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Restless legs syndrome and pregnancy: A review

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Abstract

Restless legs syndrome (RLS) is a common sensorimotor neurological disorder that is diagnosed according to the revised criteria of the International RLS Study Group (IRLSSG). The pathophysiology of RLS is still unknown and its prevalence is influenced by ethnicity, age, and gender. RLS is divided into two types by etiology: primary or idiopathic and secondary. Primary RLS is strongly influenced by a genetic component while secondary RLS is caused by other associated conditions such as end-stage renal disease or peripheral neuropathy. Another common condition associated with RLS is pregnancy. The prevalence of RLS during pregnancy is two to three times higher than in the normal population and is influenced by the trimester and the number of parity. The main mechanisms that may contribute to the pathophysiology of RLS during pregnancy are hormonal changes and iron and folate status. Standard medications for treating RLS during pregnancy are not established. Most medications have been used according to the evidence from non-pregnant patients. Therefore, consideration of the medical treatment for treating RLS during pregnancy should be balanced between the benefit of relieving the symptoms and maternal and fetal risk. In general, the prognosis of RLS during pregnancy is good and symptoms are usually relieved after delivery.

Keywords

Restless legs syndrome; Pregnancy; Hormones; Iron

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Introduction

Restless legs syndrome (RLS) or Willis-Ekbom disease (WED), is a common sensorimotor neurological disorder that is characterized by an urge to move the legs due to unpleasant sensations. The symptoms occur at rest, are relieved by movement, and usually worsen in the evening. The key to diagnosing RLS is a careful history. The diagnosis is dependent upon the clinical criteria that were proposed by the International RLS Study Group (IRLSSG) in 1995 [1] and revised in 2002 [2]. The revised criteria are composed of essential and supportive criteria (Table 1). The supportive criteria are helpful to distinguish RLS from other movement disorders such as akathisia or leg cramping. RLS prevalence varies in different races [3] and is influenced by gender. A current systematic review showed that the prevalence of RLS in women is twice that in men (4). However, the relationship between prevalence of RLS and age is still controversial [5,6,7,8,9,10,11,12]. The pathophysiology of primary RLS is still unknown. Many factors that might contribute to its pathophysiology have been proposed, of which three are the most discussed, but are not independent. First is dysfunction of the nigro-striatal dopaminergic system; second is depletion of iron and ferritin; and third is genetic influence. Indeed, there might well be a genetic cause for abnormal iron metabolism leading to deficient dopaminergic function, the latter being the proximate cause of symptoms. Recently, a role for thyroid hormone (TH) in the pathophysiology of RLS was also proposed [13,14].

RLS can be secondary as well as primary [15]. Secondary RLS can arise from etiologies such as peripheral neuropathy, end-stage renal disease, iron deficiency or pregnancy. In general, if symptom onset begins after age 45, secondary RLS should be suspected and possible etiologies should be considered [15,16,17]. In the past decade, many aspects of the epidemiology and pathophysiology of RLS in pregnancy were studied. In this article, we include recent data relating to various aspects of RLS during pregnancy such as epidemiology, recent hypotheses of pathophysiology, management, and prognosis.

Methods

References for this review were found by searching PubMed using the terms “RLS” or “Restless Leg Syndrome”, “Pregnancy” and “RLS” or “Restless Leg Syndrome” from January 1970 to May 2013, and from a search of Google Scholar with the terms “Pregnancy and RLS” and “Pregnancy and Restless leg syndrome”, any time until June 2013. Only reports published in English were included. We also did additional searching using textbooks for “Restless Leg Syndrome”. We identified a large number of search results and the cited references reflect our personal selection of papers as being the most informative.

