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CLINICAL REVIEW

Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation

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SUMMARY

Restless legs syndrome (RLS)/Willis-Ekbom disease (WED) is common during pregnancy, affecting approximately one in five pregnant women in Western countries. Many report moderate or severe symptoms and negative impact on sleep. There is very little information in the medical literature for practitioners on the management of this condition during pregnancy. Accordingly, a task force was chosen by the International RLS Study Group (IRLSSG) to develop guidelines for the diagnosis and treatment of RLS/WED during pregnancy and lactation. A committee of nine experts in RLS/WED and/or obstetrics developed a set of 12 consensus questions, conducted a literature search, and extensively discussed potential guidelines. Recommendations were approved by the IRLSSG executive committee, reviewed by IRLSSG membership, and approved by the WED Foundation Medical Advisory Board. These guidelines address diagnosis, differential diagnosis, clinical course, and severity assessment of RLS/WED during pregnancy and lactation. Nonpharmacologic approaches, including reassurance, exercise and avoidance of exacerbating factors, are outlined. A rationale for iron supplementation is presented. Medications for RLS/WED are risk/benefit rated for use during pregnancy and lactation. A few are rated "may be considered" when RLS/WED is refractory to more conservative approaches. An algorithm summarizes the recommendations. These guidelines are intended to improve clinical practice and promote further research.

Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is 2–3 times more prevalent during pregnancy than in the general population, affecting about 15–25% of pregnant women in Western countries [1–3]. There is a peak in the number of women affected by RLS/WED in the third trimester and resolution of symptoms for many by one month after delivery [1,4].

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Abbreviations

ADHD	attention-deficit/hyperactivity disorder
BZ	benzodiazepine
BZRA	benzodiazepine receptor agonist
CNS	central nervous system
EMA	European Medicines Agency
FDA	Food and Drug Administration
IRLS	International Restless Legs Study Group rating scale
IRLSSG	International Restless Legs Study Group
IV	intravenous
OR	odds ratio
OSA	obstructive sleep apnea
OTIS	Organization of Teratology Information Specialists
RDA	recommended daily allowance
RLS	restless legs syndrome
SIDS	sudden infant death syndrome
SSRI	selective serotonin reuptake inhibitor
US	United States
WED	Willis-Ekbom disease

Independent predictors of RLS/WED during pregnancy are a past history of RLS/WED when not pregnant (odds ratio (OR) 12.91), a family history of RLS/WED (OR 8.43), a history of RLS/WED during prior pregnancy (OR 53.74), and hemoglobin ≤11 g/dL (OR 2.05) [5]. Preexisting RLS/WED also predicts greater severity during pregnancy than before pregnancy [6]. Interestingly, women are 1.5–2 times more likely than men to have RLS/WED [7]. The gender difference is explained at least in part by parity, with nulliparous women at the same risk of RLS/WED as age-matched men, but increased risk for women after one pregnancy (OR 1.98), two pregnancies (OR 3.04), and three or more pregnancies (OR 3.57) [8,9].

Symptoms of RLS/WED during pregnancy range from very mild to quite severe. Severe to very severe symptoms, as assessed by the International Restless Legs Syndrome Study Group (IRLSSG) rating scale, were reported in 45% and 54% of pregnant women in two recent studies [2,10], with a third study reporting only 14% at this level but 75% with at least moderate symptoms [11]. Negative impact on sleep is common, affecting both sleep onset and maintenance [2,3,11–14]. RLS/WED is reported as the third most common reason for insomnia during pregnancy [15]. This is relevant to emerging data that show an association between sleep disorders and adverse pregnancy outcomes [16–18]. Thus far, increased rates of preeclampsia, cesarean delivery, and depressed mood have been reported in women with RLS/WED but data are limited and further research is needed [11,19–21].

Although the pathophysiology of RLS/WED has been defined, with genetics, the brain dopamine system, and iron found to play important roles [7,22–25], factors specific to pregnancy have not been adequately delineated. Familial predisposition, iron deficiency, iron availability, folate deficiency, estrogen status, and stretch/compression of nerves with fetal growth have all been implicated but much of the limited evidence is conflicting [26,27].

Because RLS/WED is common during pregnancy and may negatively impact maternal and fetal well-being, the IRLSSG Executive Committee appointed a committee to develop guidelines for the diagnosis and management of RLS/WED during pregnancy and lactation. This report summarizes the rationale and recommendations of the committee. These conclusions have been officially endorsed by the IRLSSG Executive Committee and the WED Foundation Medical Advisory Board.

Methods

A panel of experts was approved in November 2011 by the IRLSSG Executive Committee to provide recommendations on the diagnosis and treatment of RLS/WED during pregnancy and lactation. The committee was composed of the authors of this paper, with emphasis on multidisciplinary representation, including maternal–fetal medicine, clinical sleep medicine, restless legs research, pharmacology, nurse-midwifery, patient advocacy, and international sleep medicine.

The committee had monthly teleconferences for over one year and a single face-to-face meeting in June 2012. Consensus questions were agreed upon and subsequently discussed in depth. The 12 questions covered prevalence, diagnosis, treatment, and research recommendations (Supplementary Table S1) with responses elaborated in the next section.

To help integrate the medical literature into the recommendations, the committee conducted a formal literature review. Using the PubMed database, first in December 2011 and updated in February 2014, the key words “restless legs AND pregnancy” identified a total of 156 articles. Abstracts from these were reviewed to determine if the articles included information on pregnancy, and if they contained original data and/or any diagnosis or treatment recommendations. To be inclusive, no minimum number of subjects was applied. Review articles that did not focus specifically on RLS/WED during pregnancy were not retained. Based on the literature search and pearling (checking of reference sections for any articles otherwise missed) 50 original research papers were found: 24 reported prevalence, only six reported treatment data, and none reported data on lactation.

Also, in depth safety/risk reviews of potential treatments for RLS/WED during pregnancy and lactation were done. The following resources were utilized: PubMed searches for data on other uses of these treatments during pregnancy; “Drugs in Pregnancy and Lactation,” Briggs et al. [28]; “Medications and Mothers' Milk,” Hale [29]; Motherisk [30]; the Organization of Teratology Information Specialists (OTIS) [31]; LactMed [32]; and Micromedex [33]. Published safety categories for vitamins, minerals, and medications reviewed are summarized in Table S2. Of note, the United States Food and Drug Administration (FDA) is retiring its letter risk category system for pregnancy and lactation [34]. Due to numerous concerns about this system, the committee decided not to emphasize it in this review [28].

