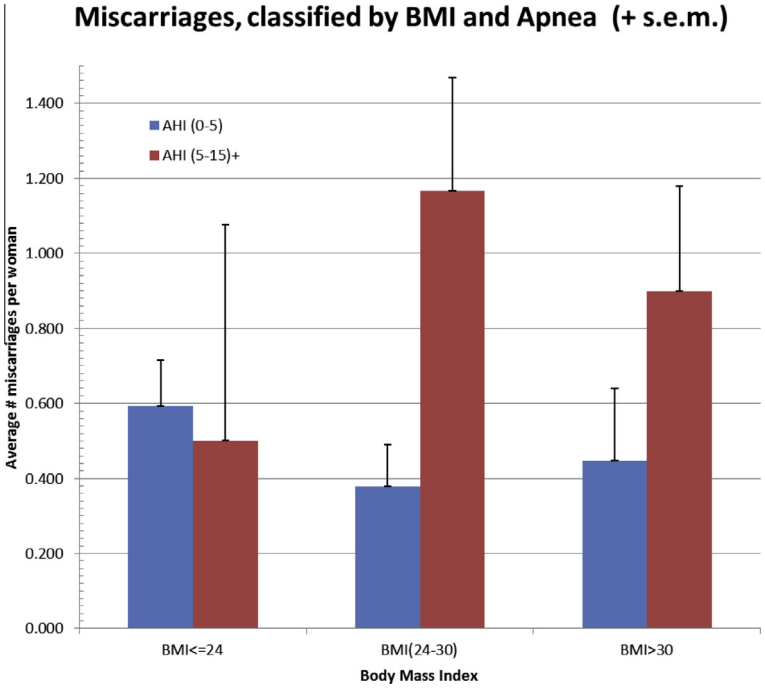

Fig. 1. Average number of miscarriages per woman (n = 147), classified by Body Mass Index (BMI) and Apnea Hypopnea Index (AHI). Error bars are s.e.m.'s. The rate of miscarriage for those with normal BMI and AHI (<5/hr) was low, whereas miscarriage rates were much higher for those with elevated BMI plus mild to moderate OSA (AHI 5–15/hr). The latter group also included 6 women with moderate to severe OSA (AHI > 15), hence the "+".

(2) Since all of the subjects had been referred to the Sleep Disorders Clinic for some presumed abnormality, there was no control group. The addition of a control group of healthy women would be advisable in future work. (3) Since the data were retrospective, neither the timing of miscarriage nor the age of onset of each patient's SDB were known. For example, it is possible that SDB began only some years following their pregnancy (-ies), and as a result of weight gain. However, the latter does not explain our finding that some thin women with high rates of SDB had substantial miscarriage rates (see Fig. 1, the large error bar in the column second from left. (4) It is not clear whether miscarriage might have occurred because of consanguinity, although this would likely be minimal, given our knowledge of the local population. (5) Finally, there is a possibility that recall bias could affect the results; however, given that miscarriage early in pregnancy is an emotional event not likely to be forgotten, we feel that the effect of this issue was also likely minimal.

Future studies

The pilot data obtained here suggest a relationship between SDB and miscarriages. Future prospective studies in this area should include the measurement of prolactin, estrogen, FSH, LH, glucose, and blood pressure throughout pregnancy. Additionally, noting the frequency of other medical conditions and the use of medications that affect weight (e.g., antipsychotics) or breathing (e.g., benzodiazepines) would be important. Ideally, a measurement of SDB plus all of the above variables could be included in a (large) study using a Cox Proportional Hazards model to properly assess the relative contribution of each to miscarriage.

Implications

While it is reasonable to speculate that conception and fetal and/or placental development might be adversely affected by any condition that affects female hormones or a woman's general health status, our results suggest another avenue for intervention to prevent miscarriages: early diagnosis and treatment of SDB. The benefits could be objectively assessed in a future prospective study of proper design. To our knowledge, only one study [52] has so far examined this question, with no suggested benefit. It was, however, a study of only 12 cases in which only one patient experienced a miscarriage; such a small "n" makes this study highly susceptible to Type-II statistical error. A case report [35], already mentioned, described a woman with severe OSA who subsequently had a successful pregnancy after CPAP therapy was initiated, despite two previous miscarriages.

In addition to investigating miscarriage, assessment of SDB may also prove useful in the work-up of women with infertility. Since fertility has become a significant issue for an increasing number of couples, and given the advent of new artificial reproductive technologies, simply assessing the sleep of infertile women may prove to be both fruitful and cost-effective. Women who struggle with fertility may frequently experience miscarriage. A significant part of the distress of miscarriage occurs because the cause is not known in many cases. Pregnancy loss can be a devastating experience, particularly to first time prospective parents. New approaches to preventing this problem and associated sequelae need to be found. Our results may be of interest to obstetricians and infertile couples because SDB is a readily treatable condition. Its resolution might eventually be shown to decrease pregnancy losses and possibly even improve fertility outcomes. From the point of view of the sleep disorders clinic evaluation, a history of spontaneous abortions or other pregnancy complications such as preeclampsia should raise the suspicion for SDB.

Our data suggest a possible link between SDB and subsequent miscarriage but further study is needed, as it may be mediated through several different mechanisms. If this relationship is indeed validated, it suggests another avenue for intervention, since SDB is readily treatable.

Conflict of interest

All 3 authors (Dr. Elliott Lee, Dr. Spencer Gutcher, Dr. Alan Douglass) have no conflict of interest to declare. No sources of funding were used for the production of this text.

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