Sleep breathing disorders in pregnancy

Ahmet URSAVAŞ, Mehmet KARADAĞ

Uludağ Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Bursa.

ÖZET

Gebelikte uykuda solunum bozuklukları

Horlama, üst solunum yolu rezistans sendromu ve obezite hipoventilasyon sendromu uykuda solunum bozuklukları olarak tanımlanır. Gebelik boyunca fiziksel ve hormonal nedenlerle solunum ve uyku fizyolojisinde birçok değişiklik ortaya çıkar. Gebeliğin 3. trimestırında fonksiyonel rezidüel kapasite, total uyku süresi, REM uykusu ve non-REM evre 3 uyku azalır. Horlama gebelerde, gebe olmayanlara göre daha sık görülür. Gebelikte horlama, gestasyonel hipertansiyon, preeklampsi, intrauterin gelişme geriliği ve yenidoğanda düşük Apgar skoru ile birlikte olabilir. Gebelikte uyku apne prevalansı bilinmemektedir. Tüm gebelerde, özellikle obez ve preeklamptik olanlarda uykuda solunum bozuklukları sorgulanmalıdır. Bu derlemede, öncelikle gebelikte solunum sistemi ve uykuda oluşan fizyolojik değişiklikleri, ikinci olarak uykuda solunum bozukluklarının maternal ve fetal etkilerini ve son olarak gebelikte uykuda solunum bozuklarının tedavisini özetledik.

Anahtar Kelimeler: *Gebelik, horlama, preeklampsi.*

SUMMARY

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Ahmet URSAVAŞ, Mehmet KARADAĞ

Department of Chest Diseases, Faculty of Medicine, Uludag University, Bursa, Turkey.

Snoring, upper airway resistance syndrome, sleep apnea syndrome and obesity hypoventilation syndrome are all defined as sleep-disordered breathing. Many changes occur in the respiratory system and sleep physiology during pregnancy due to physical and hormonal causes. Functional residual capacity, total sleep time, rapid eye movement (REM) sleep and stage 3-4 non-REM sleep are reduced during the third trimester of pregnancy. Snoring is more prevalent in pregnant women than nonpregnant women. Snoring during pregnancy may be associated with pregnancy induced hypertension, preeclampsia, intrauterine growth retardation and low APGAR scores in infant. The prevalence of sleep apnea syndrome during

Yazışma Adresi (Address for Correspondence):

Dr. Ahmet URSAVAŞ, Uludağ Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı,

16059 Görükle, BURSA - TURKEY

e-mail: ahmetursavas@gmail.com

pregnancy is unknown. All pregnant women, especially obese and preeclamptic were asked to possibility of sleep disordered breathing. In this review we summarized, first normal physiological changes of respiratory system and sleep during pregnancy, second maternal and fetal outcome of sleep disordered breathing and finally treatment of sleep disordered breathing in pregnancy.

Key Words: *Pregnancy, snoring, preeclampsia.*

PHYSIOLOGICAL CHANGES in RESPIRATORY SYSTEM DURING PREGNANCY

Several physiological changes which alter the functions of many organs and systems occur during pregnancy. Respiratory system anatomy and physiology are markedly altered in pregnancy. The changes observed during pregnancy in the respiratory system can be listed as follows: The enlarging uterus elevates the diaphragm 3-4 cm, subcostal angle increases and thorax transverse diameter increases by 2 cm. Functional residual capacity is reduced by elevation of the diaphragm, during sleep and furthermore by adoption of the supine position. However, the motion of diaphragm and other inspiratory muscles remain normal and, as a rule, vital capacity as well as total lung capacity are preserved (1,2).

High levels of estrogen and progesterone are required to maintain pregnancy. Along with estrogen and progesterone, the changes occurring during pregnancy in prostaglandin and cortisol levels also may have an impact on the respiratory physiology. Elevated progesterone levels stimulate central chemoreceptors and upregulates ventilatory drive. As a result, there is hyperventilation, increased minute ventilation during pregnancy. Arterial blood gas values have been reported to be 27-32 mmHg for $PaCO_2$ and 7.44 for mean pH (7.40 for non-pregnant women), while oxygen saturation remained stable in pregnancy (1,3). However, recent studies have suggested a drop in oxygen saturation in the supine position, particularly in the 3rd trimester (4). A study investigating arterial blood gases in the last trimester of pregnancy and postpartum 4-6 months reported no differences between the last trimester and post-partum in the sitting position. However, significantly lower oxygen levels were reported in the supine position during both sleep and wakefulness in the last trimester when compared with the values of the post-partum period Bourne et al. reported that 3 of the 13 normotensive and 4 of the 15 hypertensive pregnant women during the last trimester of pregnancy were observed with oxygen saturation of 90% or lower for over 20% of the night (5).

