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Management of Restless Legs Syndrome in Pregnancy and Lactation

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Abstract

Restless legs syndrome (RLS) affects about 20% of all pregnant women. RLS symptoms are usually moderate to severe in intensity during pregnancy and can result in insomnia, depression, and other adverse outcomes. Although iron deficiency has been implicated as a potential etiological factor, other mechanisms can also play a role. Nonpharmacologic methods are the primary recommended form of treatment for RLS in pregnancy and lactation. Iron supplementation may be considered when the serum ferritin is low; however, several patients are unable to tolerate iron or have severe symptoms despite oral iron replacement. Here, we describe a case of severe RLS in pregnancy and illustrate the dilemmas in diagnosis and management. We review the literature on the prevalence, diagnosis, course, possible underlying pathophysiologic mechanisms and complications of RLS in pregnancy. We describe current best evidence on the efficacy, and safety of nonpharmacologic therapies, oral and intravenous iron supplementation, as well as other medication treatments for RLS in pregnancy and lactation. We highlight gaps in the literature and provide a practical guide for the clinical management of RLS in pregnancy and during breastfeeding.

Keywords

Willis-Ekbom disease, gestation, breastfeeding, treatment, medications, pharmacologic, restless leg, refractory

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Report of Case

History, Examination, and Laboratory Results

A 33-year-old gravida 2 para 1 medical professional was referred to Sleep Medicine from Psychiatry at 29 weeks gestation for an evaluation of her restless legs syndrome (RLS). She was taking escitalopram at 20 mg in the morning for a long-standing major depressive disorder. She endorsed severe, daily, typical symptoms of RLS that began in the early second trimester. There was also a history of RLS in the previous pregnancy. Her obstetric team had tried trazodone at 50 to 100 mg at bedtime due to significant sleep onset and maintenance difficulty but this was ineffective and therefore discontinued by her psychiatrist. Clonazepam was substituted at 0.5 mg at bedtime for severe RLS resulting in insomnia, worsening mood and anxiety symptoms. Due to concerns with long-term daily use of clonazepam in pregnancy, she was referred to Sleep Medicine for further management.

With clonazepam, the patient was able to sleep from 9:00 PM to 6:00 AM on weekdays and 10:00 PM. to 8:00 AM on weekends. She was able to initiate sleep within 45 minutes and had up to 4 brief awakenings to use the restroom. She had been taking a 1-hour nap on the weekends during her pregnancy. She noted mild grogginess in the morning but no other side effects from the clonazepam. Without this medication, she would fall asleep at 3 to 4 AM, which was extremely frustrating to her and caused her significant stress. She estimated that she was not getting more than 2 to 3 hours of sleep. She would find it difficult to reinitiate sleep after an awakening and pace around or do squats in order to help with the symptoms. This was very distressing, and she endorsed crying for hours in the middle of the night. She felt that the stress and lack of sleep caused by RLS contributed to preterm labor in her previous pregnancy.

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The patient reported RLS symptoms in her arms occurring earlier in the day. The worst symptoms were at bedtime, noted in both thighs and lower legs, which she described as a creepy-crawly sensation. She had read about the condition and tried moderate physical activity, avoidance of salt and caffeine, massage, warm and cold water baths, and had even purchased a transcutaneous electrical nerve stimulation (TENS) unit, all of which were minimally effective in alleviating her symptoms. There were no leg movements in sleep noted by her or her husband and the bed covers were not messy in the morning. Sometimes she would get up and eat a snack in the night and was aware of doing that. She denied significant daytime sleepiness and her Epworth Sleepiness Scale score was 3/24. The remainder of the sleep history was negative.

There was no history of smoking, alcohol, or recreational drug use before or during pregnancy. She drank one soft drink per day. There was no family history of sleep disorders. Past medical history was significant for generalized anxiety disorder, major depressive disorder, irritable bowel syndrome, and preterm labor at 35 weeks gestation 2.5 years ago. She had been taking oral ferrous sulfate 325 mg daily since the beginning of the pregnancy in addition to a prenatal vitamin. She was not taking any other over-the-counter medications or supplements.