Epidemiologic Studies of RLS during Pregnancy

Pregnancy and Prevalence of RLS—The prevalence of RLS during pregnancy includes pre-existing primary RLS prior to pregnancy and new onset of RLS during pregnancy. In the era before diagnostic criteria were developed, the reported prevalence of RLS during pregnancy ranged from 11.3–19% [3,18]. After the IRLSSG created the first diagnostic criteria, studies reported prevalence ranged from 20–27% [19,20,21]. After the revised criteria were published, reported prevalence varied from 2.9–32%

[22,23,24,25,26,27,28,29,30] likely indicating an uneven implementation (Table 2). The prevalence of RLS during pregnancy appears to be approximately 2 to 3 times higher than in non-pregnant women.

Trimesters and Prevalence of RLS—In an early study, prevalence of RLS during pregnancy was reported to be highest in the third trimester; it increased from 0% before pregnancy to 23% in the third trimester [33]. Thereafter, various studies showed concordant results [22,25,28]. Some studies showed that the prevalence of RLS increased from the first to the second and from the first to the third trimester but did not increase from the second to the third trimester [27,31].

Parity and Prevalence of RLS—A population-based study in Germany reported that the prevalence of RLS in pregnant women was strongly associated with the number of children that a woman had given birth to. Women who had given birth to one, two or at least three children had an increased odds ratio (OR) to develop RLS when compared with nulliparous women (OR were 1.54, 2.37 and 2.79, respectively). In addition, this study provided data that the prevalence of RLS in nulliparous women was equal to that of men [7]. This finding was reproduced [28,32]. It seems clear that there is an increased prevalence of RLS in parous women compared with nulliparous women.

Pathophysiology of RLS in Pregnancy—Because the pathophysiology of pre-existing RLS resembles that of RLS in the general population, this review focuses on the possible pathophysiology of newly-developed RLS during pregnancy. The possible mechanisms that might contribute to the pathophysiology of RLS during pregnancy are divided into three categories: hormonal mechanisms, iron and folate metabolism, and other hypotheses.

Hormonal mechanisms—There are four major hormones, estrogens, progesterone, prolactin, and thyroid hormone that may play a role in the pathophysiology of RLS during pregnancy. In the normal physiology of pregnant women, all these hormones rise during pregnancy and all hormonal levels peak near term [33]. However, hormonal levels during pregnancy cannot be the full explanation because RLS during pregnancy occurs in less than a third of the patients.

While the estrogen hypothesis is often favored, a full explanation is not forthcoming. The high prevalence of RLS occurring in the third trimester which has the highest level of estradiol compared to the other two trimesters. Both prevalence and severity of RLS subsequently decrease after delivery again correlating with the reduction in estradiol levels. A study showed that the levels of estradiol during the third trimester in pregnant women with RLS were significantly higher than in those without RLS [26]. Nonetheless, there has been some disagreement over this hypothesis. A study from TunÇ et al [25] failed to show the difference in estradiol levels between pregnant women with RLS and without RLS. However, this study did not specify the number of pregnant women in the third trimester in each group which is a crucial point for demonstrating the significance of the difference in estradiol levels between groups.

How estrogens would lead to RLS is unknown. However, if we consider that dysfunction of dopamine within the nigro-striatal circuit is a possible pathophysiology of RLS, there are some data from a previous animal study to show that prolonged exposure or high concentrations of 17 β -estradiol in the striatal tissue from female rats reduced striatal dopamine responsiveness; conversely, the physiological concentrations of 17 β -estradiol could have stimulated dopamine release and increased striatal dopamine responsiveness [34]. Another action of estradiol is inhibiting dopamine-release into the blood circulation of the anterior pituitary gland causing loss of lactotroph suppression. A consequence would be elevated levels of prolactin; however, there is no known direct effect of prolactin that might contribute to the pathophysiology of RLS [35,36].

Levels of progesterone also increase during pregnancy and peak during the third trimester. How progesterone might be relevant is also unknown. However, there are interactions between progesterone and dopamine in the striatum.

