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Restless legs syndrome and pregnancy: prevalence, possible pathophysiological mechanisms and treatment

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Abstract

Restless legs syndrome (RLS) is a common sleep disorder that may be associated with pregnancy. Studies have found that the prevalence of RLS among pregnant women ranged from 10 to 34%. Typically, there is complete remission of symptoms soon after parturition; however, in some patients, they may continue postpartum. RLS has been shown to be associated with a number of complications in pregnancy including preeclampsia and increased incidence of Cesarean sections. Although multiple hypotheses have been proposed to explain this association, each individual hypothesis cannot completely explain the whole pathogenesis. Present understanding suggests that a strong family history, low serum iron and ferritin level, and high estrogen level during pregnancy might play important roles. Vitamin D deficiency and calcium metabolism may also play a role. Medical treatment of RLS during pregnancy is difficult and challenging considering the risks to mother and fetus. However, in some cases, the disease may be severe enough to require treatment.

Keywords

pregnancy; prevalence; restless legs syndrome; treatment

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Conflict of interests

None to disclose.

Introduction

Restless legs syndrome, sometimes referred to as Willis-Ekbom disease (WED/RLS), is a sleep disorder that is diagnosed according to the criteria proposed by the International RLS Study Group (IRLSSG) (1, 2). RLS has a bimodal distribution of age of onset. However, the cut-off age for differentiating between early and late onset is controversial (3, 4). Cases of early onset are likely to have a family history of RLS and low serum iron levels, and usually develop the symptoms before the age of 35–45 years and the symptoms are typically severe. Cases of late onset often have identified secondary causes and usually develop the symptoms after the age of 45 years and the symptoms usually progress within 2–3 years (5).

On the basis of etiology, RLS may be divided into an idiopathic form with or without family history and secondary forms. Secondary RLS has been shown to be associated with a variety of conditions including iron deficiency, diabetes, uremia, pregnancy, Parkinson's disease, neuropathy, myelopathy, rheumatoid arthritis, antipsychotics, and antidepressants (3–5). Distinction between idiopathic and secondary RLS may be more virtual than actual. 'Secondary' *per se* carries the meaning that once the 'causative' factor is removed, RLS will cease to exist. However, this is not always the case as RLS associated with iron deficiency has not been found to improve or to have limited improvement in some patients even after iron therapy (6–8). To make the situation even more complicated, dopamine agonists have been reported to provide relief even in cases with iron deficiency (9). Similar evidence has been found in RLS associated with pregnancy.

RLS is commonly associated with pregnancy, and the symptoms of RLS negatively impact the quality of life in pregnant women (4). To date, various hypotheses of developing or exacerbating the symptoms of RLS during pregnancy as well as medical treatment for controlling symptoms of RLS have been proposed (10). In this article, we comprehensively review the prevalence of RLS during pregnancy, possible pathogenesis, negative impact of RLS on pregnancy, and risk of future development of chronic RLS.

Prevalence of RLS during pregnancy

The association between RLS and pregnancy is well known (4). In most cases, symptoms appear transiently and subside after delivery (4). However, in some cases, symptoms appear for the first time during pregnancy and persist after delivery as idiopathic RLS (4). In general, it seems that RLS first manifested during pregnancy has a good prognosis (11). Pregnancy appears to be an independent risk factor for the development of RLS as it has been observed that even among those with a family history of RLS, the prevalence of RLS was higher in parous women when compared with nulliparous women or men (12). It may also account for the observed gender differences in the prevalence of RLS, especially in the late-onset form (12). The available literature suggests that a sizable number of pregnant females (10–34%) were found to be suffering from RLS during pregnancy (4, 11, 13–21). The prevalence differed in these studies due to differences in the assessment methods, population, and gestational age when the study was conducted (Table 1).

In a number of studies, RLS symptoms first developed during pregnancy, suggesting that pregnancy triggered RLS (4, 14, 17). Pregnancy did not only trigger RLS, but RLS has been

shown to have some relation with the timing of the pregnancy as the prevalence was found to increase with advancing gestational age, with a major shift occurring during the second trimester (22) and the prevalence and severity of RLS being greatest during the third trimester (18, 19).