Furthermore, heart rate, stroke volume and cardiac output increase significantly in the cardiovascular system during pregnancy while marked reductions are observed in peripheral vascular resistance. Consequently, minor decrease in blood pressure is observed in pregnant women and normal diurnal blood pressure changes remain stable (6).

Reduced pharyngeal dimensions during pregnancy have been demonstrated (7). Nasal zone is responsible for 50% of upper airway resistance. Nasal congestion and rhinitis are common during pregnancy due to elevated estrogen levels; these may predispose to snoring and upper airway obstructive events. A study reported nasal congestion and rhinitis symptoms in 42% of the subjects at the 36th week of gestation. Infact, rhinitis symptoms have been reported to be higher even during the luteal phase of the menstrual cycle (8).

PHYSIOLOGY of SLEEP DURING PREGNANCY

Sleep and wakefulness have a circadian rhythm regulated by suprachiasmatic nucleus of the hypothalamus. Mechanical and hormonal alterations occurring during pregnancy have an impact on regular sleep duration and patterns. Estrogen and progesterone progressively increase during pregnancy. A number of evidence in-

dicates that estrogen decreases rapid eye movement (REM) sleep, while progesterone increased non-REM sleep. Ovariectomy enhances REM sleep in rats; subsequent estrogen administration reduces REM sleep (9). It has been known that exogen progesterone administration has a sedative effect on men and women, leading to increased non-REM sleep. The sedative quality of progesterone has been attributed to the agonist effect of gamma-aminobutyric acid A receptor (10). Cortisol concentrations increase twofold in late pregnancy and fourfold during labor. Furthermore increased levels of progesterone also elevate free cortisol levels due to progesterone shares binding sites on corticosteroid-binding globulin. Prolactine and luteinizing hormone may also contribute to the increase in non-REM sleep. Insomnia during the third trimester of pregnancy may explain to oxytocin peaks at night (11-13).

There are also mechanical factors with an impact on sleep during pregnancy. The most common reasons are uterine contractions, fetal movement, general abdominal discomfort, urinary frequency, leg cramps and heartburn (14). Factors which have an impact on normal sleep during pregnancy are given in Table 1.

A Summary of Changes in Sleep in the Pregnant Women

1. First trimester: Total sleep time, daytime sleepiness, insomnia and nocturnal awakenings increase, stage 3-4 non-REM sleep and overall sleep quality decreases.

2. Second trimester: Total sleep time becomes to normalize but nocturnal awakenings increase, stage 3-4 non-REM sleep and REM sleep decreases

3. Third trimester: Insomnia, nocturnal awakenings, daytime sleepiness, waking after sleep onset, stage 1 non-REM sleep increase, total sleep time, stage 3-4 non-REM sleep and REM sleep decreases. Most pregnant women awaken 3 to 5 times per night in the 3rd trimester (15-17).

4. Post-partum period: Sleep pattern appears to normalize after 3 months to delivery. Kang et al. monitored 10 healthy pregnant women during the last trimester and after delivery at home by using an actigraph (18). They reported that there were more frequent awakenings and less sleep in the days immediately after delivery when compared with the last trimester. These parameters returned to normal values only after the 12th week. However, these findings are difficult to interpret due to other factors such as the crying of the baby (14).

SNORING and SLEEP APNEA DURING PREGNANCY

Pregnant women have an increased tendency to snoring and apnea. Certain changes in pregnancy may provide protection from sleep disorders breathing (SDB), whereas others may put women at risk (19).

Factors Which Increase the Risks for SDB in Pregnancy

1. Increased upper airway resistance;

a. Decreased pharyngeal diameter,

b. Estrogen induced nasal congestion and rhinitis.

Table 1. Factors effecting quality and stages of sleep during pregnancy.

Positive factors on non-REM sleep	Positive factors on REM sleep	Mechanical factors resulting in arousals
Progesterone	Estrogen	Uterine contractions
Luteinizing hormone	Cortisol	Fetal movement
Prolactin		Stomach ache
		Frequency of urination
		Leg cramps
		Gastroesophageal reflux

REM: Rapid eye movement.

