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An observational study of assessment of obstructive sleep apnea by berlin questionnaire and its association with preeclampsia and eclampsia on second trimester pregnant women

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Abstract

Objective: To know the magnitude of Obstructive Sleep Apnea in pregnant women and to determine the association of high risk and low risk cases of Obstructive sleep apnea (assessed by Berlin Questionnaire) with the development of preeclampsia and eclampsia followed by assessment and comparison of the foetomaternal outcome in pregnant women with low risk and high risk of Obstructive sleep apnea.

Materials and method: A prospective hospital based observational study was carried out in the Department of Obstetrics and Gynecology at SMS Medical College, Jaipur, Rajasthan. 1600 pregnant women in their second trimester were screened with Berlin Questionnaire to identify those having high risk and low risk of obstructive sleep apnea and followed till delivery to verify the association of high risk of obstructive sleep apnea with preeclampsia and eclampsia as compared to the low-risk obstructive sleep apnea group. The feto maternal outcome among these two groups were also studied.

Results: Approximately, 11.87% pregnant women in their second trimester had high risk of obstructive sleep apnea and 12% among them resulted in the development of preeclampsia and eclampsia, while the incidence of preeclampsia and eclampsia in the low-risk obstructive sleep apnea group was only 2% suggesting that high risk of obstructive sleep apnea is significantly associated with increased incidence of preeclampsia and eclampsia in pregnant women as is seen in general population. A significant association was found between high risk of Obstructive Sleep Apnea with the age group 26-30 years, with pre-pregnancy BMI and with caesarean section as the mode of delivery.

Conclusion: Hypertensive disorders of pregnancy form one of the triads of maternal mortality and morbidity in

India. The others being sepsis and hemorrhage. Early identification of high-risk cases for development of preeclampsia and eclampsia would help a lot in reducing the maternal mortality ratio. In the present study, it was found that those pregnant women in their second trimester of pregnancy evaluated by Berlin Questionnaire who had high risk of obstructive sleep apnea results in the development of preeclampsia and eclampsia at a later stage of pregnancy or even after delivery. Berlin Questionnaire is a simple and effective way to identify high risk cases of obstructive sleep apnea. Hence, the authors recommend this to be used as a part of routine antenatal care as this will help in proper risk stratification of pregnant women and provide them with proper antenatal care.

Keywords: obstructive sleep apnea, preeclampsia and eclampsia, Berlin Questionnaire, antenatal care. (Word count of the main text 4507)

Synopsis: Identification of women having high risk of obstructive sleep apnea can help us in screening the women who are at risk of developing preeclampsia and eclampsia.

Introduction

Preeclampsia and eclampsia remain one of the most significant causes of maternal and fetal mortality and morbidity. Various measures have been taken to reduce the incidence of the same and to manage and provide these patients with better care so as to reduce further contribution to adverse pregnancy outcomes.

Preeclampsia is a multiorgan disease process which is characterized by development of hypertension and proteinuria after 20 weeks of gestation. The underlying pathophysiology of preeclampsia points to a decrease in the uteroplacental perfusion. The repeated episodes of placental hypoxia and reperfusion results in exaggerated endothelial cell activation with a hyperinflammatory response generation contributing to systemic maternal disease. An extremely severe form of preeclampsia is eclampsia which is characterized by sudden onset of tonic clonic seizures or coma which can lead to permanent neurological deficits in some rare cases.[1]

Although, several risk factors have been recognized which directly or indirectly cause preeclampsia and eclampsia, Obstructive sleep apnea has been recently identified to be a novel risk factor. Obstructive sleep apnea is the most common form of sleep disordered breathing in general population as well as in pregnant women. This is characterized by repeated episodes of obstruction in upper airway that results in brief periods of breathing cessation(apnea) or a decrease in tidal volume(hypopnea).[2] These episodes, thus result into intermittent hypoxia, enhanced inflammatory and oxidative responses, endothelial damage, and metabolic derangements.[3]

This shows that a mechanistic link might exist in the development of Obstructive sleep apnea as well as preeclampsia and eclampsia. If an association is found between these two, then by predicting high risk cases of Obstructive sleep apnea we can identify at risk pregnancies of preeclampsia and eclampsia and provide them with early and proper management and care so as to reduce incidence of adverse fetal and maternal outcome.