The symptoms of RLS usually improve during the first 4 weeks of the postpartum period (11, 21–23). Thus, even with studies from different countries and using different methods, we can conclude that RLS is relatively frequent during pregnancy and its prevalence and severity increase with gestational age. In addition, the prevalence of RLS during pregnancy also increases in multiparous women compared with nulliparous women (24).

What causes RLS in pregnancy?

As noted earlier, the prevalence of RLS has been found to vary with the state of pregnancy, increasing until the third trimester and improving soon after delivery (17, 19, 20, 25). It has been found that pregnant women with symptoms of RLS had lower serum ferritin and folate levels before conceiving and during each trimester of pregnancy (26). History of RLS before conception, RLS during previous pregnancy, hemoglobin <11 g/dl and inadequate supplementation of iron and folate during pregnancy, particularly when the women have iron deficiency, coffee consumption before pregnancy, and peptic ulcer disease were found to be the risk factors for development of RLS during pregnancy (17, 21, 27–29). Thus, dietary and hormonal factors have been found to be associated with RLS during pregnancy. In the following sections, we will discuss the evidence for these factors.

Dietary factors during pregnancy and RLS

Recent studies suggest that age, BMI, folate and iron supplementation, ferritin and hemoglobin level, and number of previous pregnancies may be the most important risk factors for the development of RLS (4, 11, 15, 16, 22). Iron status is influenced by the number of pregnancies. Iron levels tend to decrease with each pregnancy if iron stores are not restored to normal during the interval between pregnancies. This might be the reason why multiparity is associated with a higher risk of RLS (27). Currently, iron supplementation along with folic acid is considered as a part of routine antenatal care, irrespective of the iron status, and the presence of anemia (30). In pregnant women with chronic RLS of moderate to severe category, intravenous iron therapy prior to pregnancy to correct iron deficiency has been found to remit the symptoms of RLS during pregnancy and postpartum period (31). However, some studies suggest that improvement in RLS symptoms after delivery is independent of iron and folate levels, which take a longer time to replenish (32, 33). This makes the role of iron in the development of RLS during pregnancy questionable.

Another factor that has been found to be associated with RLS is vitamin D deficiency (34, 35). Two studies have reported an inverse correlation between serum levels of vitamin D and severity of RLS (34, 36). A relationship between RLS and growing pains has been observed among not only adults but also children, and both have been found to respond to the administration of vitamin D (37). Vitamin D deficiency is not uncommon during pregnancy (38, 39), and this deficiency has been found to be related to impaired dopaminergic

neurotransmission through various means (32, 33, 40). Thus, in addition to iron and folate deficiency, vitamin D deficiency might be another contributor to the pathogenesis of RLS during pregnancy. Vitamin D concentration is in close relationship with parathyroid hormone. An association between high parathyroid hormone level and RLS has been reported in uremic patients (41). Other studies reported improvement in RLS after parathyroidectomy in uremic patients (42, 43). Some women develop hyperparathyroidism during pregnancy, which could be related to the onset of RLS (44). The role of vitamin D was further substantiated by the fact that patients with RLS have higher concentration of vitamin D binding protein in their CSF (45).

Hormonal factors

Hormonal factors are thought to play a role in the manifestation and development of RLS, especially during pregnancy (25). It has been suggested that high estradiol, increased prolactin, and increased progesterone during pregnancy may trigger RLS (25, 46). These hormones drop to prepregnancy levels soon after the delivery associated with resolution of RLS symptoms (47). However, Hubner et al. (16) did not find any difference in the estrogen levels in women with and without RLS, questioning its role. An animal study showed that prolonged exposure of the striatum to 17beta-estradiol increases dopamine activity and cell survival (48), and this might be protective against the development of RLS.

