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The Role of Obstructive Sleep Apnea in Developing Gestational Hypertension and Preeclampsia

Laura LUNGEANU-JURAVLE[a], Natalia PATRASCU[b], Oana Claudia DELEANU[b], Mircea CINTEZA[b]

[a] Department of Cardiology, University Emergency Hospital, Bucharest, Romania
[b] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Gestational hypertension and preeclampsia are the most frequent medical complications in pregnancy and major causes of maternal and fetal morbidity and mortality. It is also known that these conditions are associated with a long term increased cardiovascular global risk for these young women. Obstructive sleep apnea (OSA) seems to be not only a frequent pathology associated with pregnancy but also an independent factor for developing gestational hypertension. It is well known the relationship between gestational hypertension, preeclampsia and intrauterine growth restriction of the foetus so the outcomes of this pathologies are important for both mother and child. Increasing awareness of OSA among pregnant women with gestational hypertension and preeclampsia is important given the potential benefits of the treatment with continuous positive airway pressure (CPAP) on these patients.

Keywords: Gestational hypertension, preeclampsia, obstructive sleep apnea, continuous positive airway pressure, pregnancy

Abbreviations: GHT, gestational hypertension; PE, preeclampsia; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of CO_2; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

BACKGROUND

Gestational hypertension (GHT) complicates 6-8% of pregnancies (1). GHT is defined as a new diagnosed systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg after 22 weeks of pregnancy. When associated with proteinuria or other signs and symptoms of damaged target organs it is named preeclampsia (PE) or alternatively gestational hypertension with proteinuria (2). It is associated with fetal intrauterine growth restriction, neonatal intensive care admissions and poorer neonatal outcomes and with maternal HELLP syndrome and sometimes eclampsia. Gestational hypertension or preeclampsia are independent risk factors for chronic hypertension, fatal stroke, cardiovascular death, and metabolic syndrome (3).

Risk factors for PE are heterogeneous and of many types: general (familial history of GHT, age, obesity, black race, living in high altitude zones), obstetrical (nulliparity, gemelar gestation, hydati-

Address for correspondence:
Laura Lungeanu-Juravle,
Postal address: University Emergency Hospital of Bucharest, Splaiul Independentei 169, Bucharest 050098, Romania
Tel: +40 21 3180576; fax: +40 21 3180576;
E-mail: lungeanulaura86@yahoo.com

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form mole, personal history of PE) and medical diabetes (4), insulin resistance, dyslipidaemia (5), depression (6), renal disease, asthma (7), thrombophilia (8), collagen vascular disease/autoimmune diseases (9, 10).

Among all these numerous conditions, a new risk factor that has emerged recently is sleep-disordered breathing (SDB), a condition characterized by repeated closure of the upper airway during sleep with disrupted ventilation and sleep fragmentation (11). By far the most common form of SBD is obstructive sleep apnea (OSA) in which repeated dynamic collapse of the upper airway during sleep leads to frequent, intermittent cessation of air flow despite ongoing respiratory effort. The marker of OSA is snoring and breathing pauses. Emerging evidence indicates that OSA increase during pregnancy (10). Among normotensive pregnant women with high risk pregnancies, the prevalence of OSA is high and it is even higher among those with gestational hypertension/preeclampsia. Moreover, recent studies indicate that OSA is an independent risk for GHT and PE (10).

It is important to focus on all possible evidences that link pregnancy with OSA since many complications of pregnancy, such as GHT, PE and fetal growth disorders are considered to be associated with sleep disorders (10, 12, 13).

Physiological changes in pregnancy appear in upper and lower respiratory system's anatomy and function and makes it a period of high vulnerability to OSA. Some of these changes are noted in the first trimester (10), such as mucosal edema, capillary congestion, hyperemia and reduction of the pharyngeal size (14). Histologic examination of the upper respiratory mucosa during pregnancy reveals, apart from hyperemia that is already mentioned, glandular hyperactivity, increased phagocytic activity, and increased mucopolysaccharide content (14). Estrogens increase tissue hydration and edema also causing capillary congestion and hyperplastic and hypersecretory mucous glands (14-16). Many pregnant womens suffer from estrogen-dependent rhinitis caused by increased estrogen levels and often seen is also nasal polyposis. Clinically, all these anatomic changes of the upper airway system force women to breathe through mouth instead of nostrils (14, 17).

Changes in the lower respiratory system are: elevation of the diaphragm because of the uterus, the increased chest diameter so the lung capacity decreases slightly and progressively. The ligamentous attachments of the ribs are gradually relaxed, so that the subcostal angle broadens almost by 50%. As a result, the functional residual capacity is decreased by 20% and the total lung capacity decrease in the third trimester. Moreover, the partial pressure of oxygen (PaO_2) is increased and the partial pressure of carbon dioxide ($PaCO_2$) is decreased, so due to these changes in O_2 and CO_2, the exchange of these two molecules is enabled between the foetus and the mother (14, 18-21). These changes makes symptoms such as snoring very likely to appear in pregnant woman and are often considered physiological.

A common sleep disorder, SDB represents a spectrum of respiratory disturbances that include habitual snoring, increased upper airway resistance, and OSA, the latter being the most severe (3). Snoring and witnessed apnea are considered key symptoms of OSA. The diagnosis of OSA is established by overnight polysomnography including electroencephalogram. The number of partial and complete obstructive events *per* hour of sleep that are associated with decreased blood oxygenation or arousals is calculated and reported as the Apnea-Hypopnea index (AHI) (22).

