

Original Research Article

Prevalence of components of metabolic syndrome in pregnant women with obstructive sleep apnoea hypopnoea syndrome

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ABSTRACT

Background: Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) related cardiovascular and metabolic risk factors such as hypertension, diabetes mellitus and dyslipidaemia which together are commonly known as metabolic syndrome (MS) is often overlooked in pregnancy. OSAHS is known to cause higher maternal morbidity and bad foetal outcome. Aim was to study the prevalence of components of MS among third trimester pregnant women with OSAHS.

Methods: A total of 100 cases and 100 controls each amongst third trimester pregnant females admitted in the Department of Obstetrics and Gynecology at the Government Medical College, Kozhikode, Kerala, India were enrolled in the study. All subjects underwent a thorough clinical, anthropometric, obstetrical examination and biochemical tests such as complete blood count, blood sugar and lipid profile. The parameters were compared between cases and controls.

Results: OSAHS positive pregnant women had a higher prevalence of elevated systolic ($P=0.01$) and diastolic ($P=0.002$) blood pressure, abnormal fasting ($P<0.0001$) and post prandial ($P=0.02$) blood sugar, abnormal cholesterol ($P=0.006$) and triglyceride levels ($P<0.001$), and abnormally low HDL levels ($P<0.001$).

Conclusions: This study showed that metabolic syndrome was highly prevalent among OSAHS positive third trimester pregnancy (52%) versus OSAHS negative (8%) pregnant women.

Keywords: Metabolic syndrome, OSAHS, Polysomnography, Third trimester pregnancy

INTRODUCTION

Untreated obstructive sleep apnea/hypopnea syndrome (OSAHS) manifest as recurrent episodes of partial or complete cessation of breathing during sleep leading to heavy snoring, sleep fragmentation and excessive daytime sleepiness and is associated with reduced health-related quality of life (HRQoL).¹⁻³ OSAHS has been recognized as an independent risk factor for disorders such as hypertension, coronary heart disease, rhythm/conduction disorders and cerebrovascular disease.^{1,4-6} The ensuing reduction of air flow often leads to acute derangements in gas exchange and recurrent

arousals from sleep.^{8,10} The health consequences of OSAHS are numerous.^{8,9} The mechanisms contributing to these include tonic elevation of sympathetic neural activity by the augmentation of peripheral chemoreflex sensitivity (intermittent hypoxia at night), direct effects on sites of central sympathetic regulation and the disturbance of nocturnal renin and aldosterone levels due to severe sleep fragmentation.⁴ It has been reported that the patients with OSAHS are often overweight and obese and they frequently present with the clinical features of the metabolic syndrome (MS), also called insulin-resistance syndrome, an emerging disorder associated with accelerated atherosclerosis.¹ The majority of

OSAHS patients show the cluster of metabolic and non-metabolic cardiovascular risk factors of MS, i.e. abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance with/without glucose intolerance, proinflammatory state and prothrombotic state suggesting that OSAHS may be a further risk factor of MS.¹

A number of studies using large sample representatives of the general population are now available and provide prevalence estimates for OSAHS.^{3,8} The prevalence of OSAHS associated with accompanying daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% for adult women in the general population.^{4,8,16} Disease prevalence is higher in different population subsets, including overweight or obese people, those of a minority race, and older individuals.^{8,12} The fact that prevalence estimates of OSAHS from North America, Europe, Australia, and Asia are not substantially different suggests that this disease is common not only in developed but also in developing countries.⁸

Pregnancy is another condition associated with a higher prevalence of OSAHS, particularly during the third trimester.⁴ Pregnancy is also associated with a higher prevalence of snoring, particularly in the third trimester.^{8,22} While some of the physiologic changes that accompany pregnancy (e.g. higher progesterone levels, decrease in sleep time in the supine position) may protect against OSAHS, whereas gestational weight gain, decrease in pharyngeal luminal size, and alterations in pulmonary physiology increase the tendency for disordered breathing during sleep.^{8,21,22} Pregnancy may be a period of particular risk for OSAHS in women. By the end of pregnancy, the sleep experience changes significantly. Most of the time, it is disrupted and fragmented. Dream content is often permeated by disturbing images stemming from concern about impending childbirth and mounting fears for body integrity and safety.¹⁸ Longitudinal data collected by the Wisconsin Sleep Cohort Study over a 4-year period have shown that weight change is an important determinant of disease progression and regression.^{5,8,14} Compared with participants with a stable weight, those that have a 10% increase in their weight had a 32% increase in their AHI and a six-fold risk of developing moderate to severe OSAHS.