Another hormonal factor that has been reported during pregnancy is hypothyroidism. It has been reported that between 3 and 15% of pregnant women suffer from subclinical hypothyroidism (49, 50). Rates of overt hypothyroidism are small, ranging between 2 and 3% (51). We could not find any study that has reported an association between RLS and hypothyroidism. However, the relationship between RLS and hyperthyroidism has been reported. Pereara et al. (52) proposed a role of thyroid function in the expression of RLS during pregnancy. They proposed that pregnancy which is associated with higher levels of thyroid hormone and hyperthyroidism *per se* can induce RLS presentation and symptoms. According to this hypothesis, lower iron levels during pregnancy not only reduce the production of endogenous dopamine but also reduce the catabolism of thyroxin, thus inducing RLS (52). This might be an explanation why iron therapy improves RLS during pregnancy. However, it must be noted that values depicting optimal levels of thyroxin and thyrotropin during pregnancy are not known yet and that the absolute value of thyroid hormones may not be an accurate indicator of thyroid status during pregnancy (49–51).

Other factors found to associate RLS and pregnancy

Some studies have suggested that genetic factors and smoking during pregnancy may trigger RLS (12, 16, 31). Moreover, family history and past history of RLS have been found to predict RLS during pregnancy (27). Balendran et al. (18) found that only a childhood history of RLS and a family history of RLS predicted RLS during pregnancy. Obesity, particularly abdominal obesity, has been found to be associated with RLS in a population-based study (53). Similarly, weight gain during pregnancy has been found to be associated with RLS (4). However, it must be remembered that weight gain occurring during pregnancy cannot be equated with obesity. Pregnant women usually gain weight owing to the retention of water (54–56). This also alters the hemodynamics and causes venous stasis especially in the lower

limbs, which has been found to be associated with RLS (54, 55). In addition, treatment of venous insufficiency has been found to improve symptoms of RLS (54). Moreover, changes in hemodynamics during pregnancy may lead to peripheral hypoxia that could be one reason behind the onset of RLS during pregnancy. Hypoxia could be related to obstructive sleep apnea, which has been found to increase the prevalence of periodic limb movements of sleep (PLMS) and RLS in non-pregnant subjects as well as in pregnant women. However, contradictory literature is also available (57–59). One study has reported peripheral hypoxia in legs of patients with RLS, which improved on pramipexole therapy (60). Hypoxia has been found to induce hypoxia-inducible factor (HIF) in the substantia nigra of patients with RLS leading to deficiency of iron (61). Thus, changes in peripheral hemodynamics may lead to symptoms of RLS during pregnancy.

In summary, we do not have sufficient data regarding the pathogenesis of RLS during pregnancy. It may be possible that pregnancy unmasks RLS in susceptible women through a variety of pathways including iron deficiency, vitamin D deficiency, hormonal changes, weight gain, and venous insufficiency in the legs. These factors must be taken into account when studying RLS in pregnancy in the future. Moreover, future research on genetic association of RLS in pregnancy is needed.

Impact of RLS on pregnancy

Pregnant women who are suffering from RLS may also have an increased incidence of PLMS, nocturnal leg cramps, and excessive daytime sleepiness (3, 4, 13, 15, 17, 19, 20, 29). These factors could be associated with insomnia in these women.

Insomnia related to RLS may manifest as an increase in sleep onset latency, sleep interruption, or terminal insomnia (15, 26). Sleep duration and sleep quality can influence the type of delivery, length of labor stages, neonate’s Apgar score, and birthweight (62, 63). Pregnant women with an average of 8 h restorative sleep had normal vaginal delivery and their infants had an Apgar score higher than 9 (63). On the other hand, women with <6 h of sleep or non-restorative sleep had prolonged labor with higher chances of having Cesarean deliveries (62). Chronic sleep deprivation during pregnancy, irrespective of the etiology, has been found to activate the hypothalamo–pituitary–adrenal axis and thus causing abnormal immune responses leading to adverse outcomes (64).

The existing data on the effect of RLS on pregnancy indicate that RLS may have a negative impact on pregnant women. Pregnant women with RLS reported more complications related to pregnancy and labor such as threatened abortion, premature labor, difficult delivery, and intrauterine growth retardation; however, the results were only marginally significant (4, 25).