Thyroid hormone (TH) has been speculated to play a role in the pathophysiology of RLS. During pregnancy, the thyroid gland is over-stimulated by human chorionic gonadotropin (HCG) produced by the placenta [33]. The effect of HCG over-stimulation only occurs in the first 10 weeks of gestation so this cannot be the responsible mechanism. Other factors may also elevate TH levels in the third trimester. There is a negative relationship between TH and dopamine [13,14] and therefore diminished dopamine activity might increase TH. Thus, if high levels and prolonged exposure of estradiol [34] and progesterone [37] diminish dopamine activity then TH activity might increase and consequently transient RLS during pregnancy may occur. Since dopamine deficiency appears to be a proximate cause of RLS, the TH hypothesis of RLS, at least in pregnancy, seems backwards and hence unlikely.

Iron and folate metabolism—Iron and tetrahydrobiopterin are co-factors of tyrosine hydroxylase for synthesizing dopamine while folate plays a role in regenerating tetrahydrobiopterin. Therefore, if levels of iron or folate are depleted, dopamine synthesis may be reduced [38,39]. During pregnancy, serum folate, iron and other iron indicators such as ferritin and hemoglobin are lower than in the non-pregnant state. Possible explanations are increased total blood volume creating a dilution effect and utilization of iron and folate for fetal development. Fetal iron and folate utilization starts early in pregnancy leading to a rapid decline in iron stores and decreased serum ferritin. In addition, this process might be extremely stressful to the mother if maternal iron stores are low at the beginning of pregnancy [40]. Low serum ferritin before or during early pregnancy was reported to be a predictor of RLS occurring during the pregnancy [25]. However, the symptoms of RLS rapidly decrease after delivery, and this is independent of iron and folate levels as it will take a longer time to replenish their levels. Hence, this mechanism should not be considered a major contributor in the pathophysiology of RLS during pregnancy.

Other mechanisms—During pregnancy, there are many psychological conditions that exacerbate RLS symptoms including anxiety, stress, tension, insomnia, and easy fatigue [20]. Neuropathy and radiculopathy might cause RLS symptoms. The growing size of the fetus causes a mechanical strain effect on the lumbrosacral nerve roots producing RLS symptoms which resolve at delivery. However, one study found a similarity of newborn

anthropometric values between the RLS group and non-RLS group that did not confirm this hypothesis [22]. Finally, peripheral venous distension progressively increases during pregnancy while peripheral vascular resistance decreases. These circumstances cause leg edema and increased pressure of the tissues surrounding the peripheral somatosensory system receptors, thus enhancing their stimulation [41]. However, this hypothesis is weakened by another investigation that showed no significant difference of leg circumference between pregnant women with and without RLS [30]. According to the uncertain data from these hypotheses and the lack of generality, it is unlikely that any of them are typically responsible for RLS symptoms during pregnancy.

Management—First, managing the symptoms of RLS should begin with a non-pharmacological approach including mental alerting activities such as crossword puzzles, abstinence from caffeine, and removal (if possible) of drugs known to aggravate RLS such as antidepressants, neuroleptics, anti-emetics, and sedating antihistamines. If the above approach does not reduce the symptoms of RLS then a pharmacological approach should be considered for further management. Recommendations for treating the symptoms of RLS in non-pregnancy were proposed by the American Academy of Sleep Medicine (AASM) [42] and jointly by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society (EFNS/ENS/ESRS) [43] in 2012. However, when treating RLS during pregnancy, the physician must consider the effect of medication on the fetus, especially the possibility of congenital malformations. Controlled studies of RLS during pregnancy have been limited. As a result, most evidence of therapeutic results come from reported cases or small case series. The medications that were studied include iron supplementation, dopaminergic agents, benzodiazepines, opioids, and anti-epileptic agents. The potential medications for treating RLS during pregnancy are summarized in Table 3.

