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Review

Prevalence, Hormonal Factors, and Treatment of Restless Leg Syndrome in Pregnancy

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Abstract

Restless leg syndrome (RLS) is a sensorimotor sleep condition that causes pain or a "creepy-crawly" feeling in the legs. The association between pregnancy and RLS is well established. The incidence and progression of RLS are influenced by hormonal factors, notably during pregnancy. RLS is more prevalent among pregnant women than among the general population and its prevalence and severity increase with gestational age. In addition, multiparous women are more likely to experience RLS during pregnancy than single-birth mothers. The symptoms often improve over the first four weeks following childbirth. Pregnancy-related hormones, especially estrogen, likely play important roles. Dopaminergic agents, antiepileptics, and benzodiazepines can be used for treatment. The prognosis is good, and most patients recover quickly. Attention to serum ferritin levels is also important. A definite statement regarding it being the safest therapy strategy cannot be established because of the varying techniques used by various investigations and the paucity of data concerning the impact of RLS in pregnancy and its long-term consequences. Non-pharmacological treatments and nutritional supplements may be tried first in pregnant women with RLS.

Keywords: *Restless leg syndrome, pregnancy, prevalence, treatment*

Introduction

Restless leg syndrome (RLS) or Wills-Ekbom disease is a sensorimotor sleep condition that causes pain or a "creepy-crawly" feeling in the legs during rest and is alleviated by movement. RLS has a diverse clinical course, ranging from moderate to severe, and symptoms tend to change over time. North America and Europe are reported to have the highest prevalence, whereas Asia has the lowest (1). It affects 5.5% to 11% of the general populations with women suffering twice as frequently as males (1, 2). It is believed that hormonal changes during periods of pregnancy, menstruation, and menopause may be the cause of this gender difference (3). Moreover, the incidence of nulliparous women is comparable to that of men, and pregnant women are more likely to have RLS (4), suggesting that pregnancy may increase the risk of having RLS.

Restless leg syndrome can develop either as the primary disorder, with no apparent explanation other than a probable genetic susceptibility, or as a secondary syndrome, which is frequently associated with iron shortage, end-stage-renal disease, or majorly during pregnancy (5). All of these secondary causes share the common component of iron deficiency, supporting the notion that an abnormal iron metabolism contributes to the development of RLS. Nonetheless, RLS has a complex pathophysiology that is not entirely understood. The available research suggests that three connected factors may be involved: dopaminergic dysfunction, poor iron homeostasis, and hereditary susceptibility (6).

Numerous elements of the epidemiology and pathophysiology of RLS in pregnancy have been investigated during the past decade. In this study, we present recent data on the prevalence, hypothesis regarding hormonal impact, and therapy of RLS during pregnancy.

Methodology

This review's references were found by searching PubMed with the terms "RLS" or "Restless Leg Syndrome", "Pregnancy" and "RLS" or "Restless Leg Syndrome" until December 2022, and by searching Google Scholar with the terms "Pregnancy and RLS" and "Pregnancy and Restless leg syndrome" from any period until December 2022. Only English-language reports were included. We discovered a huge number of search results, and the listed references represent our selection of the most informative works.

Discussion

Prevalence of RLS among pregnant women

Pregnancy is strongly linked to RLS. Minar *et al.* (7) showed that the prevalence of RLS in pregnant women is relatively higher than in the general population. More than 30% of positive cases had clinically significant symptoms, and 50% report sleep problems. In the majority of instances, symptoms appear to increase most between the first and second trimesters and diminish after birth; nevertheless, a small proportion of women with RLS during pregnancy may still experience symptoms three years after delivery (8). The correlation between the prevalence of RLS in pregnant women and the number of children a woman had given birth to (9-11) suggests that parity is a risk indicator for RLS later in life. In a meta-analysis, the prevalence of RLS in pregnant women was estimated to be 21.4% [95% confidence interval: 17.7–25.1]. Asia had the lowest prevalence of RLS, at 18.5% [95% CI: 13.8–23.1], whereas Europe had the highest incidence, at 25.5% [95% CI: 19.5–31.6] (12). According to the World Health Organization's regional classification, the European, Western Pacific, Eastern Mediterranean, and American regions accounted for 22%, 14%, 30%, and 20% of the world's population, respectively (13). In the first, second, and third trimesters of pregnancy, the prevalence of RLS was reported at 8%, 16%, and 22%, respectively (13). RLS symptoms often improve over the first four weeks following childbirth. Therefore, in a nutshell, RLS is rather common throughout pregnancy, and its prevalence and severity increase as the gestational age advances. In addition, multiparous women are more prone to develop RLS than single-birth mothers during pregnancy (9).

