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ORIGINAL RESEARCH

Development of a Stepped-Care Pathway for Managing Willis-Ekbom Disease/Restless Legs Syndrome During Pregnancy: A Best Evidence Synthesis

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Background and Aims: Pregnancy-related Willis-Ekbom disease/restless legs syndrome (WED/RLS) is associated with adverse maternal outcomes, such as preeclampsia, an elevated risk of cesarean delivery, and perinatal depression. Although several guidelines address the management of WED/RLS, most target the general population, with only limited and fragmented recommendations specifically for pregnant women. Furthermore, existing guidelines vary substantially in quality and evidentiary basis, hindering the development of a clear, actionable care pathway for gestational WED/RLS. This study therefore aimed to systematically retrieve, appraise, and synthesize available evidence on the management of WED/RLS during pregnancy to inform obstetric clinical care practice.

Methods: Evidence retrieval was guided by the 6S evidence pyramid, using a top-down approach to identify relevant guidelines, expert consensus statements, evidence summaries, clinical decision aids, systematic reviews, and meta-analyses. Literature published from database inception to December 2025 was included. Four reviewers independently screened and appraised the evidence. Evidence extraction and synthesis were subsequently conducted by two sleep medicine physicians using the JBI Grading of Evidence and Recommendation System.

Results: From nine included publications (three guidelines, two evidence summaries, three clinical decision aids, and one algorithm), 27 practice recommendations were formulated. These span five core domains: (1) avoidance and management of aggravating factors, (2) preconception counselling and health education, (3) iron supplementation, (4) non-pharmacological treatments, and (5) pharmacological treatments. Together, they outline a stepped-care management strategy for gestational WED/RLS, progressing from pre-pregnancy prevention, through post-diagnosis prioritization of non-pharmacological interventions alongside iron repletion, to pharmacological therapy—restricted to the lowest effective dose and shortest necessary duration in the second or third trimester—only for severe, refractory cases.

Conclusion: This study proposes a stepped-care pathway for managing pregnancy-related WED/RLS. Implementation should align recommendations with patient preferences and locally available healthcare resources to ensure contextual applicability and clinical utility.

Keywords: iron supplementation, RLS/WED, clinical practice guidelines, pregnant, sleep disorder, summary of evidence

Background

Willis-Ekbom disease (WED), also known as restless legs syndrome (RLS),[1] is a chronic progressive movement disorder.[2] Its characteristic features include distressing paresthesia—often described as creeping, tugging, or pulling sensations in the lower

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extremities—accompanied by an irresistible urge to move.[1,3] Symptoms display diurnal variation and are temporarily relieved by movement.[4] Pregnant women face a two- to three-fold increased risk of WED/RLS compared with the general population.[5] Prevalence estimates during pregnancy vary by region: 30% in the Eastern Mediterranean, 22% in Europe, 20% in the Americas, and 14% in the Western Pacific.[6] Pregnancy-related WED/RLS is linked to maternal complications, including hypertensive disorders of pregnancy (eg., preeclampsia),[6] depression, and increased risk of cesarean delivery,[7] as well as adverse neonatal outcomes such as intrauterine growth restriction and lower birth weight.[6] Effective management is therefore critical for both maternal and fetal health.

Pharmacological treatments, particularly dopaminergic agents, are considered first-line for WED/RLS in the general population.[5] However, medication use during pregnancy is complicated by potential maternal and fetal risks.[8]

Clinical practice guidelines (CPGs), including those from the International Restless Legs Syndrome Study Group (IRLSSG), prioritize non-pharmacological interventions (eg., reassurance, low-impact exercise) and recommend pharmacotherapy only for refractory cases at the minimal effective dose and shortest duration.[9] Other professional bodies, including the AASM[10] and the GSS,[11] have periodically updated their guidelines to include recommendations for managing WED/RLS. Although multiple CPGs exist on this topic, most are oriented toward the general population, leaving recommendations for pregnant individuals fragmented and lacking a unified framework. Moreover, considerable heterogeneity persists across guidelines, consensus statements, and clinical decision aids in terms of objectives, evaluation criteria, and specific recommendations. For example, a 2018 clinical decision aid from Switzerland recommended limiting Clonazepam to 0.5 mg/day for pregnant women with WED/RLS,[12] whereas the 2021 Chinese guidelines extended the upper limit to 1 mg/day.[13] Similarly, a 2020 evidence summary endorsed low-molecular-weight iron dextran as the preferred intravenous iron formulation,[7] while a 2016 decision aid favored Ferric Carboxymaltose for the same indication.[8] To address this gap, we conducted a systematic review to identify core intervention components, appraise evidence quality, and synthesize best practices to inform clinical management of pregnancy-related WED/RLS.