Various methods are available which help us in identifying cases of Obstructive sleep apnea: Polysomnography, Home Sleep Apnea, Berlin Questionnaire, Epworth questionnaire and STOP Bang questionnaire. Among these, polysomnography is a conclusive test, but because of its limited availability it is not widely used. Home sleep apnea test is an at-home version of polysomnography. Among the questionnaires, studies have shown increased sensitivity of Berlin Questionnaire as compared to other questionnaires.[4] It

has been found that even with Berlin questionnaire the findings were similar to those using standard tests (polysomnography) or portable home monitoring systems.[2] Berlin Questionnaire is a simple and useful tool for screening Obstructive sleep apnea risk in the general population including pregnant women. The Berlin Questionnaire was developed in 1996, consisting of three categories designed to elicit information regarding snoring (category 1), daytime somnolence (category 2) and the presence of obesity and/or hypertension (category 3). Consideration for high risk for obstructive sleep apnea (high risk group) required the presence of at least two symptom categories, otherwise it would be considered as low risk for obstructive sleep apnea (low risk group). Berlin Questionnaire is a useful and practical method of screening for Obstructive sleep apnea and can easily be incorporated into routine antenatal care. Studies have demonstrated that Berlin questionnaire has different predictive values, depending on the trimester of pregnancy when it is administered. The Berlin questionnaire appears to be most advantageous during the second trimester of pregnancy. During the first trimester, the amount of sleep increases, coinciding with the subjective worsening of the sleep quality. General sleep disturbances and fatigue are more common with advancing gestation, particularly during third trimester, whereas during second trimester, normal characteristics of sleep, such as sleep duration or sleep quality prevail.[2]

According to National Health Portal of India, the incidence of preeclampsia is reported to be around 8-10% and up to 7.5% worldwide.[2] Incidence of eclampsia in India however, is around 1.5%. Studies show that eclampsia is still prevalent in India with a high case fatality rate. And for the last 40 years, there has been little or no reduction in incidence of eclampsia.[5] Therefore, the need of the hour is in timely and early screening of preeclampsia eclampsia so as to prevent its further progression to avoid adverse maternal and fetal outcomes. If a relationship is established it can be used as a tool in diagnosing preeclampsia and eclampsia at the earliest and help us in better management of preeclamptic and eclamptic pregnant women.

Material and Method

A prospective hospital based observational study was conducted in the Department of Obstetrics and Gynaecology, SMS Medical College and Associated group of hospitals, Jaipur between April 2019 to September 2020. Pregnant women attending antenatal clinic at the Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur were included in the study after taking written informed consent and applying Berlin Questionnaire. The patients were then divided into two groups. The high-risk obstructive sleep apnea group included subjects having at least two symptom categories positive in Berlin Questionnaire and the low-risk obstructive sleep apnea group which included subjects with one or less than one symptom category positive in berlin Questionnaire.

1600 second trimester pregnant women at SMS Medical College, Jaipur was screened with Berlin Questionnaire. 150 high risk obstructive sleep apnea cases among them and equal number of low-risk obstructive sleep apnea cases were followed till delivery. The low-risk obstructive sleep apnea cases were considered as the control group in the study.

Eligible participants were pregnant women who were in their second trimester having singleton pregnancies and women giving written and informed consent. Pregnant women who had chronic renal disease, chronic hypertension, past history of disorder of pregnancy and body mass index > 40kg/m^2 were excluded. Applying the

inclusion and exclusion criteria, women were selected for the study and explained about the study and its benefits. A written informed consent was taken from women who were participating in the study.

The data was recorded in a pre-structured proforma. Statistical analysis was done from the data. Data collected was entered in MS Excel sheet. Continuous data were summarized in the form of mean and standard deviation (SD). Difference in means of the two groups were analysed using unpaired student's t test. Counted data were expressed in form of proportions and chi square test was used for their analysis. The level of confidence was kept 95% for all the statistical analysis. P-value <0.05 was taken as statistically significant. MedCalc statistical software version 16.4 was used for all statistical calculations.