Increase in estrogen and progesterone levels during pregnancy, and other endocrinological changes (e.g. increases in prolactin and plasma cortisol) affect normal sleep patterns. Increase in estrogen tends to reduce rapid eye movement (REM) sleep; on the other hand, exogenously administered progesterone increases non-REM sleep.¹⁹ During the first trimester, sleep duration, daytime sleepiness, and sleep disturbance caused by frequent awakenings and insomnia are increased.²⁰ Objective investigations with polysomnography (PSG) have shown an increase of total sleep time and a decrease of sleep efficiency and slow wave non-rapid eye

movement (NREM) sleep (stages 3 and 4).^{20,21} In the second trimester, the total nocturnal sleep time decreases to normal duration but sleep related complaints increases resulting in nocturnal awakenings.²¹ Slow wave sleep remains reduced, whereas REM sleep is slightly decreased.²¹ During the third trimester, most women report sleep disturbances and nocturnal awakenings and daytime naps.^{20,21} The sleep architecture is altered with decreased total sleep time, increased waking time after sleep onset, increased stage 1 of non-REM sleep, decreased stages 3 and 4, and decreased REM sleep.²¹ The American Sleep Disorders Association has proposed the existence of “pregnancy-associated sleep disorder.” The association between OSAHS and MS during pregnancy is only sparsely mentioned in currently available literature. As pregnancy is known for inducing glucose intolerance and hypertension the possibility of increased incidence of MS in the presence of OSAHS cannot be ruled out.⁷ If that is so, treatment of OSAHS during pregnancy is more prudent to control MS related complications in pregnancy. In view of the aforementioned hypothesis this study has been designed to determine the prevalence of MS in pregnant ladies diagnosed with OSAHS. OSAHS may be subdivided into varying degrees of breathing abnormality based on the polysomnography scores, depending on the AHI (Apnoea Hypopnoea Index).^{9,10}

- Mild: AHI 5-14/hours
- Moderate: AHI 15-30/hours
- Severe: AHI >30/hours.

Clinically significant OSAHS is likely to be present when AHI ≥ 15 events/hour slept, in association with unexplained daytime sleepiness. A questionnaire administered to 502 Swedish women at the time of delivery found that 23% reported snoring often or always during the week before delivery, whereas only 4% reported snoring before pregnancy. Most of the increase in snoring occurred in the third trimester.¹² There are several screening tools (questionnaires) available for making a high pretest probability of possible moderate and severe OSAHS amongst a group of suspected cases. Berlin questionnaire is one amongst the several questionnaires available to us. It was an outcome of the Conference on Sleep in Primary Care in April 1996 in Berlin, Germany.^{13,14} It includes 11 questions organized into the three categories, 5 questions related to snoring and the cessation of breathing in category I, 4 questions related to daytime sleepiness in category II, 1 question about high blood pressure, and 1 question regarding BMI in category III. When two of three categories are classified as positive for a patient, the patient is rated as being at high risk of having OSAHS. The predictive performance of the Berlin questionnaire for OSAHS varies greatly among different patient populations. In primary care patients, the sensitivity and specificity were found to be 86% and 77%, respectively, at a cut-off of AHI greater than 5, and 54% and 97% at a cut-off of AHI

greater than 15.¹⁴ It is the most commonly used screening questionnaire with validated versions available in India.¹⁵

Repetitive episodes of obstructive respiratory events during sleep give rise to cyclic episodes of maternal hypoxemia.²³ Furthermore, hypertension and peripheral vasoconstriction are commonly associated with OSAHS, with both complications being associated with reduced placental delivery to the fetus.³⁵ Frank OSAHS during pregnancy may lead to lower Apgar scores and birth weights.^{8,15} Louis et al reported that women with OSAHS had more common preterm delivery, cesarean delivery, and maternal morbidities.^{24,29} Thus, early case identification during pregnancy may have implications for maternal and fetal outcomes.^{8,22} Among the women with OSAHS, indicated preterm birth was more common than in the obese and normal-weight control groups. Indicated preterm births in the OSAHS group were for the following conditions:

- Severe pre-eclampsia
- Maternal cardiac decompensation
- Ovarian torsion with fetal growth restriction.^{15,24}

Women with OSAHS were more likely to have a primary cesarean delivery for arrest of labour compared with obese controls and normal-weight controls.