The committee considered several published rating systems for this project. The majority of these emphasize data from large, randomized clinical trials, none of which have been performed for this clinical situation and are unlikely to be done for most medications during pregnancy. However, there is a substantial literature on the efficacy of treatments for non-pregnancy RLS/WED and substantial data on the safety of some medications when used during pregnancy for another indication, e.g., carbamazepine and gabapentin for epilepsy. In addition, members of the committee have a significant combined clinical experience managing pregnancy-related RLS/WED. Thus, instead of simply stating that little to no high-level evidence exists, the committee decided to take a more integrative approach to the existing literature and our accumulated clinical experience. That said, we acknowledge and present these results as clinical guidelines, rather than high-level standards. In addition, we hope these guidelines present enough of a framework to promote further

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research in this area and thereby improve the level of evidence for the clinical management of RLS/WED during pregnancy and lactation.

Table S3 lists criteria the committee used to assess potential treatments: published evidence for effectiveness and safety for non-pregnancy RLS/WED; direct evidence of effectiveness and safety for RLS/WED during pregnancy and lactation; overall safety/risk profile during pregnancy and lactation; and expert clinical opinion. For the sections on general comments and guidelines, diagnosis, and severity/impact assessment, most, but not all of the recommendations are based on expert clinical opinion. Where there is published evidence, this is noted. For example, there are multiple studies on prevalence and clinical course but no validation studies on the IRLSSG diagnostic criteria or severity scale during pregnancy. There was a high level of committee consensus for these sections.

For the purpose of these guidelines, "refractory RLS/WED" is defined as an inadequate response to at least one non-pharmacologic intervention and iron (if ferritin <75 mcg/L), tried over an adequate period of time. "Very severe, very refractory RLS/WED" is defined as a score of >30 on the IRLSSG rating scale (IRLS) and failure to respond to at least one non-pharmacologic intervention, iron (if ferritin <75 mcg/L), and one non-opioid pharmacologic treatment. The IRLS is a 10-question scale that classifies RLS/WED as mild, moderate, severe, or very severe [35]. It is available for clinical and research use at www.irlssg.org.

After approval of the written report by all nine committee members, the guidelines were forwarded to the IRLSSG executive committee for review, to the IRLSSG membership for comment, and to the WED Foundation Medical Advisory Board for review.

Results

General comments and guidelines

Table 1 lists nine general comments and guidelines agreed upon by the committee. Because accurate diagnosis of RLS/WED is essential, this is discussed in detail in the following section and includes specific differential diagnosis considerations for pregnant women. The typical clinical course of RLS/WED during pregnancy is important for the treating provider and pregnant woman to understand, especially the symptom peak during the 3rd trimester and marked decline soon after delivery. This is discussed further below. When making treatment decisions, it is relevant to discuss the overall 3–5% risk of birth defects (1–3% major) for any pregnancy [36]. The risk of anatomic malformations is greatest for drug exposure during embryogenesis (the 1st trimester), suggesting a potential benefit for delaying medication until later in pregnancy when possible.

Table 1
RLS/WED during pregnancy and lactation – general comments and guidelines.

1) Accurate diagnosis of RLS/WED is essential.
2) RLS/WED prevalence and severity typically peak in 3rd trimester, after embryogenesis.
3) Soon after delivery there is a marked decrease in the prevalence and severity of RLS/WED.
4) With every pregnancy there is a 3–5% chance of a congenital anomaly.
5) Treatment decisions should be based on symptom severity and impact, risks vs. benefits, and individual patient considerations.
6) Consider non-medication treatments as primary.
7) For medications: use the lowest effective dose and shortest duration possible; reassess periodically; reassess after iron stores are repleted; reassess at delivery.
8) Information on adverse drug reactions should be provided with any new prescription.
9) Understanding that placebo effect is common in RLS/WED and other CNS disorders is important.

Abbreviations: CNS, central nervous system; RLS, restless legs syndrome; WED, Willis-Ekbom disease.

Because there are no high-level outcome data for the treatment of RLS/WED during pregnancy, and it is unlikely that randomized, controlled treatment trials will be done, treatment decisions should be approached in a collaborative, individualized manner between the provider and affected woman, balancing risks and benefits. In general, the committee recommends that nonpharmacologic treatments and iron be considered as primary for RLS/WED during pregnancy. When medications are chosen for refractory cases, it is recommended that the lowest effective dose and shortest duration possible be used. There should be periodic reassessment of ongoing medication need, especially after iron stores are repleted and at delivery. After delivery, symptoms often subside and volume of distribution for medications decreases. Information on potential adverse reactions should be provided for any new prescription. In addition, there are a number of free, online resources for women to access, including Motherisk [30], the Organization of Teratology Information Specialists (OTIS) [31], and LactMed [32].

Understanding placebo effect is important since there is an approximate 20–40% placebo-response rate in blinded studies for non-pregnancy RLS/WED [37]. This rate is typical for central nervous system (CNS) disorders, including Parkinson disease, and may be due to up-regulation of brain dopamine in response to the expectation of improvement [37,38]. Therefore, starting with safer nonpharmacologic treatments may produce good results even though the level of evidence for those treatments in non-pregnancy RLS/WED is lower than for some medications.

These guidelines are not inclusive of all proper approaches to care or exclusive of others. The ultimate decision regarding treatment is an individual decision between a woman and her provider, reflecting specific circumstances, preferences, and risks for that patient. These guidelines are based on data available at the time of this review. Practitioners and patients should be vigilant for further research that may alter these guidelines. It should be noted that currently only three treatments have specific approval for RLS/WED by both the United States FDA and European Medicines Agency (EMA) (ropinirole, pramipexole, rotigotine patch) with FDA approval for one more (gabapentin enacarbil). Thus, all other treatments are considered "off-label."

Diagnosis of RLS/WED during pregnancy

Diagnostic criteria and differential diagnosis

Accurate diagnosis of RLS/WED is essential. The IRLSSG RLS/WED diagnostic criteria (2014) are recommended, including consideration of differential diagnosis.

For pregnancy-related RLS/WED, the literature supports use of the same criteria used for the diagnosis of non-pregnancy RLS/WED (Table S4) [39]. All recent studies of RLS/WED during pregnancy used IRLSSG criteria and there has been no evidence to indicate pregnancy-related RLS/WED should be diagnosed differently. Furthermore, research has emphasized the similarity of pregnancy-related RLS/WED to idiopathic RLS/WED, based on: 1) the high rate of positive family history for RLS/WED in pregnant women with RLS/WED [1,5,40]; 2) a four-fold increased risk of developing RLS/WED when not pregnant if new-onset RLS/WED occurred during pregnancy [41]; and 3) pregnancy-related RLS/WED as a characteristic feature of familial RLS/WED [42]. Considering pregnancy as an exacerbating factor for RLS/WED in those with a genetic diathesis for RLS/WED moves beyond a simplistic "secondary" construct of RLS/WED during pregnancy [41,43,44].