The patient's body mass index was 26.8 kg/m^2 and blood pressure was normal. Oropharynx was Friedman palatal position class II and neck circumference less than 16 inches; the remainder of the examination was unremarkable.

Review of laboratory tests revealed a hemoglobin of 11.1 g/dL (nonpregnant reference range: 12-14 g/dL), hematocrit of 33.1% (nonpregnant reference range: 37%-48%), red blood cell count of 3.74 million/μL (nonpregnant reference range 4.2-5.4 μg/μL) and normal mean corpuscular volume. One-hour glucose was normal, ferritin was 14 μg/L (nonpregnant reference range for laboratory: 12-150 μg/L) 1 month prior and 6 μg/L shortly before the Sleep Medicine evaluation. Serum iron was 247 μg/dL (nonpregnant reference range: 40-155 μg/dL), total iron-binding capacity was increased at 454 μg/dL (nonpregnant normal values: 240-450 μg/dL), and transferrin saturation low at 10% (nonpregnant normal values: 20%-50%). Electrocardiogram from 3 years prior was normal.

Assessment and Plan

The potential risks of preterm labor in this case of severe RLS included the RLS symptoms themselves, worsening depression, previous preterm labor, stress, anemia, and possibly the use of benzodiazepine medication. The Sleep Medicine, Psychiatry, and Obstetric teams collaborated in the management of the patient. The risk of RLS worsening with escitalopram was thought to be low and the medication was continued. Low-molecular-weight iron dextran was considered but was out of stock. Due to insufficient evidence regarding the use of ferric carboxymaltose in pregnancy, a joint decision was made by the patient and the medical teams to proceed with a trial of up to 4 weekly iron sucrose infusions. The patient was also advised to continue with oral iron supplementation and nonpharmacologic measures for RLS.

Follow-up

After the first infusion, symptoms improved; the patient reported using clonazepam only on 2 nights. She was seen in the outpatient setting with a rash at the infusion site after the second infusion and was advised to hold off on further infusions. The patient had noted RLS symptoms the preceding night and was concerned since she was planning a long airplane ride. Serum ferritin at that time was 95 μg/L. Reassurance was provided and a decision was made to take a wait-and-watch approach. A week later, when she returned from her trip, she was doing well and canceled her follow-up appointment. She had a few visits to the Labor and Delivery unit to rule out preterm labor but there was no recurrence of RLS symptoms for the remainder of the pregnancy. The patient had a vacuum-assisted delivery at 39 weeks without complications and did not report significant RLS symptoms postpartum.

Discussion

Expected Course and Potential Complications of RLS in Pregnancy

Prevalence and Predictors of RLS in Pregnancy. There are number of studies reporting the prevalence of RLS in pregnancy.[1-3] The prevalence of RLS in the general population is 5% to 10%, with women being 1.5 to 2 times more likely to report symptoms than men.[4,5] The prevalence of RLS has been found to correspond with parity. Pregnant women in Europe and the Americas have shown rates of up to 20%, while Asian women may have a lower prevalence but the rates are still higher than those in the nonpregnant population.[3,6-9] Predictors for RLS in pregnancy include a past medical history of RLS (odds ratio [OR] 13), RLS in a prior pregnancy (OR 54), hemoglobin of ≤11 g/dL, and family history.[1,10]

Diagnosis and Differential Diagnoses. The diagnosis of RLS is clinical and based on 4 cardinal symptoms corresponding to the mnemonic "URGE", same as in patients who are not pregnant: (1) an irresistible (U)rge to move the lower extremities, (2) worse at (R)est, (3) relieved by (G)etting up and moving, and (4) worse in the (E)vening/night.[11] The International RLS Study Group (IRLSSG) questionnaire can help rate the severity of symptoms; however, this questionnaire has not been validated for use in pregnancy.