2. Hypocapnia and respiratory alkalosis: Progesterone enhances respiratory center sensitivity to CO_2. As a result there is a reduced PaCO_2 and an associated respiratory alkalosis. Hypocapnia can lead to central apnea.

3. Negative inspiratory pressure of upper airway: Upregulation of central respiratory drive increase diaphragmatic activity. This can lead to greater negative inspiratory pressure and increased tendency for the upper airway collapse.

Protective Factors Against Sleep-Disordered Breathing in Pregnancy

1. Respiratory stimulating effect of progesterone,

2. Progesterone stimulates the upper airway dilator muscle (genioglossal) activity which maintains the upper airway unblocked,

3. The decrease observed during pregnancy in REM sleep and sleep in the supine position may have a protective role against apnea.

Snoring and Sleep Apnea Prevalence in Pregnancy

There are 2 major studies in the literature dealing with snoring prevalence in pregnancy. The incidence of snoring in a US population of healthy pregnant women was found to be 14%, significantly greater than the 4% incidence found in age matched non-pregnant population (20). In a similar study carried out by Franklin et al. in Sweden, 502 pregnant women were asked to fill in a questionnaire (21). They found that 23% of pregnant population reported regular snoring. While only 4% of the same sample reported regular snoring before pregnancy.

However, actual prevalence of SDB during pregnancy is unknown. Although the increase in incidence of snoring during pregnancy suggests a positive correlation with SDB, there are not enough studies to reach a final conclusion. Guilleminault et al. investigated 267 pregnant women in their II-staged study (22). All subjects were monitored in their sleep through a 6-channel polygraph and pre-pregnancy snoring prevalence was established to be 3.7%, while it was observed to be 11.8% during the last trimester. They also established excessive sleepiness during the day to be 37% at the 6^{th} week of gestation according to visual analog scale and 52% at the 6^{th} month of gestation. In the II. stage of the study, 26 subjects underwent polysomnography (PSG) based on symptoms, blood pressure values and polygraph results. Abnormal respiratory patterns were detected but none of the subjects were established with apnea or hypopnea.

It has been proposed that obesity which constitutes a risk factor for sleep-disordered breathing may also present a risk for snoring and sleep apnea syndrome during pregnancy. A total of 11 obese pregnant women with a pre-pregnancy body mass index of over 30 were compared with 11 non-obese pregnant women with a pre-pregnancy body mass index of 20-25 by conducting PSG at the 12^{th} and 30^{th} weeks of pregnancy. Both PSG results revealed that duration of snoring, apnea hypopnea index (AHI) and oxygen desaturation index were significantly higher in the obese group. Only one of the obese subjects was established to have an AHI of 10. Although the other subjects had significant differences, they remained below the pathological AHI limit (23).

Prodromakis et al. performed PSG on 21 healthy pregnant women in the last trimester and postpartum 4^{th} and 6^{th} months (4). They did not find any correlation between oxygen levels neither apnea hypopnea index nor percent of REM sleep. They reported that the frequency of apnea and hypopnea significantly lower during pregnancy than postpartum, which could be due to raised level of progesterone.

MATERNAL OUTCOME of SDB

Sleep-disordered breathing has several maternal and fetal consequences. Gestational hypertension and preeclampsia are the most important ones. Preeclampsia is a multisystem disorder observed in 7-9% of pregnant women. It is characterized with proteinuria, elevated hepatic enzymes, renal dysfunction, peripheral and cerebral edema and hypertension, developing after the 20^{th} week of pregnancy in general (24,25). Nocturnal blood pressure values are higher when compared with daytime values in preeclampsia and diurnal variations are observed

(26). The association between sleep apnea and hypertension has not been clearly elucidated. Moreover, diurnal variations are observed in hypertension in such patients, as well. Therefore, an association between preeclampsia and sleep-disordered breathing has been postulated.

There is some evidence that maternal snoring is a poor prognostic factor for the mothers, who have a greater risk of hypertension and preeclampsia (21). Gislason et al. demonstrated a strong correlation between hypertension and snoring in pregnancy (27). Izci et al. investigated 167 healthy pregnant, 82 preeclamptic pregnant and 160 non-pregnant women (28). They reported 32% of control, 55% of pregnant and 85% of pre-eclamptic women snored. Another study investigating a total of 22 pregnant women (11 obese and 11 non-obese) by utilizing PSG reported preeclampsia in one obese subject and stated that the same subject had a mild case of sleep apnea syndrome as well (23). Information regarding pregnancy in patients diagnosed with sleep apnea is limited to case presentations. During the follow-up period, pre-eclampsia was established in 4 of the 7 pregnant women diagnosed with sleep apnea through PSG in the literature (29).