Consideration of all five RLS/WED diagnostic criteria, including differential diagnosis, greatly enhances specificity of diagnosis and limits misdiagnosis [39]. About 40% of individuals without RLS/WED will report some urge to move their legs at rest [45]. Based on studies that have used structured diagnostic interviews, fulfilling diagnostic criteria 3 (relief with movement) and 4 (worse night/evening) improves specificity for RLS/WED to about 70% [45–47]. However, differentiating RLS/WED from positional discomfort and leg cramps improves specificity to 94%, highlighting the importance of differential diagnosis [46]. Table 2 lists "mimics" of RLS/WED [45,48]. The committee considers the most important during pregnancy as: leg cramps, positional discomfort, venous stasis, leg edema, and compression or stretch neuropathies [49].

While it is imperative that RLS/WED symptoms not be "solely accounted for" as symptoms primary to another condition, it should also be recognized that any of these conditions can co-occur in someone who has RLS/WED, including leg cramps or neuropathy. This requires attention to each possible condition in the diagnostic process and the assessment of impact [45].

Severity and impact assessment

Symptom severity and impact, as assessed by the clinician and the patient, are important to consider. For mild cases, simple reassurance may be sufficient.

There is a wide spectrum of severity and impact in RLS/WED, from mild, nuisance symptoms to profound disruption of sleep, mood, and daytime function [50,51]. The 2014 revision of the IRLSSG diagnostic criteria defines clinically significant RLS/WED as causing "significant distress or impairment in social, occupational, educational, or other important areas of functioning by its impact on sleep, mood, cognition, health, daily activities, behavior, or energy/vitality" (Table S4). For severity of symptoms, "at least twice a week and moderate-to-severe distress" are commonly considered for classification of moderate-to-severe RLS/WED in research studies [52]. In a recent study of women with RLS/WED during pregnancy, more than half (53.5%) reported severe or very severe RLS/WED symptoms, based on the IRLS [10].

Prevalence and clinical course of RLS/WED during pregnancy

Twenty-four studies were found that address the prevalence of RLS/WED during pregnancy (Table S5). A wide prevalence range, from 2.9 to 34% has been reported. The lowest prevalence of 2.9 was in an Asian population [53], where lower general population rates have been found [54]. Potential sources of variability other than geographic and ethnic factors include diagnostic criteria used, ascertainment methods, rigorous exclusion of "mimics," and phase(s) of pregnancy assessed. Use of the newest version of the IRLSSG diagnostic criteria [39] and careful application of differential diagnosis (Table 2), are likely to result in a prevalence range of approximately 15–25% for Western countries but lower for some Asian countries [54]. However, the majority of current studies indicate a two to three fold increased prevalence of RLS/WED in pregnant women compared to non-pregnant individuals in similar geographic/ethnic populations. Most RLS/WED during pregnancy is of new onset. Studies indicate that preexisting RLS/WED accounts for 9.9–33% of cases during pregnancy [5,10,11,14,55].

The prevalence and severity of RLS/WED has been found to progressively increase over the course of pregnancy in most studies, with a peak around the seventh to eighth month and stability or a slight decrease in the last month of pregnancy [3,14,56–59]. There is a clear and profound drop in RLS/WED symptoms around delivery, with complete resolution of symptoms for approximately 70% of affected women and a significant decrease in severity for the remainder [2,13,14,59]. For women with new onset of RLS/WED during pregnancy, the resolution rate appears to exceed 90% [41,55]. However, for women who experience the transient form of RLS/WED during pregnancy, there is a significant four-fold increased rate of subsequently developing RLS/WED independent of pregnancy [41].

Table 2
Differential diagnosis of RLS/WED during pregnancy.

Common mimics
Leg cramps
Positional discomfort
Venous stasis
Leg edema
Compression and stretch neuropathies
Sore leg muscles
Ligament sprain/tendon strain
Positional ischemia (numbness)
Dermatitis
Bruises
Less common mimics
Arthritis
Other orthopedic disorders
Peripheral neuropathy
Radiculopathy
Myelopathy
Myopathy
Fibromyalgia
Complex regional pain syndrome
Drug-induced akathisia
Sickle cell disease

Abbreviations: RLS, restless legs syndrome; WED, Willis-Ekbom disease.

Evaluation of treatments for RLS/WED during pregnancy and lactation

Treatments reviewed

Table 3 lists the 48 treatments in nine different categories that were reviewed and rated. Rather than review only the most common treatments for non-pregnancy RLS/WED, a broad approach was taken to include treatments with modest evidence for efficacy in non-pregnancy RLS/WED but better known safety profiles during pregnancy. The committee used the five levels listed in Table S3 to rate each treatment. Although only six studies have looked directly at treatments for RLS/WED during pregnancy, the committee agreed, based on clinical experience, that treatments for non-pregnancy RLS/WED are likely to be effective for RLS/WED during pregnancy. The following treatments were reviewed but not rated due to insufficient evidence for efficacy in non-pregnancy RLS/WED: forehead wrapping, injection of Morton neuroma, L-tyrosine, sour cherry extract, rifaxmin for small intestinal bacterial overgrowth, amantadine, diazepam, levorphanol, botulinum toxin, and deep brain stimulation.

Nonpharmacologic treatments

Moderate-intensity exercise, yoga, massage, pneumatic compression devices, treating obstructive sleep apnea, and avoidance of aggravating factors may be considered for the treatment of RLS/WED during pregnancy and lactation.

Fifteen different nonpharmacologic treatments were reviewed (Table 3). While safety issues during pregnancy and lactation were not a major concern for most of the nonpharmacologic treatments, efficacy data in non-pregnancy RLS/WED were too limited for all but six to be recommended for treatment of RLS/WED during pregnancy and lactation (Table 3).

Efforts to avoid aggravating factors for RLS/WED are suggested when possible. Table 4 lists known and suspected exacerbating factors. Iron deficiency and serotonergic antidepressants are

Table 3
Consensus ratings for treatments of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation.