The differential diagnosis for RLS in pregnancy is wide and includes muscle cramps, discomfort related to venous stasis, edema or position, and compression or stretch-related neuropathy.[1] Approximately 40% of patients who report an

Table 1. Treatment Options for Restless Legs Syndrome in Pregnancy and Lactation.

Treatment	Pregnancy[a]	Breastfeeding[a]
I. Nonpharmacologic treatments[b]	Yes	Yes
II. Iron supplementation		
1. Ferrous sulfate PO	Yes	Yes
2. Low-molecular-weight iron dextran IV	Yes	Insufficient evidence
3. Ferric carboxymaltose IV	Yes, but limited evidence	Insufficient evidence
4. Iron sucrose IV	Yes, but may be less effective	Insufficient evidence
III. Pharmacologic treatments		
1. Dopamine agonists	Yes (carbidopa-levodopa)	No
2. GABA analogs	Insufficient evidence	Yes (gabapentin)
3. Benzodiazepines/NBBRAs	Yes (low-dose clonazepam) in selected cases	Yes (low-dose clonazepam) in selected cases
4. Opioids	Yes (low-dose oxycodone) in very severe, very refractory cases	Yes (tramadol preferred) in very severe, very refractory cases

Abbreviations: PO, per os (oral); IV, intravenous; GI, gastrointestinal; GABA = γ-aminobutyric acid; NBBRA, non-benzodiazepine receptor agonist.
[a]Medications in parentheses are the recommended ones in the respective class, to be used in the second and third trimesters only (particularly benzodiazepines and opioids); others are to be avoided if possible.
[b]These include moderate intensity exercise, yoga, massage, sequential compression devices, avoidance or treatment of aggravating causes of restless leg syndrome and treatment of obstructive sleep apnea.

urge to move their lower extremities do not have RLS.[12] Ruling out RLS "mimics" in addition to inquiring about the 4 cardinal symptoms of RLS markedly increases the specificity of the diagnosis.[13]

Onset, Progression, and Severity of Symptoms. RLS symptoms generally start in the second trimester, peak in the third trimester, and plateau in the last month of pregnancy.[1,3,6] Resolution of symptoms occurs in approximately 70% of patients by the time of delivery and in 90% of cases with de novo RLS by about 1-month postpartum.[14] A majority (50%-100%) of pregnant mothers with RLS experience moderate to severe symptoms.[2,8,15] Symptoms occurring 2 or more times a week and causing moderate to severe distress is termed "severe" RLS.[1] "Refractory" RLS refers to failure of at least 1 nonpharmacologic treatment and adequate iron supplementation (if the serum ferritin is $<$75 μg/L). "Very severe, very refractory" RLS is defined as an IRLSSG score of more than 30 and failure of at least 1 nonopioid medication.

Possible Pathophysiological Mechanisms. The pathophysiology of RLS in pregnancy is uncertain but is thought to involve genetic mechanisms, central dopaminergic pathways, iron, folate, and/or estrogen deficiency, and stretch of nerves in pregnancy.[4,16-18]

Potential Implications of RLS in Pregnancy. RLS can result in sleep onset and maintenance difficulties and is a very common cause of insomnia in pregnancy.[2,9,15,19] RLS has also been associated with adverse pregnancy outcomes, including preeclampsia, increased risk of Caesarean section, and depression. However, further data are needed to assess the degree of associated risks and determine if RLS is truly a causative factor independent of comorbidities or etiologic factors for RLS.[1,15,20,21] In those with de novo RLS, which represents the majority (67%-90%) of cases of RLS in pregnancy, the future risk of RLS is 4 times compared with that in pregnant women without RLS.[8,10,15]Additionally, there is a 30% risk of recurrence of RLS in future pregnancies.[14]

Treatment

A summary of treatment options in pregnancy and lactation is presented in Table 1.

