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Review Article

Restless Leg Syndrome during Pregnancy

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Abstract

Sleep disturbances are common during pregnancy. Pain, discomfort and frequent urination lead to sleep disturbances. While polysomnographic studies in pregnant women are limited, it has been reported that increased snoring, restless leg syndrome (RLS), non-restorative sleep, insomnia, periodic leg movements and sleep respiratory disorders are common in pregnant women and result in poor sleep quality.

RLS is a sensorimotor disorder characterized by the urge to move the legs and with unpleasant sensations, which generally peaks during night and rest periods. Its prevalence during pregnancy is estimated to be higher than the general population.

Pregnancy-related RLS is a disorder with unclear etiology, many possible contributing factors and a good prognosis. Non-pharmacological therapies should be considered first for treatment, and risks and benefits of therapy should be evaluated individually if pharmacological treatment will be given.

Keywords: Pregnancy; Restless leg syndrome; Sleep disturbances

Introduction

Sleep disturbances are common during pregnancy [1]. Pain, discomfort and frequent urination lead to sleep disturbances [2]. While polysomnographic studies in pregnant women are limited, it has been reported that increased snoring, RLS, non-restorative sleep, insomnia, periodic leg movements and sleep respiratory disorders are common in pregnant women and result in poor sleep quality [1-3].

RLS is a sensorimotor disorder characterized by the urge to move the legs and with unpleasant sensations, which generally peaks during night and rest periods [4]. Ekborn first defined the relation between pregnancy and RLS in 1945 [5]. The diagnosis of RLS is based on four major criteria established by the International RLS Study Group. While its incidence varies by age, sex and race [4], it is reported at a rate of 5-15% in the general population [6,7]. It is reported to develop twice more in females than in males [8]. Its prevalence during pregnancy is higher than the general population [9].

RLS prevalence during pregnancy

RLS prevalence during pregnancy has been reported at a wide range of 13.5-34% [10-18]. Its prevalence during pregnancy is reported to be 13.5% in Brazil [10], 19.9% in Japan [11], 26% in Turkey [12], 26% in Italy [13], 30% in Pakistan [14], 31.2% in the USA [15], 32% in France [16], 34% in Norway [17] and 17.8% in Iran [18]. This significant difference in RLS prevalence can be explained by geographic and ethnic factors, the use of different diagnostic criteria, differences in elimination of other conditions which may imitate RLS and evaluation of patients in different phases of pregnancy.

Pregnancy-related RLS is usually observed during the 3rd trimester [10,16]. Only 15% of the cases develop in the first trimester [19]. During pregnancy, RLS is often experienced for the first time or the symptoms of patients previously diagnosed with RLS are reported to aggravate [13]. The prevalence of RLS is reported to increase with the week of pregnancy. In a study by Facco et al., RLS prevalence was found to be 17.5% in the 13th week of pregnancy versus 31.2% in the 30th week of pregnancy [15]. The average onset of pregnancy-related RLS is reported to be 3.1±2.1 months before delivery [18].

Etiopathogenesis

Hormonal status and changes associated with iron-folate metabolism are held responsible in the etiopathogenesis of pregnancy-related RLS [20]. Also, pregnancy-related RLS and familial history of RLS have been found to be closely related in these patients [21]. Growth pains, which are frequently seen in childhood and night, is defined as self limiting pains in musculoskeletal system and no observed clinical features of inflammation [22]. Pregnancy-related RLS and presence of growing pain in family have also been found to be related [23]. This suggests that a hereditary disposition could be involved in pregnancy-related RLS.

Iron metabolism-Folate metabolism

Iron and tetrahydrobiopterin are cofactors of the tyrosine hydroxylase enzyme, which is involved in dopamine synthesis. Folate is involved in the regeneration of tetrahydrobiopterin. Therefore, iron or folate deficiency affects dopamine biosynthesis negatively. During pregnancy, the use of these substances for fetal development or the dilutional effect of increased blood volume may lead to a decrease in the level of these elements [24]. There is a 3-4-fold increase in the need for iron [25] and 8-10-fold increase in the need for folate [26] during pregnancy. It is considered that early stages of pregnancy and prior low levels of ferritin could be determinant for RLS development [20]. However, the quick improvement of RLS symptoms after delivery suggests that iron and folate levels may not play a major role in the etiopathogenesis of RLS [24].