On the other hand, it was suggested that the increase in the incidence of snoring and sleep apnea syndrome in preeclamptic pregnant women could be attributed to the presence of upper airway edema. Upper airway diameters of 37 preeclamptic and 13 non-preeclamptic pregnant women in the third trimester, as well as 50 non-pregnant women were measured by using acoustic reflection method and then compared. Upper airway diameters in preeclamptic pregnant women were observed to be significantly narrower than both those of the non-pregnant women and those of the non-preeclamptic pregnant women (30). Connolly et al. enrolled 15 healthy and 15 preeclamptic pregnant women along with 15 non-pregnant women in their study (31). The subjects were monitored over the night for blood pressure and respiration. They were also monitored with an oximeter. While none of the subjects was established with significant sleep apnea syndrome, preeclamptic pregnant women were observed with significant inspiratory flow limitation. Episodic inspiratory flow limitation observed in upper airway resistance syndrome is brief and results in arousal. However, these subjects were observed with long episodes of minutes at a time.

Fetal Outcome of SDB

The impact of snoring and other sleep-related breathing disorders on the fetus has not been investigated in detailed. However, it has been reported that snoring may lead to intrauterine growth retardation and low Apgar scores. It is also known that hypoxia is observed in pregnant women particularly in the last trimester due to physiological changes occurring in the respiratory system. It has been reported that PaO_2 level dropped below 90 mmHg in the supine position in 25% of pregnant women in the last trimester. As hypoxia can occur even during wakefulness, a minor alteration in respiration pattern during sleep may impair maternal and fetal oxygenation severely (32).

Previous studies conducted on pregnant subjects living in higher altitudes or those with hypoxia due to pulmonary parenchyma demonstrated that maternal hypoxia led to retarded fetal development (33). Experimental rat studies revealed that prenatal hypoxia impaired the development of the chemoafferent pathway, as well as the ventilatory and metabolic responses to hypoxia (34). Gozal et al. demonstrated that newborns of pregnant rats exposed to intermittent hypoxia, a hallmark of sleep apnea syndrome, had lower birth-weight when compared with newborns of pregnant rats exposed to normoxia (35). The same study also established that normoxic ventilation was higher in newborn rats whose mothers had been exposed to intermittent hypoxia.

Franklin et al. established impaired fetal development in 8 (7.1%) of the 113 pregnant women with habitual snoring and 10 (2.6%) of the 379 pregnant women with no habitual snoring (21). The difference was statistically significant. Furthermore, the incidence of an Apgar score of fewer than 7 was significantly higher in the babies of pregnant women with habitual snoring. In

contrast Loube et al. reported that pregnant women who snorers did not have deliveries resulting in infants with evidence of an increase in compromised outcomes (20).

PREGNANCY and CPAP THERAPY

Continuous positive airway pressure (CPAP) is used in standard sleep apnea syndrome management. It was reported that CPAP therapy could be administered safely in pregnant women with sleep apnea syndrome (29,36). It was reported that CPAP therapy assisted blood pressure control in the presence of inspiratory flow limitation observed in preeclamptic pregnant women, even when apnea was not present. A total of 11 preeclamptic pregnant women underwent PSG in a study conducted by Edwards et al. (37). While none of the subjects was established with apnea, a typical breathing pattern during sleep, defined as upper airway inspiratory flow limitation, was observed in all of the subjects. When these subjects were administered with automatic CPAP therapy accompanied by somnography on their second night, a significant drop in blood pressure was noted after the 5th minute of therapy. The mean blood pressure value for the second night was observed to be significantly lower when compared with the value of the night when CPAP was not administered.

Guilleminault et al. monitored a total of 12 pregnant women with sleep apnea syndrome (7 diagnosed before pregnancy and 5 diagnosed in the 1st trimester of pregnancy) during the course of their pregnancy in terms of CPAP therapy and established that symptoms improved and none of the subjects were observed with hypertension or preeclampsia (38). Furthermore, all babies were healthy and side effects were not different than the ones observed in other CPAP users.

CONCLUSION

Many physiological changes occur during pregnancy, having a major impact on respiratory system and sleep physiology. Pregnant women should be evaluated in terms of sleep-disordered breathing if they snore, are obese or preeclamptic, have a pregnancy induced hypertension or a history of unexplained low-birth weight delivery. PSG should be performed if deemed necessary. CPAP therapy can safely use in pregnancy if necessary.

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