Results

Among 1600 pregnant women screened for obstructive sleep apnea, 190 women had high risk of Obstructive Sleep Apnea. 150 women each among the low risk and high risk for obstructive sleep apnea were followed uptil delivery to look for the development of preeclamspia and eclampsia. Fetomaternal outcome was assessed and compared between women with low risk and high risk of obstructive sleep apnea.

The most common age group for women in high-risk obstructive sleep apnea was 26-30 years i.e., 41.33%, next most common age group was 21-25 years (39.33%) followed by 31-35 years (10.67%), >35 years (4.67%) and ≤20 years (4%) respectively. A significant association was found between obstructive sleep apnea and 26-30 years age group. There is an increased chance of women suffering from obstructive sleep apnea if they belonged to 26-30 years of age group (p-value<0.05). Among women who had low risk of obstructive sleep apnea, the most common age group was 21-25 years (44%) followed by 26-30 years (33.33%), ≤20 years (14.67%), 31-35 years (6%) and >35 years (2%) respectively. A large number of women with high risk of obstructive sleep apnea i.e., 52% were multigravida and 48% were primigravida, but the findings were not statistically significant (p-value=0.245). Similarly, in women with low risk of obstructive sleep apnea majority of women were multigravida (59.33%) and rest were primigravida (40.66%). A large number of high-risk obstructive sleep apnea cases i.e. 61.33% belonged to urban area and 38.66% cases belonged to rural area. Similarly, 69.33% of women with low risk of obstructive sleep apnea lived in urban area and 30.66% women lived in rural area. However, the findings were not statistically significant (p-value=0.182). But one would expect a higher proportion in urban area due to pollution and environment. Majority of pregnant women with high risk of obstructive sleep apnea belonged to lower socioeconomic status i.e., 71.33% and 19.33% belonged to middle socioeconomic status. Only 9.33% belonged to upper socioeconomic status. Among the low risk of obstructive sleep apnea cases, 69.33% belonged to lower socioeconomic status, 15.33% belonged to middle and 15.33% belonged to upper socioeconomic status. However, the results were not statistically significant (p-value=0.232). A large number of pregnant women with high risk of obstructive sleep apnea i.e., 68% were hindu and 32% were muslim. Similarly, among the low-risk obstructive sleep apnea cases, 60% were hindu and 40% were muslim. However, the findings were not statistically significant (p-value=0.186). Majority of pregnant women having high risk of obstructive sleep apnea i.e., 88% had no history of previous abortion and 12% had history of at least 1 or more abortions. Similarly, in the low-risk obstructive sleep apnea cases 85.33% had no history of abortion while 14.66% had history of at least one