Estrogen

RLS is most commonly seen in the 3rd trimester during pregnancy. The fact that estradiol, one of the hormones that increase during pregnancy, is detected at higher levels in this trimester than

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the other trimesters suggests that estradiol may be responsible for the etiopathogenesis of RLS [20]. It is believed that estrogens may cause dopaminergic dysfunction in nigrostriatal pathways. In rat studies, long-term exposure to 17 beta estradiol levels decreases striatal dopamine response. On the contrary, 17 beta estradiol levels at physiological limits stimulate the release of dopamine [20].

Thyroid hormone

During pregnancy, thyroid tissue is stimulated due to release of chorionic gonadotropin from the placenta [20]. Thyroid hormones are increased in the 3rd trimester. The negative relationship between thyroid hormones and dopamine suggest that they could play a role in the etiology of RLS [27].

Other mechanisms

It is considered that the mechanical pressure on lumbosacral nerve roots resulting from the growing fetus may pave the way for the development of RLS [13]. However, in a study conducted, no relationship was found between neonatal anthropometric measurements and development of RLS during pregnancy [13].

Peripheral venous distension occurs due to reduced peripheral vascular resistance during pregnancy. Edema develops in legs. There is increased pressure on the tissue surrounding somatosensory system receptors and it is considered that increased stimulation may contribute to the development of RLS [28]. However, lack of a significant difference in leg diameter in women with and without RLS in one study does not support this theory [29].

Comorbidities observed with pregnancy-related RLS

It has been reported that sleep disorders could be associated with pregnancy-related complications including gestational diabetes, gestational hypertension, preeclampsia, fetal growth disorders and preterm delivery [30]. Ramirez et al. observed RLS more often in patients with preeclampsia. This was reported to be associated with impaired iron distribution or impaired blood pressure regulation developing due to increased sympathetic activity [31]. These patients have problems with falling asleep and maintaining sleep [18,32]. While preeclampsia, increased cesarean delivery rates and depressed mood are reported to be more common in pregnant women with sleep disorders [18,31,33], further studies are needed in this subject.

Diagnosis and differential diagnosis

Accurate diagnosis is essential. Diagnostic criteria of the International Restless Legs Syndrome Study Group (2014) are recommended to be used for diagnosis [34]. Specifically, leg cramps, positional discomfort, venous stasis, leg edema, compression neuropathies, sore leg muscles, ligament-tendon strains, positional ischemia, radiculopathy and arthritis are other pathologies which should be considered in differential diagnosis [35].

Approach to the patient and treatment of RLS during pregnancy

In 2014, the International Restless Legs Syndrome Study Group prepared a guideline for the follow up and treatment of patients diagnosed with RLS during pregnancy and lactation, in which specific points were highlighted. First of all, the importance of accurate diagnosis of RLS was mentioned. It was emphasized that RLS more often develops after embryogenesis, especially in the 3rd trimester, and peaks in severity during this trimester. There is a 3-5% risk of congenital anomaly in every pregnancy. It was highlighted that the treatment decision should be based on the severity of symptoms and their degree of effect. Risks and benefits of treatment should be evaluated individually. Non-medical approaches are first-line therapy. If medication will be given, the lowest effective dose should be given for a short period of time and the treatment should be reviewed periodically. Iron stores should be checked in these patients, iron replacement should be done in case of deficiency and delivery should be reviewed. The patient should be informed about the side effects of new drugs to be given [35]. Plasebo effect is high in RLS. Placebo response has been reported to be 20-40% in non-pregnant patients with RLS [36]. It should be kept in mind that the expectation of recovery causes upregulation of brain dopamine response in diseases of the central nervous system, potentially leading to a high placebo effect [36]. Further studies are needed to evaluate the effectiveness of non-pharmacological therapy in these patients.

Non-pharmacological approaches

It is important that the patient is informed about RLS and factors aggravating the symptoms are avoided. In particular, prolonged immobilization, the use of serotonergic antidepressants, sedative antihistamines, and dopamine antagonists, consumption of caffeine and alcohol and smoking should be avoided since they can aggravate the symptoms.

Mentally stimulating activities such as puzzles and crossword puzzles, moderate intensity exercises (brisk walking, water aerobics, ballroom dancing and general gardening, yoga) and massage are recommended as non-pharmacological approaches [9,35].