Nonpharmacologic Treatments. Reassurance is important in these cases; a placebo response rate of 20% to 40% has been reported in nonpregnant patients with RLS.[22,23] Nonpharmacologic methods should be the primary form of treatment, where possible. Of 15 nonpharmacologic modalities evaluated in the systematic review by Piccheti et al,[1] 5 treatments were found to be of benefit: moderate-intensity exercise, yoga, massage, sequential compression devices, avoidance of aggravating causes of RLS and treatment of obstructive sleep apnea. Moderate intensity exercise can be advised to most patients, with an emphasis on avoidance of contact sports.[24] Often, patients use warm baths to help alleviate symptoms of RLS, but they should be advised to minimize the duration of exposure to warm water since hyperthermia has been associated with neural tube defects.[25]

Iron Supplementation

Oral iron. There is limited direct evidence of benefit with oral iron supplementation for RLS in pregnancy and lactation.[1] Serum ferritin tends to drop to about 50% of

prepregnancy levels by the middle of the pregnancy.[26] It is worth noting that ferritin is an acute phase reactant and can be elevated for about 4 weeks following an infection or other inflammatory reactions. Iron supplementation is generally recommended in pregnant mothers in addition to a prenatal vitamin if the ferritin is less than 30 μg/L and/or the transferrin saturation is less than 20%.[27] However, if a pregnant or lactating mother has significant RLS symptoms and the serum ferritin is less than 75 μg/dL, oral iron supplementation can be recommended at a frequency of once or twice daily. In this situation, additional iron studies could be considered, and ferritin should be rechecked after about 6 to 8 weeks of iron supplementation.

Ferrous sulfate at 325 mg (65 mg of elemental iron) per tablet is the preferred form of therapy. Patients should be counseled about keeping iron tablets out of reach if there are toddlers at home to avoid accidental overdoses. Vitamin C–containing preparations such as Vitron-C that are frequently used in the treatment of RLS in nonpregnant patients are not recommended in pregnancy.[28] Regarding other over-the-counter supplements, folic acid is routinely recommended, but there is no evidence supporting the use of vitamin E or magnesium, and safety data on the use of valerian or other herbal supplements during pregnancy are sparse.[1]

Intravenous iron. Generally intravenous (IV) iron preparations are administered in severe cases of RLS after the first trimester if oral iron therapy fails and the ferritin remains <30 μg/L. There are a few studies investigating the use of IV iron for RLS in pregnancy.[29-32] The preparations to consider for use are low-molecular-weight iron dextran (InFed), ferric carboxymaltose (Injectafer), and iron sucrose (Venofer).[1,33] Iron sucrose is used most commonly for the treatment of anemia in pregnancy, but ferric carboxymaltose has been noted more efficacious than iron sucrose for RLS in pregnancy, possibly because it is capable of crossing the blood-brain barrier.[34,35] Ferric carboxymaltose is the most expensive of these preparations; however, iron sucrose usually requires a total of 3 to 4 doses and associated infusion administration costs need to be taken into account when considering the overall cost of therapy. The other 2 preparations usually require only one dose. Due to the potential risk of anaphylaxis, the infusions should be administered by staff familiar with them and in some centers pretreatment with IV antihistamine and/or steroid medication is given to non-pregnant patients.[27] Low-molecular-weight iron dextran is administered at 100 mg over an hour. Ferric carboxymaltose is given at a dose of up to 1000 mg in 15 minutes and iron sucrose at 100 mg every 1 to 2 weeks until the course is complete.