abortion or even more. The results were however not statistically significant (p-value=0.610). 45.33% of pregnant women with high risk of obstructive sleep apnea were not anemic, 33.33% had mild anemia, 21.33% had moderate anemia and no pregnant women had severe anemia. Similarly, in low-risk obstructive sleep apnea cases, 57.33% were not anemic, 23.33% had mild anemia, 19.33% had moderate anemia and no women had severe anemia. However, no significant association was found between the severity of anemia and high risk for obstructive sleep apnea (p-value=0.086). High risk of obstructive sleep apnea in pregnant women was seen in 46.66% with normal pre-pregnancy body mass index, 32% in those pregnant women who were overweight, 14.66% were those who were obese and around 6.66% in underweight women. A statistically significant association was found between obstructive sleep apnea and pre-pregnancy body mass index(p-value<0.05). Among low-risk obstructive sleep apnea cases, 60% had pre-pregnancy body mass index within normal range, 28.66% were underweight, 10.66% were overweight and 0.66% were obese. Among pregnant women who had high risk of developing obstructive sleep apnea 52.66% gave birth by lower segment caesarean section (LSCS), 46% gave vaginal birth, 0.66% had preterm vaginal delivery and 0.66% had preterm lower segment caesarean section. The findings suggest that there is a significant association between obstructive sleep apnea and mode of delivery. When chances of obstructive sleep apnea increase there is more chance of delivery by lower segment caesarean section(p-value<0.05). Among the low-risk obstructive sleep apnea cases, 66% had vaginal delivery, 30.66% had LSCS, 2.66% had vaginal birth after caesarean (VBAC) and 0.66% had preterm vaginal delivery. 71.33% babies of pregnant women with high risk of obstructive sleep apnea had their birth weight in 2.0-2.9(kg) group, 19.33% had their birth weight ≥3kg and only 9.33% had their birth weight in 1.0-1.9(kg) group. Similarly, among the low risk of obstructive sleep apnea, 62.66% had babies whose birth weight was between 2.0-2.9(kg), 26% had birth weight ≥3kg and 11.33% had birth weight between 1.0-1.9(kg). The findings are not statistically significant (p-value=0.272). 96.66% babies of pregnant women with high risk of obstructive sleep apnea required no Neonatal ICU admission and 3.33% of babies required Neonatal ICU admission. Similarly, in low-risk obstructive sleep apnea group 93.33% required no Neonatal ICU admission while 6.66% required Neonatal ICU admission. The findings are not statistically significant (p-value=0.289).

Table 1: Demographic Characteristics of High and Low risk obstructive sleep apnea group along with the fetomaternal outcome

Demographic Characteristics	High risk OSA(n=150)		Low risk OSA(n=150)		
	No.	%	No.	%	
Age (in years)					
≤20	6	4	22	14.67	Chi-square=14.38, p-value=0.006, degree of freedom=4
21-25	59	39.33	66	44	
26-30	62	41.33	50	33.33	
31-35	16	10.67	9	6	
>35	7	4.67	3	2	

Gravida					Chi-square=1.351, p-value=0.245, degree of freedom=1
Primigravida	72	48	61	40.66	
Multigravida	78	52	89	59.33	
Residence					Chi-square=1.781, p-value=0.182, degree of freedom=1
Rural	58	38.66	46	30.66	
Urban	92	61.33	104	69.33	
Socioeconomic status					Chi-square=2.94, p-value=0.232, degree of freedom=1
Lower	107	71.33	104	69.33	
Middle	29	19.33	23	15.33	
Upper	14	9.33	23	15.33	
Religion					Chi-square=1.751, p-value=0.186, degree of freedom=1
Hindu	102	68	90	60	
Muslim	48	32	60	40	
Number of previous abortions					Chi-square=0.260, p-value=0.610, degree of freedom=1
0	132	88	128	85.33	
≥1	18	12	22	14.66	
Anaemia					Chi-square=4.89, p-value=0.086, degree of freedom=2
Non anemic	68	45.33	86	57.33	
Mild anemia	50	33.33	35	23.33	
Moderate anemia	32	21.33	29	19.33	
Severe anemia	Nil	Nil	Nil	Nil	
Pre-pregnancy BMI (kg/m^2)					Chi-square=58.221, p-value<0.00001, degree of freedom=1
Underweight (<18.5)	10	6.66	43	28.66	
Normal (18.5-24.9)	70	46.66	90	60	
Overweight (25-29.9)	48	32	16	10.66	
Obesity (>30)	22	14.66	1	0.66	
Mode of Delivery					Chi-square=19.06, p-value<0.05, degree of freedom=4
Vaginal delivery	69	46	99	66	
Preterm vaginal delivery	1	0.66	1	0.66	
LSCS	79	52.66	46	30.66	
Preterm LSCS	1	0.66	Nil	Nil	
Vaginal birth after caesarean (VBAC)	Nil	Nil	4	2.66	
Birth weight (in kg)					Chi-square=2.602, p-value=0.272, degree of freedom=2
1.0-1.9	14	9.33	17	11.33	
2.0-2.9	107	71.33	94	62.66	
≥3	29	19.33	39	26	
Neonatal ICU Admission					Chi-square=10.036, p-value=0.289, degree of freedom=1
Yes	5	3.33	10	6.66	
No	145	96.66	140	93.33	

In the present study, preeclampsia and eclampsia was seen only in 2% in low-risk obstructive sleep apnea cases in comparison to high-risk group i.e., 12% (Table 2) and there is a significant association between the development of preeclampsia and eclampsia with obstructive sleep apnea. When obstructive sleep apnea increase, there are more chances of development of preeclampsia and eclampsia (p-value < 0.05).