Pharmacological approaches

Pharmacological therapies are recommended for patients whose symptoms persist with non-pharmacological approaches. [9,35]. Since controlled studies investigating RLS in pregnancy are limited, many associations have argued that treatments should be assessed for the potential risk of congenital malformations in the fetus [9,35]. There is insufficient evidence about the use of nutraceuticals in patients with RLS during pregnancy [35]. Oral iron is recommended if the ferritin level is <75 mcg/l but the data on its benefit is very limited [35,37,38]. It is recommended to check the serum ferritin levels of these patients every 6-8 weeks [35]. If oral iron is not enough, IV iron can be administered in patients with refractory RLS in their second or third trimester whose ferritin levels are <30 mcg/l. Treatment options other than IV iron should be considered in the first trimester [35]. While IV iron was shown to be very effective particularly in non-pregnant patients with RLS [39], there are very few studies which show that it is effective during pregnancy [37]. In particular, anaphylaxis and infusion reactions should be watched for during this treatment [34]. There is insufficient evidence in literature about magnesium, folate, and Vitamin D, C and E therapies in the treatment of RLS during pregnancy [35,40,41]. While it is reported that low doses of clonazepam can be used for refractory RLS in 2nd and 3rd trimesters (0.25-1 mg/night), concomitant use of diphenhydramine and anticonvulsants should be avoided [35]. Eszopiclone and zolpidem are not recommended during pregnancy due to limited data and safety concerns. Temazepam is not recommended since it is known to increase fetal mortality when

combined with diphenhydramine. While significant teratogenic risk has not been demonstrated with clonazepam, it is recommended to be avoided during the first trimester of pregnancy [35]. Although it was initially stated that gabapentin could be used for epilepsy during pregnancy, intraperitoneal injection of high doses of gabapentin in mice was found to impair the development period of synaptogenesis which corresponds to the last trimester of pregnancy in humans [42]. Therefore, there is insufficient data on its use [35]. Dopaminergic agents are first-line therapy for RLS outside pregnancy [43]. Although there is less data on the efficacy of carbidopa and levodopa than on pramipexole, ropinirole and rotigotine, they seem to be safer during pregnancy. No major malformations were reported with the use of carbidopa and levodopa [35,44,45]. Combination of levodopa and benserazide should be avoided due to its adverse effect on bone development [46]. Carbidopa and levodopa can be given to patients with refractory RLS during pregnancy but the dose is recommended to be lower than 50/200 mg/day [47]. There is insufficient data in literature on the use of pramipexole, ropinirole and rotigotine [35]. Opioids were reported to be effective on RLS outside pregnancy. Brosaurd et al. found the use of opioid analgesics in early pregnancy to be associated with some birth defects including conoventricular septal defect, hypoplastic left heart syndrome, atrioventricular septal defect, spina bifida and gastroschisis [48]. Some investigators emphasized that neonatal abstinence syndromes may develop in the babies of mothers using these drugs [49]. While it is reported in literature that low doses of oxycodone can be given to pregnant women with very severe or refractory RLS after the 1st trimester [35], the risk of congenital malformation should be considered.

A detailed medical history and clinical examination are especially important for differential diagnosis and accurate diagnosis in the approach to a patient who is considered to have RLS during pregnancy. The severity, frequency and effects of symptoms as well as comorbidities such as depression and sleep disorders should be evaluated. RLS training should be given after the diagnosis becomes clear. Information should be provided about factors that aggravate RLS and about recommended exercises. Non-pharmacological approaches should be the first option. The patient should be examined for iron stores. Oral iron can be given if ferritin is <75 and IV iron can be administered if ferritin is <30. If there is no response to these therapies, carbidopa and levodopa 25/100 - 50/200 mg/evening or night or a low dose of clonazepam (0.25 -1 mg/night) can be given. In very refractory cases or where symptoms are very severe, it is recommended to start a low dose of oxycodone and review delivery [35].

Prognosis

The prognosis of RLS during pregnancy is usually good. RLS developing during pregnancy tends to recede in the first months postpartum [13]. The symptoms often disappear in 2/3 of patients within 2 weeks following delivery [13,50]. In a study by Uglane et al. [17] it was reported that symptoms disappeared in many patients 2 or 3 days after delivery. RLS may recur in subsequent pregnancies in more than 30% of patients who develop RLS during pregnancy [20].

Conclusion

Pregnancy-related RLS is a disorder with unclear etiology, many possible contributing factors and a good prognosis. Non-pharmacological therapies should be considered first for treatment, and risks and benefits of therapy should be evaluated individually if pharmacological treatment will be given.

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