Although low-molecular-weight iron dextran crosses the placenta there are several studies demonstrating its safety in pregnancy.[27,36] A practical aspect to consider is that it is frequently out of stock in pharmacies. On the other hand, there are only 2 studies evaluating the safety of ferric carboxymaltose in pregnancy.[29,34] An open-label study of ferric carboxymaltose in a single dose of 500 to 700 mg in 19 patients with RLS and iron deficiency anemia did not report any major adverse effects.[29] Another study of 206 patients that compared ferric carboxymaltose to iron sucrose found that the former was superior in efficacy.[34] Ferric carboxymaltose is not known to cross the placenta; however, based on current evidence, the risk to the fetus is unknown and cannot be fully ruled out.[37] Last, there are multiple studies on iron sucrose in pregnancy and no adverse effects to the mother or fetus have been described.[27,38] In 2 pregnant patients, iron sucrose given in 4 doses of 100 mg each 1 to 2 weeks apart successfully treated RLS symptoms.[30] Interestingly, the authors of one case report noted that iron sucrose administration prior to pregnancy may have helped prevent RLS symptoms during pregnancy.[39]

The World Health Organization states that low-molecular-weight iron dextran can be used during lactation, but based on the results of their study from 2017, Breymann et al[40] suggest that other preparations should be utilized if possible. Although there are data on the use of ferric carboxymaltose and iron sucrose for postpartum iron deficiency anemia, literature on their use for RLS in the lactation period are lacking.[41,42] The highest level of iron in breast milk tends to occur about 24 hours after administration of ferric carboxymaltose and potential side effects to look for in the infant include constipation or diarrhea.[41] Iron sucrose was not found in breast milk after a single dose in one study.[42]

In summary, IV iron can be used in the second and third trimesters for treatment of RLS in pregnancy, preferably the low-molecular-weight iron dextran preparation in a single dose if available; however there is insufficient evidence for the use of IV iron during lactation.

Pharmacologic Treatment. About one-third of patients require pharmacologic treatment for RLS in pregnancy.[1,43-45] Notably, the Food and Drug Administration (FDA) classification system (categories A-X) for medication use in pregnancy is no longer in use.

Dopamine Agonists. There are some safety data on the use of carbidopa-levodopa for RLS in pregnancy (n = 38).[45] The combination with benserazide should be avoided due to concerns with effects on bone development in children.[1] Compared with other dopamine agonists, this medication carries a higher risk of tolerance, augmentation, and rebound of symptoms, particularly when used on a daily basis and at higher doses.[46] Low-dose carbidopa-levodopa at 25/100 mg to 50/200 mg once daily taken 2 hours prior to the onset of worst symptoms may be considered as a treatment option for RLS in pregnancy.

Pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro patch) are recommended by the US FDA and European Medicines Agency as medication treatments for RLS outside of pregnancy, but there is insufficient evidence for the use of these medications in pregnancy.

All dopamine agonists can reduce breast milk production by suppressing prolactin, although this can rebound quickly on discontinuation. Thus, the use of dopamine agonists is not recommended during lactation.

Gabapentin and Other GABA Analogues. Gabapentin, a γ-aminobutyric acid (GABA) analog that binds to alpha-2-delta-1 receptors, is used off-label for the treatment of RLS outside of pregnancy.[47,48] Data from the epilepsy literature suggests that it is safe to use, but there are some animal studies demonstrating a possible risk of impaired synaptogenesis.[49,50] While the risk of neural tube defects in humans has been noted with some other anticonvulsants, it has not been shown with gabapentin. If gabapentin is used in pregnancy, folic acid should be supplemented at 4 mg per day, although there is insufficient evidence overall to support its use.[1,51] It does enter breast milk (1%-4%) but no adverse effects have reported.[52] In general, breastfeeding is considered acceptable when the relative infant dose of a medication is less than 10%, <5% in the case of psychotropic agents.[53-55]

Pregabalin (Lyrica), another GABA analog and gabapentin enacarbil (Horizant), a prodrug of gabapentin that is an FDA-approved for treatment of RLS, are not recommended at this time as safety data in pregnancy and lactation are lacking.[1]