An apnea is defined by a drop in peak thermistor excursion by >90% of the pre-event baseline where at least 90% of duration met amplitude reduction criteria for apnea, with ≥10 seconds duration. An obstructive apnea was defined as an apnea with continued respiratory effort. Hypopneas were scored if the nasal pressure signal excursion dropped by >50% of baseline for ≥10 seconds with ≥3% desaturation or an arousal. AHI is calculated as the number of apnea and hypopneas *per* hour of total sleep time. The presence of mild obstructive sleep apnea is defined as an AHI ≥5 and <15; moderate obstructive sleep apnea as an AHI ≥15 and <30, and severe obstructive sleep apnea as an AHI ≥30 (23).

There are case-control studies which used overnight recordings and compared women with pregnancy induced hypertension with normotensive pregnant controls for the presence of OSA.

OSA is uncommon in low risk pregnancies but was present among women with PE. A case-control study used 17 women with preeclampsia and compared them with 25 normotensive pregnant women with uncomplicated pregnancies for the presence of OSA. Age, pre-pregnancy body mass index and gestational age at the time of the sleep test were similar in both groups. Pregnant women

with PE had significantly more respiratory events *per* hour than controls and more oxygen desaturation *per* hour of sleep (10, 24).

In another case-control study, 17 pregnant women with new onset of hypertension in pregnancy were compared with 33 normotensive controls. Recruitment took place in a high risk obstetrics tertiary care facility (10). OSA was present in 82 % of the subjects with gestational hypertension *vs* 45 % of the normotensive controls. The crude *odds ratio* of having OSA given gestational hypertension was 5.6 (95% CI 1.4-23.2) and was 7.5 (95% CI 3.5-16.2), when adjusted for gestational age, maternal age, pregnancy body mass index, prior pregnancies and prior live births (25).

It seems that OSA is an independent risk factor for hypertensive disorders of pregnancy.

In some studies there where used questionnaires such as the Epworth Sleepiness Scale which is a widely used measure of daytime sleepiness, with scores ranging from 0 to 24. Excessive daytime sleepiness is defined as a total score of ≥10 (23).

There are no large –scale studies on polysomnographic data but there are some small studies that suggest an association between a diagnosis of OSA and hypertension (26-28). These studies found a high frequency of occult OSA in women with GHT and PE (10, 29).

One of these studies was performed by O'Brian et all and published in 2014, and as a result they mention that OSA was found among 21 of 51 pregnant women with hypertensive disorders (41%), but in only three of 16 women who were normotensive (19%, chi-square test, P=0.005). Non-snoring women with hypertensive disorders typically had mild obstructive sleep apnea, but >25% of snoring women with hypertensive disorders had moderate to severe obstructive sleep apnea. Among women with hypertensive disorders, after stratification by obesity, the pooled relative risk for obstructive sleep apnea in snoring women with hypertension compared with non-snoring women with hypertension was 2.0 (95% CI 1.4-2.8).

For this study the following channels were used in polysomnography: 6-channel electroencephalogram (EEG), submental electromyogram, electro-oculogram, electrocardiogram, nasal and oral airflow (thermistor, nasal pressure transducer), chest and abdominal respiratory movement using respiratory inductance plethysmography, oxygen saturation (SpO_2), snoring microphone, and body position sensor. All of the sleep studies were manually scored by a single board-certified sleep technician blinded to study group (maternal hypertensive status) and were reviewed by a board-certified sleep physician (AVS) who was also masked to study group. Scoring followed American Academy of Sleep Medicine recommandations (30).

There are also only few data concerning the direct effects of GHT and PE on the global and regional cardiac function. An ongoing longitudinal study comparing pregnant women with GHT and/or PE with a normotensive pregnant control group already showed that subclinical early cardiac systolic and diastolic dysfunction was recorded in the group of pregnancy-induced hypertension (31). These results highlight the importance of preventing GHT, if possible, as a way to prevent an evolution to subclinical heart failure in these patients.

The relationship between OSA and fetal outcomes is also receiving increasing attention. It is plausible that OSA, with recurrent episodes of hypoxia and hypercapnia, systemic inflammatory response and endothelial dysfunction may be an important intermediary for a poorer fetal outcome. There are studies that show that OSA pregnant women group compared to non- OSA group, OSA group was associated with more frequent PE, preterm birth, cesarean delivery and NICU admission, while no significant difference were viewed in the relationship between gestational diabetes and small gestation age <10 th percentile in both groups (32).

So it seems there is an association between OSA and GHT and PE proven in small studies using as a tool for diagnosis polysomnography but there are no data on the effect of treating OSA neither on preventing nor on improving the outcome of gestational hypertension.

OSA is treated by using continuous positive airway pressure (CPAP) and study performed on 12 pregnant women showed that CPAP improved blood pressure in women with GHT and PE and associated mild OSA without any adverse outcomes. However, more studies need to confirm the existing data and to bring new information on the future of this therapy in preventing and/or improving the outcome of gestational hypertension and preeclampsia (3), before and even after discharge.❑

CONCLUSION

Recent studies showed an association between OSA and gestational hypertension, with or without associated preeclampsia. Milder degree of disease than what is usually considered clinically significant among men or non-pregnant women appears to be relevant for fetal-maternal outcomes. OSA is a common, most often unrecognized condition of pregnant women with GHT and PE. Poor data on CPAP therapy used in pregnant women showed an improved blood pressure on short term, without any severe outcomes. At this time there are not enough data to sustain a strategy of universal screening and treatment for OSA in pregnant women with gestational hypertension. Further research is needed to increase our understanding on the interaction between OSA and gestational hypertension, to determine whether treatment of OSA during pregnancy and gestational hypertension can improve pregnancy outcomes and future cardiovascular risk for this patients.❑

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