Hormonal influence on RLS

There have been postulated potential mechanisms underpinning the pathophysiology of RLS associated with pregnancy. Iron and folate deficiency due to diluted impact and utilisation for foetal development, hormonal changes, psychological disorders, lumbosacral radiculopathy, and peripheral venous congestion are all common during pregnancy. It is hypothesised that hormonal variables, particularly during pregnancy, have an impact on the initiation and progression of RLS (14). The plasma levels of estrogens, progesterone, and prolactin rise during pregnancy, reaching a peak in the third trimester, with a sharp decline in estrogen, progesterone, and prolactin secretion following delivery. The RLS condition was closely associated with the third

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trimester of pregnancy and often vanished by the time of delivery (15). RLS is associated with transiently elevated estradiol levels in pregnant women, suggesting that estrogens have a pathophysiological role in inducing RLS symptoms during pregnancy (16). It has been suggested that elevated levels of estradiol, prolactin, and progesterone during pregnancy may promote RLS (17). Shortly after birth, these hormones recover to pre-pregnancy levels, which is related to the remission of RLS symptoms.

Dopamine inhibits prolactin secretion (18), and prolactin rise in pregnancy may impede dopamine activity, according to some writers. Given dopamine's role as an inhibitor, this drop may play a significant role in the etiology of RLS if prolactin levels are elevated during pregnancy. However, in a study that did not include pregnant women, prolactin plasma levels were not found to differ between RLS patients and controls (19). The dopaminergic system appears to play an important role in the pathogenesis of RLS. Thyroid hormone levels tend to rise during the third trimester. A negative correlation between thyroid hormones and dopamine suggests that they may contribute to the genesis of RLS (20). Thus, hormonal variables have been linked to RLS during pregnancy. Even though, Hubner *et al.* (16) did not find a difference in estrogen levels between females either with or without RLS, calling its involvement into question. A study on animals revealed that continuous exposure to 17-beta-estradiol improves dopamine function and cell survival in the striatum (21), which may be neuroprotective from the onset of RLS.

Treatment of RLS among pregnant women

Restless leg syndrome is a treatable illness that responds favorably to pharmacological treatment and has a detrimental effect on sleep. The management of RLS during pregnancy is challenging. In other words, it is widely acknowledged that, due to the potential hazards to the foetus, it is impossible to administer the vast majority of medications that are normally effective at alleviating the bothersome symptoms of RLS. There have been few controlled investigations of RLS during pregnancy. Consequently, the majority of evidence for therapy effectiveness comes from reported instances or short case series. Due to the paucity of literature on the safest, best, and most successful treatment for RLS in pregnant women, we will discuss the existing data. Non-pharmacologic therapy, iron supplementation, dopaminergic drugs, benzodiazepines, opioids, and anti-epileptic medications were among the treatments examined.

Non-pharmacologic treatment

Restless leg syndrome symptoms during pregnancy are frequently moderate to severe in intensity. Numerous treatments have been examined in randomized controlled trials, and the RLS treatment guidelines are periodically revised. In moderate cases, non-pharmacological therapies such as leg stretching prior to bedtime and the wearing of stretchy stockings are often recommended. An International RLS Study Group task force has endorsed conservative approaches as the optimal RLS treatment during pregnancy (22). The first is to avoid things that can cause RLS, like caffeine and alcohol, or at least cut back on them (23). Moderate-intensity exercise, yoga, massage (24, 25), pneumatic compression equipment, addressing obstructive sleep apnea, and minimizing aggravating variables may be used to treat RLS during pregnancy and postpartum (26). In addition to improving RLS, these approaches will also enhance the outcome of pregnancy. Although there is little evidence to support their usefulness in pregnant women, the administration of these techniques does not appear to result in any serious negative effects. Consequently, they could be administered to all pregnant women, regardless of RLS.

Iron supplementation

There is compelling evidence that iron insufficiency plays a substantial role in the pathogenesis of RLS in non-pregnant persons, and iron reserves are significantly depleted during pregnancy (27), so RLS is associated with iron-deficiency anemia. Pregnant women with RLS are more likely than those without RLS to be anemic (28). During pregnancy, intravenous iron sucrose delivery appears to be a beneficial treatment for RLS patients with low ferritin levels (29). Picchietti *et al.* found in a case study that intravenous iron administration and an increase in serum ferritin to 347 mcg/L were linked with complete remission of RLS (30). Two patients treated with intravenous iron sucrose achieved a significant reduction or remission of RLS symptoms, according to a 2013 case study (31). Schneider *et al.* (32), in an open-label research, demonstrated the safety and efficacy of intravenous ferric carboxymaltose for the treatment of moderate-to-severe RLS in pregnant women with iron deficiency or anemia with a substantial improvement in sleep quality ($P = 0.029$), and the medication was well tolerated.