Iron supplement—Ruling out low iron levels is important and if diagnosed, should be treated with iron supplementation in oral or IV forms. All studies have been conducted in non-pregnant patients, but the logic is clear for pregnancy as well. Using iron supplementation in non-iron deficient patients, however, remains controversial. Two randomized controlled trials of oral ferrous sulfate 325 mg twice daily have been reported [44,45]. Both studies included non-anemic patients, but one study had some subjects with low levels of serum ferritin (15–75 ng/mL) [45]. The improvement of the IRLS score was shown in the study that included patients with low levels of serum ferritin; moreover, the numbers of subjects in this study were small. Two forms of intravenous (IV) iron administration were studied, iron sucrose [46,47] and iron dextran [48,49]. Due to reports of anaphylactic reactions after IV iron dextran infusion, administering IV iron in another formulation such as iron sucrose would be preferred. Although controversial, IV iron might be considered for controlling RLS symptoms in refractory cases [49].

Dopaminergic agents—According to the concept of dysfunction of the nigro-striatal dopaminergic system, supplementation by dopaminergic agents might be the therapy of choice. In addition, AASM and EFNS/ENS/ESRS recommend that dopaminergic agents are the first-line medication for treating RLS [42,43]. There are ergot derivatives (bromocriptine

and carbergoline) and non-ergot derivatives (pramipexole, rotigotine and ropinirole). Most studies using dopaminergic agents were performed in endocrine disorders and Parkinson's disease. However, the efficacy and safety of these agents for treating RLS during pregnancy have not been clearly established. Data concerning pramipexole and rotigotine came from a recent case series that collected data about dopaminergic agents used in RLS during pregnancy. There were 9 and 2 cases using pramipexole and rotigotine, respectively, during the entire pregnancy and all mothers gave birth to children with no congenital anomalies [50]. In the case of ropinirole, a reported case in a pregnant woman with a history of familial Parkinson's disease due to the Parkin gene mutation, who received ropinirole for 5 weeks during her pregnancy, gave birth to normal twins [51]. The safety data of levodopa in pregnant women come from many reported cases of Parkinson's disease [52,53,54,55]. Recently, data from the earlier noted case series showed that only 3 of 42 children born to mothers using levodopa had minor anomalies such as nose deformity, patent ductus arteriosus, and patent foramen ovale [50]. In conclusion, the efficacy and safety of dopaminergic agents for treating RLS during pregnancy need to be explored further. Nevertheless, if RLS disturbs one's quality of life, it may be reasonable to use either non-ergot derivative dopamine agonists or levodopa to relieve the symptoms; however, levodopa should not be considered for long term therapy due to the high probability of augmentation [56].

Benzodiazepines—At present, benzodiazepines are used to treat symptoms of RLS in either pregnant or non-pregnant patients. Clonazepam has traditionally been used to reduce complaints of RLS, but this may simply reflect a sedative effect. Efficacy studies of clonazepam to reduce the symptoms of RLS were done in non-pregnant cases and their data have shown contradictory results. Boghen reported 3 cases of primary RLS with successful treatment of the symptoms with clonazepam [57]. Subsequently, two randomized double-blind cross-over studies with placebo control were conducted by Montagna et al [58] and Boghen et al [59], respectively (6 patients were included in each trial). The results of the two studies were discordant. Montagna et al showed that clonazepam significantly improved quality of sleep and leg dysesthesia whereas the results from Boghen et al. did not when compared with placebo. Another study showed that 1 mg clonazepam improved objective sleep efficiency and subjective sleep quality in 10 cases of RLS [60]. According to these data, AASM and EFNS/ENS/ESRS did not recommend clonazepam as a first-line treatment of RLS because of insufficient evidence [42,43]. In conclusion, clonazepam may potentially be used to treat RLS during pregnancy as adjunct treatment and there is no evidence that it causes an increased rate of major malformations [61]; however, the incidence of minor congenital malformations including cleft lip and palate are more frequent with benzodiazepine use.