In documented OSAHS syndrome, treatment is especially indicated in the presence of maternal nocturnal hypoxemia. Conservative measures include control of body weight gain, avoidance of sleep time spent in the supine position, elevation of the head during sleep, and restriction of alcohol and sedatives consumption.^{20,21,25} These general measures are useful even in non-OSAHS pregnant women who report increases of simple snoring or daytime sleepiness without the documentation of sleep apneas.^{15,24} In the presence of significant OSAHS or significant SDB-related nocturnal hypoxemia, nasal CPAP is the therapy of choice.^{20,21} The use of CPAP during pregnancy has been shown to be safe, effective, and well tolerated.^{20,21} In a study on preeclampsia CPAP has been reported to abolish inspiratory flow limitation and lower the mean nocturnal blood pressure.^{15,21} National Cholesterol Education Program-Adult Treatment Panel III (2001, 2005), at least three of the following: Central obesity- waist circumference ≥ 102 cm (male), ≥ 88 cm (female) Dyslipidaemia: TG ≥ 150 mg/dl: HDL-C < 40 mg/dL (male), < 50 mg/dL (female) Blood pressure $\geq 130/85$ mmHg, Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL).¹³ It is estimated that the age-adjusted prevalence of MS in the United States was 23.7%, with the highest prevalence in Mexican Americans. In India, a study done by Thiruvagounder et al in a study population of 1568 patients showed prevalence of metabolic syndrome as high as 33% in males and 27% in females.²⁶ Many of the known metabolic components of the MS are predictive of gestational diabetes mellitus, which could be considered as one phase of the MS.^{7,27} Striking similarities have been

described in the pathogenesis and long-term sequel of pre-eclampsia and metabolic syndrome.²⁸ The past two decades have seen a growing recognition of the presence of various types of metabolic dysfunction in subjects with OSAHS, and the association of OSAHS and MS was highlighted as ‘‘syndrome Z’’ in the late 1990s.^{11,13,30}

Aims of the study

- To identify OSAHS cases among pregnant women.
- To screen pregnant women for metabolic syndrome.
- To compare the prevalence of metabolic syndrome components among OSAHS positive pregnant women (cases) v/s OSAHS negative pregnant women (controls).

METHODS

This study was carried out in Institute of Chest Disease and Institute of Maternal and Child Health at Medical College, Kozhikode, Kerala, India. The ethical clearance was obtained from institute ethics committee.

Study population

Third trimester pregnant women selected from the Antenatal outpatient check-up clinic at Institute of Maternal and Child Health (IMCH) in Calicut Medical College.

Sample size

- Number of cases: 100
- Number of controls: 100.

Inclusion criteria

- Pregnant women
- Third trimester
- Berlin questionnaire positive subjects were considered as cases and negative subjects were considered as controls.

Exclusion criteria

- Any significant respiratory or cardiovascular disability before pregnancy
- Any significant disease affecting nervous system or musculoskeletal system
- History of infertility treatment/ Hormonal therapy

It was a prospective case control study conducted for a period of March 2011- August 2013.

Materials and methods

A total of 100 cases and controls each amongst third trimester pregnant females admitted in the Department of Obstetrics and Gynecology at the Government medical

College, Kozhikode, Kerala, India, were enrolled in the study. All subjects underwent a thorough clinical, anthropometric, obstetrical examination and biochemical tests such as complete blood count, blood sugar and lipid profile. The parameters were compared between cases and controls.