Benzodiazepines and NBBRAs. Benzodiazepine medications are not FDA-approved for treatment of RLS outside of pregnancy but are used off-label in clinical settings for refractory RLS as secondary or adjuvant medication.[48] In the first trimester, most benzodiazepines were previously classified as category D (temazepam was X) due to the possible risk of cleft palate and other teratogenic effects; however, these risks have not been confirmed.[48,56] Benzodiazepines are generally not recommended for use along with antihistamines or anticonvulsant medications in pregnancy.[56,57] If considering the use of benzodiazepines, clonazepam could be tried at a dose of 0.25 mg, increasing up to 1 mg if required.[1] Small amounts of clonazepam (less than 5%) enter breast milk; respiratory depression, hypotonia and sedation have been reported in exposed infants but the literature is conflicting.[58-61] In summary, benzodiazepines such as low-dose clonazepam may be used in the second and third trimesters of pregnancy and lactation if required.

Non-benzodiazepine benzodiazepine receptor agonists (NBBRAs) such as zolpidem should generally be avoided in pregnancy and breastfeeding due to the possible increased risk of sedation and respiratory depression in the neonate.[1,59] The risk is increased with concomitant use of other central nervous system depressants. Amnestic and sedative effects of the medication in the mother during the period of lactation also need to be weighed against potential benefits.[62]

Opioids. Most of the studies examining the use of opioid medication in pregnancy have been conducted in patients with chronic pain or in the context of heroin addiction.[1] The concerns with opioid use in pregnancy include questionable risk of birth defects, neonatal abstinence syndrome, sedation, and increased risk of side effects in patients who are ultra-fast metabolizers of codeine.[63-66] The use of opioids should be reserved for very severe, very refractory RLS in pregnancy.[67] Referral to a sleep medicine specialist should be considered in these cases. Oxycodone at 5 to 20 mg at bedtime should be used as sparingly as possible in the second and third trimesters. Tramadol is preferred during lactation, but this enters breast milk, albeit at low levels (3%), therefore the dose should be limited to 50 to 100 mg prior to symptoms once daily if possible.[39,68]

Other Considerations With Medication Treatment. In all pregnancies, there is a 3% to 5% risk of birth defects and 1% to 3% risk of major birth defects; patients should be counseled accordingly prior to starting medication.[69] Medications should generally be avoided in the first trimester during the period of embryogenesis, if at all possible. There are several free online resources available to mothers regarding potential risks of medications in pregnancy and lactation, including Motherisk, Otis, and Lactmed.[1]

Regarding other psychotropic medications, selective serotonin reuptake inhibitor antidepressants are associated with a small (<5%) risk of new-onset or worsening RLS symptoms in nonpregnant adults, the risk is slightly higher with serotonergic noradrenaline reuptake inhibitors such as duloxetine and venlafaxine.[70] Trazodone and doxepin do not appear to worsen RLS. Finally, in the context of comorbid depression and significant RLS symptoms, bupropion is the preferred drug of choice, both in pregnancy and lactation.[33,70]

Conclusions

RLS is common in pregnancy and is frequently severe. Insomnia, depression, and other adverse pregnancy outcomes have been reported in association with RLS. Symptoms usually resolve at the time of delivery. While nonpharmacologic methods are the mainstay of treatment, oral or IV iron supplementation may be required in pregnancy if the ferritin is <75 μg/L. Pharmacologic treatment should be used after the first trimester, when possible. Carbidopa-levodopa or low-dose clonazepam may be used judiciously in select patients, with low-dose oxycodone reserved for very refractory, very severe RLS in pregnancy. Collaboration between the Primary Care/Obstetric and

Sleep Medicine teams is essential in the management of these patients. During lactation, gabapentin, low-dose clonazepam or tramadol could be considered in very severe cases after carefully weighing risks and benefits.

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Patient Consent

The patient provided authorization for use of their medical information for research purposes.

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