Table 2: Association of Preeclampsia and Eclampsia in Low risk and High-risk obstructive sleep apnea cases

Preeclampsia/Eclampsia	High risk OSA(n=150)		Low risk OSA(n=150)		Chi-square=10.036, p-value = 0.002, degree of freedom=1
	No.	%	No.	%	
Yes	18	12	3	2	
No	132	88	147	98	
Total	150	100	150	100	

Discussion

Preeclampsia and eclampsia remain one of the most significant causes for maternal and fetal morbidity and mortality. Various measures have been taken to reduce the incidence of the same and to manage and provide these patients with better care so as to reduce its further contribution to adverse pregnancy outcomes. Obstructive sleep apnea has been identified to be a novel risk factor in causing preeclampsia and eclampsia in pregnant women. In present study, 1600 pregnant women in their second trimester at SMS Medical College, Jaipur were screened with Berlin Questionnaire to verify the association of obstructive sleep apnea with preeclampsia and eclampsia. In the present study, the development of preeclampsia and eclampsia in high risk obstructive sleep apnea pregnant women was found to be statistically significant and it was 12% compared to only 2% in women with low risk of obstructive sleep apnea. Similarly, in a study by Ellen M. Lockhart et al. (2015)[6], it was reported that obstructive sleep apnea-positive patients had significantly higher rates of preeclampsia, chronic and gestational hypertension. Study conducted by Jaimchariyatam N. et al. (2018)[2] also showed that the development of preeclampsia and eclampsia was 11% among the high risk group for obstructive sleep apnea and only 2.9% in low risk obstructive sleep apnea cases. According to the study of Antony et al. (2014)[7] among predominantly Hispanic pregnant women, the investigators noted that pregnant women with high risk for obstructive sleep apnea were associated with a s2.45-fold and 2.02-fold increases risk ratio of preeclampsia and eclampsia respectively, when compared to pregnant women with low risk of obstructive sleep apnea. Judette Loius et al. (2012)[8] studies 175 pregnant women who underwent an overnight sleep study using a portable home monitor, it was found that obstructive sleep apnea was significantly associated with preeclampsia after adjustment for maternal age, chronic hypertension, prior preeclampsia, body mass index, and pre gestational diabetes mellitus. Facco et al.(2017)[3] enrolled 3705 nulliparous women who underwent an in-home sleep-disordered breathing assessment. The authors reported that in early and mid-pregnancy, the adjusted odds ratios for preeclampsia when sleep disordered breathing was present were 1.94 and 1.95, respectively; hypertensive disorders of pregnancy, 1.46 and 1.73; and gestational diabetes mellitus, 3.47 and 2.79. Liwen Li et al.(2018)[9] in their study, concluded that pregnant women with sleep disordered breathing appeared to have significantly higher risk of pregnancy induced hypertension compared to those without sleep disordered breathing. Ghada Bourjeily et al.(2017)[10] also found an elevated risk of preeclampsia in women with obstructive sleep apnea. Yi-Hua Chen et al.(2012)[5] found that women with obstructive sleep apnea had higher prevalence of preeclampsia(1.4% versus 0.5%) as compared to women

without obstructive sleep apnea. K. Champagne et al.(2009)[11] observed that obstructive sleep was associated with gestational hypertension with a crude Odds ratio of 5.6.