Treatment	Pregnancy	Lactation	Safety concern	Efficacy concern	Comments
Nonpharmacologic					
Acupuncture	3	3		x	
Avoid aggravating factors	Yes	Yes			See Table 4
Cognitive-behavioral	3	3		x	
Exercise – moderate	2	2			Avoid pain, dehydration, abdominal trauma, late evening; get OB provider approval
Exercise – vigorous	4	3–4	x	x	If exercise is painful, it may aggravate RLS/WED
Hypnosis	3	3		x	
Massage	2	2			Avoid vigorous/deep or if history DVT/clotting disorder
Meditation/music/prayer	3	3		x	
Mental activity	3	3		x	
Near-infrared therapy	3	3	x	x	Nitric oxide is generated and produces vasodilation
Pneumatic devices	2	2			Appear safe, effective
Sexual activity	3	3		x	
Treat OSA	2	2			
Vibration	3	3		x	
Yoga	2	2			Same as moderate exercise?
Nutraceuticals					
Chinese herbal	3	3	x	x	
Valerian	4	4	x	x	Not proven safe during pregnancy; diazepam-like effects
Vitamins and minerals					
Folate	3	3		x	Efficacy not safety issues
Iron – oral	2	2			If ferritin <75 may benefit; if <30 likely to benefit
Iron – intravenous	2[a]	3			If ferritin <30 and failure of oral iron;
Magnesium	4	4		x	Efficacy not safety issues
Vitamin C	3	3	x	x	Preterm labor/fetal loss may be increased
Vitamin D	3	3	x	x	High doses teratogenic in animals
Vitamin E	3	3	x	x	Doses above minimum daily allowance not recommended
Alpha-2-delta ligands					
Gabapentin	3	2			↓ synaptogenesis in rats; unresolved issue of generalizability to human pregnancy
Gabapentin enacarbil	3	3			Very limited data
Pregabalin	3	3			Very limited data
Benzodiazepines|BZRA					For hyperarousal/sleep disturbance component of RLS/WED
Clonazepam	2[a]	2			Limit to 0.25–1 mg in the evening
Eszopiclone	4	4	x		No data
Temazepam	4/5	4	xx		Fetal loss with diphenhydramine; FDA X category
Zolpidem	4	4	x		Concerns about sedation/amnesia, parasomnias/sleep-related eating
Dopaminergics					Inhibit prolactin and can diminish breast milk production;
Bromocriptine	4	5	x		Ergot; fibrotic reaction risk for all three ergots
Cabergoline	4	5	x		Ergot
Carbidopa/levodopa	2	3			Not with benserazide (may affect bones in children)
Pergolide	4	5	x		Ergot
Pramipexole	3	3			
Ropinirole	3	3			
Rotigotine	3	3			
Opioids					If severe, refractory; lowest dose & duration possible
Codeine	4	3	x		
Hydrocodone	4	3			
Methadone	3	3	x		Neonatal withdrawal & sudden infant death syndrome risks
Oxycodone	2[a,b]	3			
Propoxyphene	5	5	xx	x	Withdrawn in US due to cardiac arrhythmia deaths
Tramadol	4	2[b]			Lesser efficacy than other opioids
Other					
Clonidine	4	4		x	Not that effective
Trazodone	3	3			0.6% of maternal dose to infant; helps sleep without worsening PLMS
Carbamazepine	4	4	x	x	Not that effective; associated with ↑ major malformations
If comorbid depression					
Bupropion	2	2			Lowest effective dose; caution if premature/ill neonate Most other antidepressants may aggravate RLS/WED and/or PLMS

BZRA: benzodiazepines/benzodiazepine receptor agonist; DVT: deep vein thrombosis; FDA: US Food and Drug Administration; OB: obstetrician; OSA: obstructive sleep apnea; PLMS: periodic limb movements in sleep; RLS: restless legs syndrome; WED: Willis-Ekbom disease.
Ratings: 1) Recommended (high level of evidence for safety/effectiveness); 2) May be considered (evidence for safety/effectiveness); 3) Insufficient evidence to reach consensus; 4) Probably should not be considered (evidence for risk/ineffectiveness); 5) Not recommended (high level of evidence for risk/ineffectiveness).
The following treatments were reviewed but not rated due to insufficient evidence for efficacy in non-pregnancy RLS/WED: forehead wrapping, injection of Morton neuroma, L-tyrosine, sour cherry extract, rifaximin for small intestinal bacterial overgrowth, amantadine, diazepam, levorphanol, botulinum toxin, and deep brain stimulation.
[a] Avoid use during 1st trimester.
[b] If RLS/WED is very severe and not responsive to other treatments (see Opioids section).

discussed further in sections below. There are conflicting data on alcohol and tobacco's effects on RLS/WED [60–66]. However, all women should be counseled to avoid alcohol and tobacco during pregnancy because of other harmful effects to the mother, fetus, and newborn. Treatment of obstructive sleep apnea (OSA) is warranted for the potential aggravation of RLS/WED by OSA [67], as well as for other suspected adverse consequences of untreated OSA during pregnancy [68].

Table 4
Exacerbating factors for RLS/WED.

Known
Iron deficiency
Prolonged immobility (airplane, car, etc.)
Serotonergic antidepressants
Suspected
Sedating antihistamines
Dopamine antagonists (antiemetics, antipsychotics)
Sleep deprivation
Sleep apnea
Hypoxia
Caffeine
Tobacco
Alcohol
Pain
Peripheral neuropathy
Radiculopathy
Venous insufficiency
Inflammatory/immunological conditions

Abbreviations: RLS, restless legs syndrome; WED, Willis-Ekbom disease.

In epidemiological studies a lack of exercise has been found to be a risk factor for RLS/WED [61,62,64,66] and two randomized-controlled trials have shown benefit of exercise in non-pregnancy RLS/WED [69,70]. In the absence of contraindications, moderate-intensity physical activity is encouraged for all pregnant and postpartum women for multiple reasons, including a decreased incidence of postpartum depression [71,72]. Examples of moderate-intensity exercise are brisk walking, water aerobics, ballroom dancing, and general gardening [73]. Activities with a high risk of falling or abdominal trauma, such as horseback riding, soccer, or basketball, should be avoided during pregnancy [71,73], as should exercise too close to bedtime, which can interfere with sleep onset. Vigorous/strenuous exercise can induce pain, which may aggravate RLS/WED and interfere with sleep. The American College of Obstetrics and Gynecology advises that "previously inactive women and those with medical or obstetric complications should be evaluated before recommendations for physical activity during pregnancy are made" [71]. Similar to moderate exercise, yoga may be beneficial for RLS/WED [74,75].

Massage can be beneficial for non-pregnancy RLS/WED and may be recommended for RLS/WED during pregnancy and lactation [76–78]. Similarly, pneumatic compression devices have been reported as effective for non-pregnancy RLS/WED and may be considered during pregnancy and lactation [79–82]. Both of these techniques provide counter stimulus to the unpleasant RLS/WED sensations.