Statistical analysis

Subjects will be classified into two groups such as Polysomnography positive cases, and Berlin questionnaire negative controls. Berlin questionnaire positive and Polysomnography negative intermediate group were not taken for analysis. All variables will be tested for normal distribution prior to analyses. Data will be expressed as the mean±SD for continuous variables. Student's t-test for unpaired data will be used for the comparison of mean values. Group comparisons will be performed by use of analysis of variance and test for linear trend in One-way ANOVA. Proportions and categorical variables will be tested by the χ^2 -test and by the 2-tailed Fisher's exact method when appropriate.

RESULTS

By using convenience sampling, Berlin Questionnaire screening and limited polysomnography first hundred polysomnography positive women were selected as cases and hundred Berlin Questionnaire negative women were taken as controls. In this study, a total number of 2590 third trimester pregnant women were screened with Berlin Questionnaire, out of which about 168 women were found positive as per Berlin Questionnaire. On undergoing limited polysomnography, 116 women were found to be having OSAHS with $AHI \geq 5$, first 100 patients were taken up for further work up.

Table 1: Comparison of age and anthropometric variables (n=100).

| Parameter | Cases | Controls | P-value |
|--------------------------|-----------|-----------|--------------------|
| Age (yrs) | 28.6±3.2 | 23.9±3.98 | <0.0001*** |
| Weight (Kg) | 68.2±8.4 | 61.7±8.9 | 0.003** |
| Height (cms) | 152.8±8.3 | 158.5±9.2 | 0.09 ^{NS} |
| BMI (Kg/m ²) | 28.5±3.4 | 24.9±5.0 | <0.0001** |
| Neck circumference (cm) | 37.7±4.2 | 35.2±4.5 | 0.005** |
| Gestational age (weeks) | 34.6±3.0 | 31.9±3.9 | <0.0001** |

***Highly Significant; **Very Significant; NS-Not significant.

Out of the hundred cases, 96 were found to be mild OSAHS (AHI: 5-15) and 4 were found to be of moderate OSAHS (AHI: 16-30). Due to less number of cases among moderate OSAHS, no further statistical analysis was carried out among the different level of OSAHS. The mean and standard deviation was computed for discrete parameters such as age, height, weight, BMI, neck

circumference and gestational age. The data was compared between cases and controls using Students two tailed paired t test, (Table 1).

Table 2: Comparison of occurrence of relevant clinical parameters (n=100).

| Parameter | Cases | Controls | P-value |
|-------------|-------|----------|----------|
| Pallor | 22 | 20 | <0.80NS |
| Oedema | 40 | 28 | <0.20NS |
| SBP>130mmHg | 26 | 12 | 0.01* |
| DBP>85mmHg | 44 | 24 | <0.002** |

***Highly significant; **Very significant; NS-Not significant.

The mean age of cases was 28.6±3.2 years and controls were 23.9±3.98 years. It was found that cases were having significantly higher age compared to control ($p < 0.0001$). Increased weight, body mass index and neck circumference as well as advanced gestational age were all found to have statistical significance in cases as compared to controls. Clinical and laboratory parameters used in this study were tabulated and the parameters of relevance in view of MS were used for analysis. The percentage of occurrence above or below the cut off levels mentioned in the literatures was compared between cases and controls. Chi-Square test with Fisher's exact method was used for analysis. When different clinical parameters were compared, it was found that there was a significantly higher occurrence of elevated systolic and diastolic blood pressures among cases (Table 2).

Table 3: Comparison of occurrence of relevant laboratory parameters (n=100).

| Parameter | Cases | Controls | P-value |
|----------------------------|-------|----------|------------|
| Hb<10 gm% | 22 | 24 | 0.81 |
| FBS>100 mg/dl | 34 | Nil | <0.0001*** |
| PPBS>140 mg/dl | 56 | 32 | 0.02* |
| Total cholesterol >200 mg% | 78 | 52 | 0.006** |
| Triglycerides >150 mg/dl | 68 | 44 | <0.001** |
| LDL>120 mg/dl | 74 | 68 | 0.5NS |
| VLDL>50 mg/dl | 46 | 34 | 0.22NS |
| HDL<50 mg/dl | 84 | 56 | <0.001** |

***Highly significant; **Very significant; NS-Not significant.

When occurrence of abnormal laboratory parameters was compared among cases and controls, it was found that there were significantly higher levels of fasting and post prandial blood sugar, total cholesterol and triglycerides, and significantly lower levels of HDL in cases compared to controls (Table 3). It was quite evident that there was considerable degree of metabolic syndrome amongst cases as compared to controls and hence the components of MS were analyzed for the groups. The occurrence of metabolic syndrome was, as per modified National Cholesterol Education Program (NCEP) Adult Treatment

Panel III (ATP III) diagnostic criteria in this study was tabulated (Table 4).