In the present study, significant association of obstructive sleep apnea was found in the pregnant women belonging to 26-30 years of age in comparison to those pregnant women who were younger than 25 years and who were older than 30 years of age as 41.33% of pregnant women with high risk of obstructive sleep apnea were between 26-30 years of age. There is an increased chance of obstructive sleep apnea if pregnant women belonged to this age group. Similarly, Judette Louis et al. (2012)[8] in their study found that obstructive sleep apnea group had older patients. In the general population, older age is a well identified risk factor for obstructive sleep apnea. Similar might also hold true for pregnant women. Ghada Bourjeily et al. (2017)[10] in their study found a significant association between older age group pregnant women and the risk of obstructive sleep apnea. The mean age of the 4746 sampled women in a study conducted by Yi-Hua Chen et al. (2012)[5] was 30.4±4.4 years. The average age of cohort in a study by Ellen M. Lockhart et al. (2015)[6] was 28 years.

In the present study, majority of pregnant women in high risk of obstructive sleep apnea were multiparous (52%) but the findings were not significant. As it may seem from the present study, parity doesn't influence the occurrence of obstructive sleep apnea in pregnant women. Ellen M. Lockhart et al. (2015)[6] found in their study that 76% of women were multiparous.

In the present study, majority of pregnant women with high risk of obstructive sleep apnea belonged to lower socioeconomic status i.e., 71.33% as the maximum pool of pregnant women in the present study mostly belonged to lower socioeconomic status because the study was conducted in a government hospital. The results were however not statistically significant. In a study by Judette M. Louis et al. (2014)[12] it was found that women in whom obstructive sleep apnea had been diagnosed were more likely in the lowest quartile of household income.

In the present study, the author found no significant association between anemia and obstructive sleep apnea, 45.33% of pregnant women with high risk of obstructive sleep apnea had no anemia. This result proves that anemia does not predispose to obstructive sleep apnea. Supporting this result is a study conducted by Yi-Hua Chen et al. (2012)[5]. They found no significant differences between women with or without obstructive sleep apnea and anemia.

In the present study, 78.66% of pregnant women who had high risk of obstructive sleep apnea either had normal weight or were significantly overweight. The results were statistically significant suggesting that increased body mass index is associated with increased risk of obstructive sleep apnea. Many studies have been conducted over the past years which supports this outcome. Judette Louis et al. (2012)[8] found that women who had obstructive sleep apnea also had higher body mass index. Ellen M. Lockhart et al. (2015)[6] also found that obstructive sleep apnea-positive patients had greater body mass index both before pregnancy and as measured at the time of sleep study.

Increased chances of high-risk obstructive sleep apnea was significantly associated with higher incidence of caesarean section in the present study. 52.66% pregnant women who had high risk of obstructive sleep apnea gave birth by caesarean section. Supporting this result is a study reported by Judette Louis et al. (2012)[8]. They concluded that women with obstructive sleep apnea were more likely to have a caesarean delivery than the control group. Manju Aggarwal et al. (2008)[13] also in their study

found that among snorers 24.2% landed up into caesarean delivery in comparison to 11.8% of non-snorers (p=0.076). Yi-Hua Chen et al. (2012)[5] found that women with obstructive sleep apnea had higher prevalence of caesarean section (50.4% versus 37.3%) as compared to women without obstructive sleep apnea.

In the present study, no significant association was found between the birth weight of the baby in high and low risk of obstructive sleep apnea. Similarly, Antony et al. (2014)[7] compared the average birth weight ratios between obstructive sleep apnea screen-negative and obstructive sleep apnea screen-positive groups. The average birth weight ratios were 0.96 and 0.97 respectively, with no statistically significant difference between the groups. Judette Louis et al. (2012)[8] concluded that both, women with obstructive sleep apnea and women who didn't have obstructive sleep apnea had similar birth weight of baby. Liwen Li et al.(2018)[9] found no significant difference in birth weight between pregnant women with sleep disordered breathing and those without sleep disordered breathing.

In the present study, there was no significant association found as far as Neonatal ICU admissions of the babies born to the pregnant women with high risk or low risk of obstructive sleep apnea are concerned. However, Judette Louis et al. (2012)[8] found out that babies of mothers who had obstructive sleep apnea was associated with more frequent Neonatal ICU admission.

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