Near-infrared therapy may be of benefit for non-pregnancy RLS/WED [83,84]. However, this generates nitric oxide (which induces vasodilation) and there is very little data on the effects and safety of nitric oxide during pregnancy or breastfeeding [85]. Table 3 lists several other nonpharmacologic treatments for which efficacy data were too limited to recommend them. Anecdotally, many patients mention warm or hot baths as beneficial for RLS/WED symptoms. However, hyperthermia during pregnancy (body temperature above 101 °F (38.3 °C)) is associated with an increased risk of neural tube defects and exposure for longer than 10 min to heat sources such as hot tubs, very hot baths, or saunas should be avoided [31].

Nutraceuticals

There is insufficient evidence to recommend valerian or Chinese herbal preparations for treatment of RLS/WED during pregnancy or lactation.

Valerian for non-pregnancy RLS/WED was found to have positive benefit in a single randomized clinical trial [86]. Also, the use of traditional Chinese herbal preparations for non-pregnancy RLS/WED was recently reviewed, and some promising results were noted [87]. However, the committee considered efficacy and pregnancy-related safety data insufficient for treatment recommendation.

Vitamin/mineral supplementation

Oral iron. **Oral iron may be considered for the treatment of RLS/WED during pregnancy and lactation if serum ferritin level is <75 mcg/L.**

MRI imaging [88], brain sonography [89], cerebrospinal fluid analysis [90], autopsy data [91,92], association studies [93–96], and treatment studies [97–100] implicate iron deficiency in the pathogenesis of RLS/WED. For non-pregnancy RLS/WED, recent treatment guidelines recommend oral iron therapy if serum ferritin is <50 to 75 mcg/L [101–103]. Although there is very limited direct evidence for the benefit of iron for RLS/WED during pregnancy [44,104,105], oral iron supplements are considered safe during pregnancy and lactation with potential benefits for both mother and infant [28,30,106,107]. Maternal serum ferritin drops to about 50% at midgestation due to expanding maternal red blood cell mass, as well as growth of the fetus and placental structures [106]. For all pregnancies, oral iron in addition to that in prenatal vitamins is recommended if ferritin is <30 mcg/L [107]. Thus, the committee agreed that oral iron may be considered for RLS/WED during pregnancy and lactation if the serum ferritin level is <75 mcg/L.

Iron status should be assessed by testing hemoglobin, serum ferritin, total iron binding capacity and percent iron saturation. If serum ferritin is <75 mcg/L, then ferrous sulfate at a dose of 65 mg elemental iron, one to two times daily is recommended. Concurrent use of vitamin C and taking iron without food can increase absorption but there is some controversy over the safety of vitamin C during pregnancy [108]. Serum ferritin should be rechecked after 6–8 wk. However, it should be noted that ferritin is an acute-phase reactant and that chronic inflammation or febrile illness within 4 wk prior to testing can falsely elevate the result. Consequently, iron measures such as percent iron saturation should be considered more valid under those circumstances. Safe storage of iron is very important since iron can be fatal in overdosage, particularly for toddlers.

Intravenous (IV) iron. **IV iron may be considered for the treatment of refractory RLS/WED during the second or third trimester of pregnancy and postpartum period, if there is failure of oral iron and serum ferritin is <30 mcg/L.**

Because of the demands of pregnancy it may be difficult to attain mid-normal iron stores with oral iron. Administration of IV iron should be considered after the first trimester to allow sufficient time for a response to oral iron and other nonpharmacologic interventions, as well as to avoid administration during embryogenesis. For non-pregnancy RLS/WED, IV iron has produced mostly positive results [97,100,109,110]. In addition, three small, open-label studies have reported benefit of IV iron for pregnancy-related RLS/WED [44,104,105]. Types of IV iron and dosage regimens are discussed in the references [107,111,112]. Overall, IV iron has been safe during pregnancy but because of possible anaphylaxis it should be administered at facilities with staff who are familiar with appropriate infusion rates and management of adverse reactions [107]. Iron transports very poorly to breast milk and limited data indicate that breast milk iron levels are not increased after IV infusion [29].

Magnesium, folate, vitamins C/D/E. **There is insufficient evidence to recommend magnesium, folate, vitamin C, vitamin D, or vitamin E for treatment of RLS/WED during pregnancy or lactation.**

While there is considerable evidence for the safety of magnesium and folate during pregnancy, there is little evidence for a role of either in the treatment of pregnancy- or non-pregnancy-related

RLS/WED. Magnesium levels are not significantly different for women with RLS/WED during pregnancy than in controls [113,114]. An open-label study of oral magnesium in non-pregnancy RLS/WED showed benefit but a blinded, placebo-controlled study did not [115,116]. However, a single case report of IV magnesium given for preterm labor indicated benefit for RLS/WED [117]. Lower serum folate was found in pregnant women with RLS/WED but this was not confirmed in a larger study [20,118]. A small study ($N = 21$) showed a lower prevalence of RLS/WED in pregnant women on 5 mg of supplemental folate daily compared to women who were not [119]. This study was done prior to routine dietary supplementation with folate in the US to prevent neural tube defects. Interestingly, folate deficiency can adversely affect dopamine production based on its role in tyrosine hydroxylase function [120]. There is insufficient evidence for benefit of vitamin C, vitamin D, or vitamin E for RLS/WED and some concern for harm during pregnancy at doses above the recommended daily allowance (RDA) [108,121–124].

Benzodiazepines/benzodiazepine receptor agonists (BZ/BZRA)

Low-dose clonazepam may be considered for the treatment of refractory RLS/WED during the 2nd and 3rd trimester of pregnancy and during lactation (0.25 to 1 mg in the evening). Concurrent use with diphenhydramine or anticonvulsants should be avoided during pregnancy.

Clonazepam is considered a secondary or adjunctive treatment for non-pregnancy RLS/WED [102,103]. It reduces arousals from sleep and may also reduce sensory symptoms of RLS/WED [125–127]. Although clonazepam does not appear to have a significant teratogenic risk, a conservative approach is to avoid it during the first trimester of pregnancy [28,128,129]. Early human data suggested an increased risk for orofacial clefts with benzodiazepines, leading to category D FDA ratings. However, this or increased risk for other congenital malformations were not confirmed by subsequent studies [130]. Specific data about the safety of clonazepam during pregnancy has been reassuring, unless it is used with anticonvulsants [128,129,131,132]. Also, concurrent use with diphenhydramine during pregnancy should be avoided due to possible increased fetal mortality when temazepam and diphenhydramine are combined [31,133]. Limiting the dose to a range of 0.25–1 mg in the evening reduces the risk of maternal and infant sedation.