Ramirez et al. (65) showed a high possibility to develop preeclampsia in pregnant women who had symptoms of RLS (65). The authors also reported that the incidence of RLS was more in pregnant women without prophylactic iron (65).

RLS has also been found to be associated with depressed mood in pregnant women (26). Moreover, it has been reported recently that moderate to severe RLS occurring before pregnancy increases the risk for perinatal and postnatal depression (66). RLS during

pregnancy has also been found to be associated with sleep disturbances, insomnia and early morning awakenings. RLS-associated sleep disturbances have been reported to adversely affect pregnancy, with RLS had higher rates of Cesarean sections among these women (4, 15).

In short, pregnancy is a stage where the female body undergoes various changes in a relatively short period of time. Several physiological, metabolic, and hormonal changes in addition to the psychological factors take place during pregnancy. Therefore, it becomes difficult in such a situation to categorically conclude how one factor affects the other. It is evident that RLS has a higher prevalence among pregnant women.

RLS during pregnancy is a risk factor for future RLS

Most studies have reported a good immediate prognosis for pregnancy-related RLS. The disorder appears to wane in most women after delivery (16, 21, 23, 47). However, in other cases, it may be a seed for future RLS. Transient RLS, which is reported by a significant number of pregnant women, may be a harbinger of idiopathic RLS in later life. Sarber et al. (22) reported that although symptoms of RLS disappeared soon after delivery, about one-third of women with RLS during pregnancy continued to have symptoms 3 years after childbirth. Similarly, a long-term follow-up study by Cesnik et al. (67) reported that the presence of even transient RLS during pregnancy might increase the risk of chronic RLS by nearly fourfold as compared with control population who had never experienced RLS during pregnancy. In addition, the appearance of RLS in one pregnancy increases the risk of RLS in future pregnancies by nearly nineteen times (67). Pregnancy *per se* increases the risk of developing RLS in later life, regardless of the presence or absence of symptoms of RLS. Females with greater parity show more predisposition to develop RLS in later life, and this could be related to increased stress (68). Another explanation, which still needs to be scientifically analyzed, is that pregnancy is a trigger in patients predisposed to RLS, where pregnancy brings RLS out earlier than it might have otherwise. Hence, pregnancy would not formally be etiologic. Interestingly, diagnosis of attention deficit hyperactivity in children puts their mothers at higher risk for RLS, which has been attributed to a genetic link (69). However, whether children of mothers having RLS have a higher predisposition to ADHD is not known.

Treatment of RLS during pregnancy

There is a higher propensity in patients with sleep problems to use medication or alcohol for induction of sleep (19). In addition, patients with RLS consume hypnotics frequently (19, 23). Adequate management of RLS during pregnancy should decrease self-medication, which may be detrimental and manifest as congenital malformations. Treatment of RLS during pregnancy has several advantages as it can reduce the stress, improve the quality of life, and prevent the complications secondary to RLS. Two approaches can be used to manage RLS during pregnancy, non-pharmacological and pharmacological. As there is paucity of literature regarding the safest and most efficacious management modality of RLS among pregnant women, we will discuss the currently available evidence (10).

Non-pharmacological management of RLS during pregnancy

As there are no evidence-based accepted guidelines for the treatment of RLS during pregnancy, current practice focuses on counseling and iron therapy (23). In mild cases, non-pharmacological approaches such as leg stretching before sleep and use of elastic stockings when associated with varicose veins are usually recommended (70). A task force from the International Restless Legs Syndrome Study Group has recommended conservative measures as the treatment of choice of RLS during pregnancy (71). First of these includes avoidance of factors that can increase the chances of having RLS, for example, avoiding or at least reducing caffeine and alcohol consumption (72). Moderate amount of exercise has been found to improve RLS, but heavy exercise may have a deleterious effect, especially in the evening (72). These modalities will not only improve RLS but will also improve the outcome of pregnancy. Other modalities that can be used in these women are massage of the legs and sequential pneumatic compression devices (72, 73). These modalities will not only improve RLS, but also help prevent venous stasis and deep venous thrombosis that occur during pregnancy. Although we do not have good evidence supporting their efficacy among pregnant women, the use of these modalities appears not to have any major adverse effects. Therefore, they may be tried among all pregnant women, irrespective of RLS.