Dopaminergic agents

Ropinirole and pramipexole, non-ergot dopamine agonists, were the first medications approved by the

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FDA for the management of RLS. A case series assessing the effects of the RLS medications (dopamine agonists) pramipexole, levodopa, rotigotine, and ropinirole on the foetus found that there was no higher likelihood of major anomalies or other serious complications for pramipexole and levodopa compared to baseline (33). However, Hurault-Delarue *et al.* showed that prenatal exposure to dopamine agonists such as cabergoline bromocriptine, and quinagolide with an elevated miscarriage risk and premature birth (34). However, because there are no randomized controlled trials, it is unclear how effective these medications perform during pregnancy; therefore, they should not be taken.

Opioids

Opioids and benzodiazepines are alternatives with better efficacy that have been used more frequently for RLS during pregnancy. It has been reported that oxycodone, propoxyphene, and tramadol are effective treatments for RLS. For the most severe cases as well as individuals with an inadequate dopaminergic response, powerful opioids such as methadone are suggested (35). Compared to dopaminergic medications, more data support the safety of utilising opioids during pregnancy. These medications have been widely used during pregnancy with no serious ill effects (36). However, neonates of mothers treated with opioids during pregnancy are at risk for respiratory depression and withdrawal syndrome, as well as congenital abnormalities (37) and neonatal abstinence syndrome (38). Nevertheless, at typical therapeutic levels, this is normally not a big concern.

Even though many doctors are hesitant to use long-term opioid therapy to treat symptoms for which there is no diagnostic test, people with RLS have been using these medications for a long time without showing signs of addiction or tolerance.

Benzodiazepines

Benzodiazepines are currently utilised to treat RLS symptoms in pregnant and non-pregnant patients. Clonazepam is the most studied and commonly prescribed benzodiazepine for RLS, while others, such as temazepam and triazolam, may be effective as well. Though the American Academy of Sleep Medicine and the European Federation of Neurological Societies, the European Neurological Society, and the European Sleep Research Society are against recommending clonazepam as the primary treatment for RLS (39, 40), Clonazepam may be used as an adjunct treatment for RLS during pregnancy, and there is no evidence that it results in a higher risk of major abnormalities. However, maternal benzodiazepine exposure increased the foetal incidence of cleft lip and cleft palate (41), but this has not been proven and there is evidence. If the medicine is administered after the first trimester, there is no such risk. In a meta-analysis, Dolovich *et al.* found no relationship between maternal exposure to benzodiazepines and the incidence of significant abnormalities or mouth clefts, indicating that the risk is minimal (41).

Antiepileptics

Carbamazepine has proven beneficial in lowering RLS sensory symptoms, particularly in young individuals with recent onset and severe symptoms (42). There is a substantial body of data from epilepsy databases on the comparative safety of carbamazepine use for both maternal and foetal populations, making it a viable option for the management of RLS in pregnancy. According to information from the UK Epilepsy and Pregnancy Register, carbamazepine is connected with the lowest risk of significant congenital abnormalities (43).

In resistant cases of RLS, gabapentin may be beneficial in reducing sensory symptoms and periodic leg movements during sleep (PLMS) (44). Gabapentin and ropinirole are comparably well-tolerated and efficacious in treating PLMS and sensorimotor symptoms in patients with idiopathic RLS, as measured by a reduction in the International Restless Legs Scale (IRLS) score (45). Multiple studies validated the efficacy of gabapentin enacarbil, a prodrug of gabapentin, in treating RLS in non-pregnant individuals, as measured by a significantly improved IRLS score. The safety of this medicine for the foetus is reassuring; however, knowledge is currently limited. The 2-ligands gabapentin, gabapentin enacarbil, and pregabalin were effective in clinical trials. This suggests a particular mechanism of action for these drugs in RLS (46).

Conclusion

RLS is more prevalent among pregnant women than among the general population. Pregnancy-related hormones, especially estrogen, likely play important roles. Dopaminergic agents, antiepileptics, and benzodiazepines can be used for treatment. The prognosis is good, and most patients recover quickly. Attention to serum ferritin levels is also important. A definite statement concerning the safest therapy strategy cannot be established because of the varying techniques used by different studies and the lack of data concerning

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the impact of RLS in pregnancy and its long-term effects. Non-pharmacological treatments and nutritional supplements may be tried first in pregnant women with RLS.

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Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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