While an early case study reported sedation and periodic breathing in a newborn (maternal clonazepam dose not reported) [134], subsequent case series have been reassuring reporting a lack of infant sedation or withdrawal [129,135–137]. These include a group of 11 breastfeeding mothers on a dosage of 0.25–2 mg clonazepam daily, for which 10 of 11 infants had no measurable serum concentration of clonazepam and none of the infants had any reported side effects [137]. Nonetheless, caution when initiating treatment, avoidance of combination with other CNS depressants including alcohol, and careful observation of the infant are warranted [135]. If an infant is born prematurely or is ill, then additional caution is recommended.

Eszopiclone and zolpidem were rated "probably should not be considered" during pregnancy due to limited data, especially related to safety concerns. Both are BZRAs approved for the treatment of insomnia but there is very little literature on their use during pregnancy in general [28] or for their effect on sleep disturbance associated with RLS/WED. Temazepam is a BZ that is classified "X" during pregnancy by the FDA (Table S2) because of animal data and a case report that indicate increased fetal mortality when combined with diphenhydramine [133]. All three were rated "probably should not be considered" during lactation, because of greater maternal sedation than with clonazepam and also the possibility of amnestic behaviors with BZRAs [138].

Alpha-2-delta ligands

Gabapentin may be considered for the treatment of refractory RLS/WED during lactation (300 to 900 mg in the evening or at night).

Gabapentin enacarbil, gabapentin, and pregabalin are first-line medications for the treatment of chronic non-pregnancy RLS/WED [101–103,139,140]. However, safety data on gabapentin enacarbil and pregabalin during pregnancy are so sparse the committee rated these as "insufficient evidence to reach consensus." Initially, gabapentin was rated "may be considered" for use during pregnancy based on safety data from the epilepsy literature and a previous recommendation on use for RLS/WED during pregnancy [141–145]. However, this was changed to "insufficient evidence to reach consensus" based on very high dose intraperitoneal administration of gabapentin in mice (400 mg/kg) being associated with impaired synaptogenesis at a time of development corresponding to the last trimester of pregnancy in humans [146]. Unfortunately, a study of more typical doses (10–40 mg/kg) remains to be done (personal communication, Dr. Cagla Eroglu, 10/18/2012). These animal data should be tempered by observations in humans [141–145], which include a study showing no effect on head circumference for 56 newborns exposed to gabapentin monotherapy during pregnancy [136]. Although gabapentin is not considered a hepatic enzyme inducer, it has been associated with lower mean serum folate levels. Consequently, folic acid supplementation of 4 mg per day is recommended during pregnancy to potentially reduce the risk of neural tube defects [147,148].

Gabapentin does enter breast milk but the infant is estimated to receive only 1–4% of the maternal weight-adjusted dose and no adverse effects were observed in neonates [149–151]. Caution regarding maternal sedation is recommended when initiating treatment. Data on gabapentin enacarbil and pregabalin during lactation were insufficient to recommend these [28,29].

Dopaminergics

Carbidopa/levodopa may be considered for the treatment of refractory RLS/WED during pregnancy (25/100 to 50/200 mg extended release in the evening or at night). Combination of levodopa with benserazide should be avoided. Dopaminergics inhibit lactation.

Dopaminergics are first-line medications for the treatment of non-pregnancy RLS/WED [101–103,139]. Overall, there is less evidence for the efficacy of carbidopa/levodopa than for pramipexole, ropinirole, and rotigotine, but in pregnancy there is more safety data for carbidopa/levodopa. Use of carbidopa/levodopa during pregnancy has been reported for 18 cases of Parkinson or Segawa disease and 38 cases of RLS/WED, without evidence for major malformations or other adverse outcomes [152–155]. The combination of levodopa with benserazide should be avoided due to a possible adverse effect on bone development [28,85]. It is recommended that carbidopa/levodopa be limited to a total daily dose of no more than 50/200 mg to reduce the risk of augmentation and other adverse effects [156]. Immediate-release carbidopa/levodopa may also be considered, although the elimination half-life is short (approximately 1.5 h). For both release forms, food delays absorption and protein limits maximal absorption. Nausea is more common with the immediate-release form.

Because of limited safety data on pramipexole, ropinirole, and rotigotine during pregnancy [28,154,157], the committee rated these as "insufficient evidence to reach consensus." Although there is extensive literature on the safety of cabergoline and

bromocriptine during the first trimester of pregnancy when used for hyperprolactinemia, the use of these ergots and the ergot pergolide should be avoided for RLS/WED during pregnancy due to the risk of fibrotic reactions [158].

Dopaminergics are inhibitors of prolactin and reduce breast milk production in a dose–response fashion [28,29]. However, if carbidopa/levodopa is used during pregnancy, prolactin levels rebound quickly after discontinuation and lactation can be established [28].

Opioids

Low-dose oxycodone may be considered after the 1st trimester for the treatment of very severe, very refractory RLS/WED during pregnancy. Low-dose tramadol may be considered for the treatment of very severe, very refractory RLS/WED during lactation.

Opioids are efficacious for non-pregnancy RLS/WED, especially severe cases [101–103,159]. The best evidence is for oxycodone [159]. Escalation of opioid dosage is uncommon and dependence is infrequent in long-term use for RLS/WED [160,161]. There is extensive medical literature on opioids during pregnancy for pain management and heroin addiction. The committee discussed at length the pros and cons of including any opioids in the treatment recommendations. Because RLS/WED can be refractory to all other treatments and there is substantial literature on risks vs. benefits of opioids during pregnancy, it was considered reasonable to include detailed review of opioids for very severe, very refractory cases.

A recent, large study found an increased risk of birth defects, including congenital heart disease, in infants exposed to opioid analgesics during the 1st trimester [162], prompting reconsideration of the risk vs. benefit of these medications early in pregnancy [163–165]. In contrast, another recent study found no increase in congenital malformation rate or survival rate in codeine-exposed infants [166].

Another concern with use of opioids is sedative effect. In particular, the occurrence of the ultra-fast metabolism genetic variant CYP2D6 can result in overdose-like reactions in some individuals who take typical doses [167]. This variant affects about 3% of northern Europeans, 5–10% of southern Europeans, 1–2% of Asians, and 10–30% of individuals from Arabian and northeast African countries [168]. However, it appears that oxycodone is unlikely to result in this reaction [169,170]. In addition to affecting the mother, opioids can result in sedation of the breastfed infant [171–173].

Neonatal abstinence syndrome or neonatal opioid withdrawal syndrome is a serious condition characterized by a constellation of symptoms exhibited by the neonate as he/she withdraws from an opioid used regularly by the mother during pregnancy [174]. Symptoms have been described in 60–80% of newborns exposed to heroin or methadone [175]; however, it is not clear how often this occurs with low-dose or intermittent use. If any opioids are used during pregnancy, it is prudent to communicate this information to the newborn care provider.