Pharmacological management of RLS during pregnancy

Various drugs are also available for the treatment of RLS and we will review their efficacy and safety profile during pregnancy. As a generality, all medications should be avoided, but if the symptoms are severe, this approach can be considered. Table 2 presents the safety of pharmacological agents used to treat RLS during pregnancy.

Dopaminergic drugs

Dopaminergic drugs may pose a risk to the pregnant women or to the fetus. A case series that assessed the effect of the RLS medications; levodopa, pramipexole, ropinirole, and rotigotine on the fetus showed that there was no increased risk above baseline for major malformations or other adverse outcomes for levodopa and pramipexole (74). However, the use of bromocriptine, cabergoline, and quinagolide during the first trimester was associated with an increased risk of abortion and preterm birth (75).

As oral medications achieve high concentration in blood, it is possible that a transdermal patch that releases drugs in small amounts over long time might be safer. The transdermal patch for rotigotine is available, and this has been approved for the treatment of moderate to severe RLS. However, rotigotine has been classified as pregnancy category C medication, which means that adequate trials or studies on pregnant women are not available (76). One case report suggested that pramipexole could be safe during pregnancy (77). Another case report depicted that the continued use of pramipexole up to a dose of 0.75 mg did not produce any adverse consequences on pregnancy (78). However, in the absence of randomized controlled trials, safety of these drugs during pregnancy is questionable and they should better be avoided (79).

Opioids

There is more evidence supporting the safety of using opioids in pregnancy compared to dopaminergic drugs (80). These drugs have been extensively used during pregnancy without any major adverse effects (80). Oxycodone, propoxyphene, and tramadol may be used in less severe cases, while more severe cases may require methadone (80). There is a concern of respiratory depression and a withdrawal syndrome in neonates of mothers treated with opioids during pregnancy along with the congenital malformations (81–83). Moreover, a recent report demonstrated that opioid use was associated with increased odds of threatened preterm labor, early onset delivery, poor fetal growth, and stillbirth after adjusting for confounders (84). Nevertheless, opioids have been found to be safer than dopamine agonists (80).

Benzodiazepines

Benzodiazepines are another alternative for treating RLS in pregnant women, although the evidence supporting their safety in pregnancy is limited. A potential concern for benzodiazepines is cleft palate particularly if used in the first trimester. Nevertheless, one meta-analysis showed no association between fetal exposure to benzodiazepines and the risk of major malformations or oral cleft based (85, 86). However, on the basis of pooled data from case–control studies, there was a significant increased risk for major malformations or oral cleft alone (85, 86). The neonatal withdrawal syndrome has only rarely been reported (87). Clonazepam is the most frequently studied and used benzodiazepine for RLS and has been found to be safe and effective; however, temazepam and triazolam have also been shown to be effective (88). Nevertheless, the AASM and IRLSSG did not recommend clonazepam as a first-line treatment of RLS because of insufficient evidence (79, 89). In summary, in the absence of evidence for major malformations, clonazepam may be used after the first trimester of pregnancy, when organogenesis has already taken place (90); however, there could be a higher risk of developing minor congenital malformations such as cleft lip and palate with benzodiazepines use, and this risk should be explained to the patient.

Anticonvulsants

Carbamazepine is the first anticonvulsant evaluated in a controlled double-blind study for the treatment of RLS (91). There is a large body of evidence from epilepsy registries on the relative safety of carbamazepine use both for the mother and the fetus making it a reasonable option for RLS management in pregnancy. Data from the UK Epilepsy and Pregnancy Register have demonstrated that carbamazepine was associated with the lowest risk of major congenital malformation (92). Gabapentin has been shown as well to be very effective in treating RLS. Available data on gabapentin safety for the mother and fetus are limited; however, they are reassuring (93). Gabapentin and pregabalin have been found to be effective in a recent meta-analysis of randomized controlled trials for the non-dopaminergic pharmacotherapy for RLS (94). However, consensus guidelines by the IRLSSG preclude their use during pregnancy (79).