Opioids—Opioids such as oxycodone, propoxyphene, tramadol and methadone might potentially be used to treat the symptoms of RLS in non-pregnant patients according to the recommendations of the AASM [42]. However, the efficacy of these agents on RLS during pregnancy has not been established. Considering safety, a recent large case-controlled study conducted by Broussard et al. showed an association between early pregnancy maternal opioid analgesic treatment and certain birth defects [62]. Congenital malformations included

conoventricular septal defects (OR=2.7), hypoplastic left heart syndrome (OR=2.4), atrioventricular septal defects (OR=2.0), spina bifida (OR=2.0), and gastroschisis (OR=1.8) [62]. The rates of fetal adverse events after using opioids during the third trimester, in which the greatest prevalence of RLS occurs, were not studied. However, some researchers have reported possible cases of infants who had long-term intra-uterine exposure to tramadol developed neonatal abstinence syndrome [63,64,65,66]. In conclusion, due to the risks of congenital malformations and neonatal abstinence syndrome, opioids should be avoided for treating the symptoms of RLS during pregnancy if possible.

Anti-epileptic agents—Besides benzodiazepines, other anti-epileptic agents such as gabapentin, gabapentin enacarbil, pregabalin, carbamazepine and oxcarbazepine have supportive evidence for treating the symptoms of RLS in non-pregnant patients.

Gabapentin was documented for treating RLS in two small studies. First, a randomized open study in 16 patients compared gabapentin to ropinirole and found gabapentin to be as effective as ropinirole in terms of an improved International Restless Legs Scale (IRLS) score [67]. Second, a randomized cross-over study in 24 patients, showed that gabapentin improved the IRLS score [68]. Many studies supported the efficacy of gabapentin enacarbil, a pro-drug of gabapentin, to treat RLS in non-pregnant patients in terms of a significantly improved IRLS score. The effective dosages ranged from 600 to 1200 mg/day [69,70,71,72]. A recent study showed that the rate of major malformations were similar in both pregnant women who were exposed or not exposed to gabapentin [73]. The common adverse events that were reported in the literature are somnolence and dizziness. A recent randomized double-blind placebo-controlled study using pregabalin showed that 12 weeks of treatment caused greater improvement in IRLS score in non-pregnant patients than in those receiving placebo with a mean effective dose of 322.5 mg/day [74]. The common adverse events were unsteadiness, daytime sleepiness and headache. Neither the efficacy of pregabalin on RLS during pregnancy was established nor was a systematic study of the safety profile to use pregabalin during pregnancy performed.

The efficacy of carbamazepine to treat RLS in non-pregnant patients is based on one randomized double-blind controlled trial and one case series. The randomized double-blind study showed the efficacy of 5 weeks of treatment with carbamazepine in terms of a greater improvement in the visual analog scale (VAS) compared with placebo ($p<0.03$) [75]. Zucconi and colleagues reported a series of 9 RLS and nocturnal myoclonus cases whose symptoms of RLS improved after receiving carbamazepine; however, the nocturnal myoclonus did not improve [76]. Regarding the safety data for using carbamazepine during pregnancy, a recent study showed the rate of developing major congenital malformations was 3.0% [77].

The efficacy of oxcarbazepine, a keto-derivative of carbamazepine, for treating RLS was reported in one case series. The effective dose ranged from 300–600 mg/day. Complete remission of all cases, evaluated by self-report, was reported within 6 months after receiving oxcarbazepine. Unfortunately, this case series did not include pregnant patients and had a small sample size [78]. The rate of major fetal malformations due to oxcarbazepine is not significantly different when compared to that of carbamazepine (2.2% vs. 3.0%) [77]. In

conclusion, anti-epileptic agents should be considered the last choice for treating RLS during pregnancy. Gabapentin, carbamazepine and oxcarbazepine may be reasonable choices due to their lower rates of teratogenicity. In addition, testing of HLA B*5701 is recommended before starting treatment with carbamazepine or oxcarbazepine to minimize the risk of developing Stevens-Johnson syndrome.

Predictive factors and Prognosis

The predictive factors for developing RLS during pregnancy are summarized in Table 4. The prognosis is generally good. It is important to reassure the patient that the condition is common and will almost certainly improve after delivery. Most new patients with pregnancy-related RLS recover well [22] and are asymptomatic within a month [79]. In a recent study [80] of pregnant women with symptoms of RLS, symptoms disappeared in 97% within a few days after delivery. The authors emphasized that since pregnancy-related hormones likely have an important role in the disorder, improvement was dramatic and other factors such as iron deficiency and low folate level do not have a significant role in the prognosis of pregnancy-related RLS. However, it is certainly important to check the hemoglobin in pregnancy and treat with supplemental iron if appropriate [25].