In addition, maternal methadone use has been linked to subsequent sudden infant death syndrome (SIDS) in offspring [176]. However, at least some of this relationship could be mediated by other potential confounding factors such as tobacco use, prenatal care, prematurity, low birth weight, and socioeconomic status. Dose may also be important. A case–control study of 239 infants who died of SIDS found no association between maternal recreational drug use and SIDS [177]. Of note, among opioid-exposed neonates, the risk of SIDS has been shown to relate to the severity of drug withdrawal, which correlates with the degree of maternal drug use in many studies [176].

Taking into account all of these factors, the committee limited the recommendation of opioid treatment during pregnancy to low-dose oxycodone in the extremely rare instance of very severe, very refractory RLS/WED during the 2nd or 3rd trimester. The committee defined "very severe, very refractory" RLS/WED as a score of >30 on the IRLS and failure to respond to at least one non-pharmacologic intervention, iron (if ferritin <75 mcg/L), and one non-opioid pharmacologic treatment. Low-dose oxycodone was defined as 5–20 mg/day. Formulations combining oxycodone with acetaminophen, aspirin, or ibuprofen should be avoided since the additional ingredient may be associated with risk during pregnancy [178]. As noted in the general recommendations, the lowest effective dose should be used for the shortest duration possible.

Tramadol is a weak mu-receptor agonist with low abuse potential, for which there is some evidence of efficacy in RLS/WED [101–103,179]. Its general use in pregnancy and lactation has recently been reviewed, with the conclusion that it "appears unlikely to cause harm to healthy term infants" [180]. A short-term study of 75 breastfeeding mothers found a combined relative infant dose of only 2.88% and, in contrast to oxycodone, no evidence for adverse effects in the infants [171,172,181]. Analysis of poor and extensive CYP2D6 metabolizers did not raise concern [182]. Dosage for RLS/WED during lactation should be limited to 50–100 mg daily, with caution when initiating treatment, avoidance of combination with other CNS depressants including alcohol, and careful observation of the infant. Data are insufficient for premature or ill infants.

Other medications

No other medications were found for which there was sufficient evidence to recommend for the treatment of RLS/WED during pregnancy or lactation.

Trazodone and clonidine were reviewed in detail. Neither has been proven to be effective for RLS/WED. While there is some evidence for use of trazodone to treat insomnia in depression, there is limited evidence for the treatment of insomnia in the non-depressed population, although such use is common in clinical practice [183–185]. A small study found limited efficacy of clonidine for RLS/WED [186]. Neither has been associated with significant problems during pregnancy, although data are limited [28,187,188]. Only about 0.6% of the maternal dose of trazodone passes into breast milk, whereas larger amounts of clonidine are found in breast milk [28,29,189]. Interestingly, a recent randomized clinical trial of insomnia treated with trazodone in the third trimester of pregnancy found reduced postpartum depression symptoms [190].

The low efficacy of carbamazepine for RLS/WED resulted in a "probably should not be considered" rating during pregnancy and lactation. In addition, carbamazepine use during pregnancy is associated with an increased risk of neural tube defects [101,191].

Comorbid depression

Treatment of depressive disorders is important during pregnancy and lactation due to a substantial increase in pregnancy complications and suicide risk with untreated depression. Depressive disorders are commonly comorbid with RLS/WED and treatment of RLS/WED can improve depressive symptoms. Bupropion may be better tolerated by individuals with RLS/WED than selective serotonin reuptake inhibitors (SSRIs).

A review of the management of depression during pregnancy and lactation, including the risks and benefits of antidepressants, is beyond the scope of this paper. However, recent publications are available for clinical guidance [192,193]. Nonetheless, a few

important points are worth highlighting for women with RLS/WED during pregnancy and lactation.

Depression is prevalent during pregnancy occurring in 7–13% of pregnant women [194]. It is a serious medical illness, associated with low birth weight, higher rates of miscarriage, preterm delivery, preeclampsia, and substance abuse, as well as increased risk of neonaticide and maternal suicide [192,195–197]. Interestingly, depressive disorders are very common in non-pregnancy RLS/WED (2.6–4.7 times increased risk), correlate with severity of RLS/WED, and also improve with treatment of RLS/WED [198–205]. Limited data suggest this increased risk might also occur during pregnancy for women with RLS/WED, especially for women with pre-pregnancy RLS/WED [20,21].

For non-pregnancy RLS/WED, treatment algorithms favor the use of the dopamine-norepinephrine agonist, bupropion, over the SSRIs [101,206]. SSRIs can aggravate RLS/WED sensory symptoms and periodic leg movements in sleep [207–209], whereas bupropion does not [208,210,211]. However, during pregnancy, bupropion use in the first trimester was found to be associated with an increase in congenital left heart outflow tract heart defects in a single study [212]. On the other hand, three other studies did not find increased risk and the overall magnitude of risk in the one study was small: 0.82/1000 vs. 2.1/1000 [187,212–214]. Another study raised concern about increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring of women exposed to bupropion during the second trimester [215]. However, the lack of adjustment for tobacco use and a very small number in the subgroup analysis significantly limit this finding, especially since smoking is described as a risk factor for ADHD and some of the women were likely taking bupropion for smoking cessation [216,217]. A single case has been reported of a seizure in an infant coinciding with bupropion use during breastfeeding [218]. On the other hand, a breastfeeding infant is calculated to get only about 2% of the weight-adjusted maternal dose [219].

Taking into account all these factors, including the risks of inadequately treated depression, the committee agreed that bupropion may be considered for use during pregnancy and lactation for women with RLS/WED who have depressive disorders, after discussion of alternative therapies such as counseling and discussion of the potential risks of bupropion. When possible, use should be avoided during the first trimester. Also, a minimum effective dose should be chosen. Data are insufficient regarding bupropion use during breastfeeding of premature or ill infants, who may be more prone to seizures.

Considerations for women with preexisting RLS/WED

Pre-pregnancy counseling is recommended for women with preexisting RLS/WED to address the risk/benefit during pregnancy of any current treatments, adequacy of iron stores, and potential treatments during pregnancy.