Iron therapy

As already mentioned, supplemental oral iron should be given to all pregnant females, irrespective of their hemoglobin status (95). However, pregnant women who already have RLS may benefit from the intravenous iron therapy (IIT). It has been reported that IIT leads to marked improvement or complete remission of RLS symptoms in women who had low serum ferritin (<50 mcg/l), even before pregnancy (8). Moreover, women who have RLS even before getting pregnant do not develop RLS symptoms until late in pregnancy if they receive IIT prior to pregnancy (31). Multiple preparations of injectable iron are available. Intravenous iron carboxymaltose was compared with intravenous iron sucrose among pregnant anemic women, and they were found to have similar tolerability and comparable frequency of adverse events (96). However, it has been reported that iron carboxymaltose delivers higher quantity of iron as compared to its counterpart and becomes the drug of choice for IIT especially in late second or third trimester (96). Among non-pregnant patients with RLS, intravenous iron carboxymaltose has been found to be effective in improving the RLS symptoms as a monotherapy (97). Another preparation of intravenous iron (iron dextran) has been found to be effective in treating RLS; however, it has a high incidence of anaphylactic reactions (98). We could not find any trial that has assessed the efficacy of oral iron therapy for RLS in pregnancy.

Estrogen therapy

In a case report, estrogen therapy has been reported to improve sleep quality with reductions in PLMS (99). However, in a randomized control trial in postmenopausal women, estrogen was not found to be effective (100). In view of insufficient literature, estrogen therapy cannot be recommended in pregnant women with RLS.

Conclusion

The high prevalence of RLS during pregnancy makes it a significant clinical problem. RLS can have a negative impact in pregnant women as it may induce stress and/or sleep disorders, and worsen the course of pregnancy. Many factors are thought to contribute to the pathogenesis of RLS during pregnancy; however, the exact pathogenesis is still unknown. These factors include dietary factors, hormonal factors, and physiological changes, and genetic predisposition during pregnancy. Owing to different approaches adopted across different studies and the paucity of literature regarding impact of RLS in pregnancy and its long-term consequences, a conclusive statement regarding its etiopathogenesis and the therapeutic modality that can be safely used cannot be made. However, non-pharmacological approaches along with dietary supplementations may be tried initially in pregnant women with RLS.

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Table 1

Methods adopted across different studies while examining RLS during pregnancy

References	Assessment method	Study population (N)	Period of evaluation	Severity	Remarks
Minar et al. (2013) (4)	Questionnaire	300	Third trimester pregnancy	30% had clinically significant symptoms	75% had it only during pregnancy
Neau et al. (2010) (23)	Questionnaire	1022	Pregnant females		37% had it during third trimester
Vahdat et al. (2013) (15)	Face to face interview	443	Within two days of parturition	75% had moderately severe RLS	87% had it during third trimester
Hubner et al. (2013) (16)	Face to face interview	501	During each trimester and after 8 weeks of parturition	45% had severe to very severe RLS	59% had it before 20 weeks
Chen et al. (2012) (17)	Face to face interview	461	Females admitted for delivery		
Uglane et al. (2011) (11)	Questionnaire	246	Females at delivery		In 97%, it started during pregnancy
Manconi et al. (2004) (21)	Face to face interview	642	Females at delivery and 1, 3, 6 months postpartum		Prevalence increased till third trimester
Facco et al. (2010) (20)	Questionnaire	189	Females between 6 and 20 weeks and during third trimester		Prevalence increased till third trimester

Table 2

Comparison of safety of pharmacological agents for RLS during pregnancy

Drug	FDA pregnancy rating	IRLSSG Consensus guidelines (79)
L-DOPA	C	
Pramipexole	C	Avoid
Ropinirole	C	Avoid
Rotigotine	C	–
Tramadol	C	–
Methodone	C	–
Clonazepam	D	–
Carbamazepine	D	–
Valproate	X	–
Gabapentin	C	Avoid
Pregabalin	C	Avoid
Iron Therapy	NO category assigned	Treatment of Choice during Pregnancy