RLS during pregnancy was an important risk factor for developing a chronic 'idiopathic' form of RLS in the future. In one study, [81] a history of pregnancy-related RLS was associated with a four-fold increase in the risk of developing chronic RLS in the future. One of the important limitations of the study was a higher rate of RLS (7%) in the control group as well, which was attributed to female gender, parity, and higher mean age (>35 years).

Conclusion

Pregnancy-related RLS is a complex disorder, which has multiple possible etiologies. History of RLS in a previous pregnancy and in the non-pregnant state, family history and multiparity are associated with an increased risk of RLS during pregnancy. Pregnancy-related hormones, especially estrogen, likely play important roles. If there is iron deficiency, it is critical to treat that. However, the role of iron as a risk factor for RLS in pregnancy is overstated leading to unnecessary iron supplementation. Dopaminergic agents, anti-epileptics and benzodiazepines can be used for treatment. Prognosis is good and most patients recover quickly. However, a small number of them may develop the chronic idiopathic form of RLS.

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Table 1

Diagnostic criteria for restless legs syndrome (2)

A. Essential criteria
1. Urge to move the legs that is usually accompanied by unpleasant sensations of leg paraesthesia and dysesthesias.
2. Urge to move or unpleasant sensation relieved by movements.
3. Symptoms that appear are worse at rest and are partially relieved by activity.
4. Symptoms are worse in the evening and during the night.
B. Supportive criteria
1. Presence of positive family history in primary restless legs syndrome (seen in more than 50% of patients)
2. Positive response to dopaminergic therapy
3. Sleep disturbances with periodic limb movements in sleep (seen in 85% of patients)

Table 2

Prevalence of restless legs syndrome during pregnancy according to revised International Restless Legs Syndrome Study Group criteria.

Year	Reference	Location	Number surveyed	Prevalence (%)
2013	Hübner et al. (30)	Switzerland	501	11.58
2012	Chen et al. (81)	Taiwan	461	10.41
2011	Uglane et al. (79)	Norway	251	33.86
2010	Neau et al. (28)	France	186	32.25
2010	Alves et al. (27)	Brazil	524	13.54
2010	Ismailogullari et al. (29)	Turkey	983	10.48
2008	Harano et al. (24)	Japan	19441	2.90
2008	Wesstrom et al. (23)	Sweden	3516	15.67
2007	Tunç et al. (25)	Turkey	146	26.02
2004	Manconi et al. (22)	Italy	606	26.57

Table 3Potential medications for treating restless legs syndrome during pregnancy⁺

Dopaminergic agents
Pramipexole
Ropinirole
Levodopa
Rotigotine
Benzodiazepine
Clonazepam
Anti-epileptic drugs
Gabapentin
Carbamazepine
Oxcarbazepine
Pregabalin
Gabapentin encarbil
Iron supplement [*]
Ferrous sulfate, orally
Iron sucrose, intravenously
Opioids [#]
Oxycodone
Tramadol

^{*} Iron supplement should be considered in pregnant women who are diagnosed as being iron-deficient.

[#] Opioids are not recommended for treating restless legs syndrome in pregnant women.

⁺ Since there is a lack of good evidence about efficacy from previous studies, the medications that we recommend for treating restless legs syndrome during pregnancy derive from recent treatment guidelines for the general adult population [42,43] taking into consideration a low probability of adverse events occurring to the fetus.

Table 4

Predictors for restless legs syndrome during pregnancy

History of restless legs syndrome in previous pregnancy
History of restless legs syndrome prior to pregnancy
Family history of restless legs syndrome
Multiparity
Anemia
Low iron level
Low folate level
High estrogen level