Chi-Square test was used for comparison between cases and controls. When compared between cases and controls it was found that there was significantly higher prevalence of metabolic syndrome among cases.

Table 4: Comparison of occurrence of metabolic syndrome.

| Entity | Subjects (N) | Cases | Controls |
|--------------------|--------------|-------|----------|
| Metabolic syndrome | 100 | 52 | 8 |

Chi-square value=46.1; Degree of freedom=1; P-value <0.0001

This clearly points towards the fact that a large number of pregnant females in the third trimester having OSAHS and metabolic syndrome were actually being missed and could be a modifiable risk for bad obstetric outcomes.

DISCUSSION

This study was undertaken to understand the magnitude of components of metabolic syndrome among the third trimester pregnant women suffering from obstructive sleep apnea/hypopnoea syndrome (OSAHS). As the reported prevalence of OSAHS in adult women among general population is 2-5% and no specific prevalence study on pregnant women so far available to us from Kerala, India, we have attempted screening of the pregnant women with Berlin questionnaire for OSAHS to increase the yield in polysomnography.^{4,8,16}

The difficulties faced by the subject during a conventional polysomnography was eased by the use of limited polysomnography using the commercially available equipment Apnoea Link-TM. All the cases identified for polysomnography could successfully complete the limited polysomnographic procedure without much discomfort. The procedure could be employed in the respective wards were the women were admitted rather than transporting them to the Sleep lab of our Institute. In this study mean weight of the OSAHS positive women were 68.2±8.4kg and the OSAHS negative controls were 61.7±8.9kg, and they differed significantly (P=0.003). Similarly, the BMI among the cases and controls were 28.5±3.4kg/m² and 24.9±5.0kg/cm² respectively, and differed significantly (P<0.0001). The finding indicates that the OSAHS positive cases were significantly of higher body weight than the controls. The pathophysiology of OSAHS is intimately linked with obesity with an estimated 58% of the moderate to severe cases attributable to a BMI greater than or equal to 25 kg/m².^{8,16}

However, the matter of concern is that the same finding is an important risk factor for development of metabolic syndrome (MS). Obesity is associated with insulin resistance and contributes to hypertension, high serum

cholesterol, low HDL-c and hyperglycemia, and is independently associated with higher CVD risk.¹⁷

OSAHS positive cases were found to have significantly (P<0.0001) higher mean gestational age compared to controls (31.9±3.9 weeks vs 34.6±3.0 weeks). Even though, there was no conclusive research on higher incidence of OSAHS on later pregnancy, several researchers reported higher prevalence of snoring in the late pregnancy.^{8,22} There were no significant difference (P=0.76) in the ratio of primi and multi gravida pregnancy among cases and control. The finding concludes that the number of pregnancies is unlikely to affect the risk of getting OSAHS. During clinical examination, it was found that significantly (P=0.01) higher proportion of cases are above the cut off level of systolic (>130mmHg) and diastolic (>85mmHg) values of blood pressure as per the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) diagnostic criteria for Metabolic Syndrome (MS). OSAHS has been implicated in the aetiology of cardiovascular conditions, including hypertension.⁸

Labaan et al, studied the cardiovascular risk factors in 1117 patients (834 men and 283 women) with OSAHS requiring CPAP and free from cardiovascular disease, found that prevalence of hypertension was as high as 54.1% overall, 51.4% in men and 62.1% in women.⁶ He also found that prevalence of hypertension was 45% among cases with AHI 5-29.9 and 55.7% among cases with AHI ≥30.⁶ A number of potential mechanisms in OSAHS may mediate vasculopathy that contributes to the development of hypertension. Repetitive occurrence of airway occlusion resulting in hypoxemia, hypercapnea and changes in intra thoracic pressure may elicit chemoreflex activation with consequent increase in sympathetic vascular tone to peripheral blood vessels.²²