This is similar to the approach for women with seizure disorders [220]. Discussion of the typical course of RLS/WED during pregnancy and review of nonpharmacologic treatments is suggested, with particular emphasis on moderate exercise and avoidance of aggravating factors for RLS/WED (Table 4). Because of the expected 50%

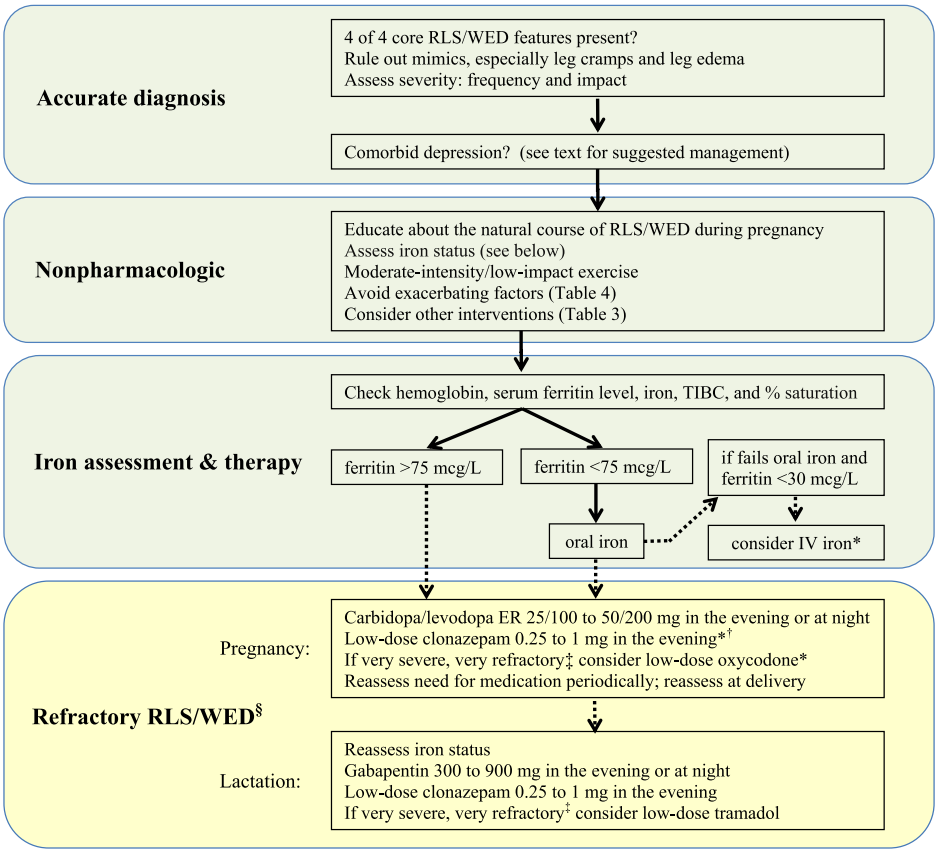

Fig. 1. Algorithm for the diagnosis and management of RLS/WED during pregnancy and lactation. Dotted arrows: proceed only after assessment of severity, risks, and benefits by provider and patient. *After 1st trimester. †Avoid concurrent use with diphenhydramine or anticonvulsants. §Refractory: an inadequate response to at least one nonpharmacologic intervention and iron (if ferritin <75 mcg/L), tried over an adequate period of time. ‡Very severe, very refractory: a score of >30 on the International RLS Study Group rating scale and failure to respond to at least one nonpharmacologic treatment, iron (if ferritin <75 mcg/L), and one non-opioid pharmacologic treatment. Abbreviations: ER, extended release; IV, intravenous; % saturation, percent iron saturation; RLS, restless legs syndrome; TIBC, total iron binding capacity; WED, Willis-Ekbom disease.

drop in maternal serum ferritin during pregnancy [106], assessment of iron stores is recommended (see iron section above), with maintenance of serum ferritin above 75 mcg/L throughout pregnancy. For women with low iron stores and failure to respond to oral iron, administration of IV iron prior to pregnancy may be considered to replete iron stores and potentially reduce the need for RLS/WED medication during pregnancy [44]. Until there are additional safety data, the committee suggests that pramipexole, ropinirole, rotigotine, gabapentin enacarbil, pregabalin, and gabapentin be tapered prior to a planned pregnancy for women with RLS/WED or at the time pregnancy is confirmed for unplanned pregnancies.

Treatment algorithm

The treatment algorithm (Fig. 1), integrates the committee's recommendations in a simplified format. The top three sections outline the primary approach: accurate diagnosis, non-pharmacologic therapy, and iron assessment/therapy. For refractory RLS/WED during pregnancy and lactation, the bottom section outlines potential medications.

Conclusions

These guidelines represent the first comprehensive approach to the diagnosis and treatment of RLS/WED during pregnancy and lactation. Based on the current medical literature and expert clinical opinion, they are intended to aid clinicians in addressing the concerns of women affected by this common condition during pregnancy.

Conflicts of interest

This was not an industry supported project. M. Manconi was an investigator in a research study in which Vifor Pharma provided iron carboxymaltose but had no other role in the study. C. Trenkwalder is a consultant to Desitin, UCB Pharma, and Mundipharma; is on an advisory board of Novartis; and has received speaker honoraria from Desitin and GlaxoSmithKline. A. Walters is a consultant to and on an advisory board of UCB Pharma and Mundipharma; has received grants from UCB Pharma and Mundipharma; and has received speaker honoraria from Mundipharma. The other authors report no personal financial interests associated with the development, testing, manufacture or marketing of any drug or product described in this manuscript.

Practice points

1) RLS/WED is common during pregnancy and can result in significant clinical distress.
2) Symptoms typically peak in the 3rd trimester and decrease markedly soon after delivery.
3) Non-medication treatments should be considered primary. These include reassurance, low-impact exercise, and avoidance of exacerbating factors.
4) Iron status should be assessed by checking hemoglobin, serum ferritin, iron, total iron binding capacity (TIBC) and percent iron saturation.
5) Oral iron may be considered for women with serum ferritin levels less than 75 mcg/L.
6) Consideration of medication should be reserved for cases refractory to more conservative treatments. Medication should be used at the lowest effective dose and for the shortest duration possible.

Research agenda

In the future we need:

1) Genomewide association studies in large populations of pregnant women, which might confirm gene associations already known in non-pregnancy RLS/WED or identify new associations.
2) Prospective investigation aimed to define the potential impact of RLS/WED during pregnancy on fetal/newborn health and on maternal depression.
3) Development of validated severity criteria to identify pregnant women with RLS/WED for whom treatment with medication should be considered.
4) Longitudinal polysomnographic studies during pregnancy and puerperium to delineate the frequency of periodic limb movements and their relationship to other RLS/WED symptoms, including sleep disruption.
5) Randomized, placebo-controlled studies during pregnancy to explore the efficacy and safety of treatments used in non-pregnancy RLS/WED, especially iron and dopamine agonists.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2014.10.009.

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