In this study, there were significantly higher prevalence of increased fasting (P<0.0001) and postprandial (P=0.02) glucose levels, total cholesterol (P=0.006) and triglyceride levels (P<0.001) in the OSAHS positive cases compared to controls. The propensity of cases being below the cut off level for HDL (<50 mg/dL) as per MS diagnostic criteria is higher among cases than controls (P<0.001) Wisconsin Sleep Cohort Study has shown that OSAHS is independently associated with prevalent diabetes mellitus.^{8,16} Identification of OSAHS is of clinical significance, as early intervention may directly or indirectly enhance glycaemia control.⁸ It is possible that intermittent hypoxemia and sleep disruption of OSAHS are deleterious to glucose homeostasis and alleviating obstructive breathing during sleep with continuous positive airway pressure therapy has direct effects in improving hyperglycemia.⁸ Alternatively, treatment can diminish daytime fatigue, foster increase in physical activity, and thus result in improved metabolic control^[8]. Preliminary results of another study which analyzed the 2003 Health Care Cost and Utilization Project nationwide inpatient data of all pregnant women

(n=3,979,840 deliveries) showed that sleep apnea might be a risk factor for gestational diabetes.²⁹ Sleep heart health study reported that on adjustment for age and BMI, there was a significant association of the respiratory disturbance index with increasing waist: hip ratio, hypertension, hypercholesterolemia in men, and with low HDL cholesterol and hypertriglyceridemia in women.¹³ Roche et al examined a cohort of 846 elderly individuals and found strong association between severity of OSAHS and low serum HDL levels.³⁰ The findings of our study were also consistent with existing literature.

The prevalence of metabolic syndrome, as per modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) diagnostic criteria, was found to be significantly high ($P < 0.0001$) among the OSAHS positive cases compared to the controls. MS and its components in particular, obesity and insulin resistance/diabetes mellitus may have conducive influence on the development of sleep apnea, and it has been proposed that OSAHS itself may well be a ‘‘metabolic disorder’’ and a component of MS.¹³

Angelico et al, studied 281 heavy snorers of both sexes, reported high prevalence of OSAHS in patients with suspected metabolic disorders and heavy snoring and suggest the presence of a strong association between OSAHS and MS. They also suggest a bidirectional association between the two conditions.¹ Gruber et al similarly found that subjects with OSAHS were about six times more likely to have MS than were the subjects without OSAHS, adjusted for body mass index (BMI), smoking, and age, but OSAHS was not independently associated with the insulin resistance state.¹³

In this study, it was evident that there is a higher possibility of occurrence of OSAHS during pregnancy. Unless the obstetrician has strong suspicion and watchful eyes, most of the cases will continue undetected. If present during pregnancy OSAHS can lead to higher prevalence of MS and its components. Such a complicated pregnancy will lead to higher maternal as well as foetal morbidity and mortality. Although there are no guidelines or consensus regarding the management of pregnancy-induced OSAHS, indications for polysomnography could be expanded according to the current evidence of the relationship between OSAHS and pregnancy.²¹ Another important outcome of this study is the validation of the utility of limited polysomnography in Pregnancy.

There were few limitations in this study. The sample size of 100 is a very small for an epidemiological case control study. Stratified random sampling matched for age, BMI and gestational period would have been ideal for the study. However due to the limited time and infrastructure constraints convenience sampling was adopted. Ideally at least double blinding should have been done during data collection. However, in this study the investigator was aware of the polysomnographic findings, clinical

parameters and laboratory values during data collection and analysis.

CONCLUSION

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) during pregnancy were found to be associated with higher prevalence of metabolic syndrome (MS). The overall prevalence of MS, as per modified NCEP ATP-III criteria, in OSAHS positive third trimester pregnancy in this study was 52% versus 8% in OSAHS negative third trimester pregnant women. Early identification of risk factors in susceptible cases and their timely management can do a long way to reduce maternal morbidity and improve foetal outcome.

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