Methods

This evidence summary was developed in accordance with the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis.[14] The reporting process involved formulating the research question, systematically searching the literature, screening and critically appraising studies, summarizing and grading the evidence, and formulating practice recommendations.[15]

Problem Formulation

Guided by the PIPOST framework,[16] the clinical question—"how to effectively and safely manage WED/RLS during pregnancy"—was translated into an evidence-based inquiry. The target population (P) was pregnant women diagnosed with WED/RLS. Interventions (I) included non-pharmacological approaches, pharmacological treatments, and iron supplementation. The intended end-users, ie., healthcare professionals (P), were providers in obstetrics and sleep medicine. Outcomes (O) encompassed WED/RLS incidence, maternal sleep quality, and childbirth outcomes. Applicable settings (S) included obstetric clinics, hospital wards, and community health centers. Evidence types (T) consisted of clinical decision aids, guidelines, expert consensus statements, evidence summaries, systematic reviews, and meta-analyses.

Evidence Retrieval

Evidence retrieval followed the 6S evidence pyramid,[17] with searches conducted hierarchically from higher- to lower-level evidence sources. Primary searches targeted guideline and best-practice repositories, including BMJ Best Practice, UpToDate, the JBI EBP Database, SIGN, GIN, NGC/AHRQ, NICE, CPG Infobase, and ACPG. Comprehensive English and Chinese databases (eg., Embase, MEDLINE, CENTRAL, CNKI, CQVIP, Wanfang, and SinoMed) and professional organization websites (eg., ACOG, SOGC, and RNAO) were also searched. Reference lists of eligible studies were manually screened to minimize omissions. Literature published from database inception to December 2025 was included. The detailed search strategy is presented in Appendix 1.1 and 1.2. The search was conducted on December 10, 2025, in accordance with the PRISMA-S Checklist (Appendix 1.3).

Literature Screening and Appraisal

Inclusion and Exclusion Criteria

Literature was included if it met the following criteria: (1) the population comprised pregnant women diagnosed with WED/RLS; (2) the content addressed management strategies for pregnancy-related WED/RLS; (3) evidence types included clinical algorithms/decision aids, CPGs (including consensus-based guidelines), expert consensus statements, evidence summaries, systematic reviews, and meta-analyses; (4) the most recent versions of updated or revised guidelines were available; and (5) publications were in English or Chinese.

Literature was excluded if it consisted of (1) study protocols, drafts, or abstracts without full text; (2) materials inaccessible through available sources; (3) methodologically unsound materials (of low or critically low quality); or (4) direct translations of existing guidelines.

Literature Screening

All records were imported into EndNote X20, and duplicates were removed. Two researchers trained in biomedical literature retrieval (P-X and QQ-F) independently screened titles and abstracts against the inclusion/exclusion criteria. Disagreements were resolved through consultation with YS-H. Subsequently, the same reviewers independently extracted data using a standardized form, blinded to each other's extraction process. Extracted data included study characteristics: first author/organization, publication year, language, source, evidence type, and article theme.

Evidence Summarization and Grading

Appropriate quality appraisal tools were selected according to the type of literature included. The quality of CPGs was assessed using the AGREE II instrument.[18] Expert consensus statements were appraised using the JBI Critical Appraisal Checklist for Textual Evidence: Expert Opinion.[19] Systematic reviews were assessed with the JBI Critical Appraisal Checklist for Systematic Reviews.[20] For algorithms and clinical decision-making, quality was evaluated based on the methodological quality of the underlying source literature (eg., guidelines, consensus statements, or systematic reviews). Evidence summaries were appraised using the Revised CASE Worksheet.[21]

Quality assessments were performed independently by four reviewers (YM-W, WJ-Z, LP-Y, and FY-Z). Discrepancies were resolved through consultation with a fifth reviewer (R-C) experienced in evidence-based research. In cases of conflicting evidence, priority was given to evidence-based sources, higher-quality studies, and the most recent and authoritative publications.[22]

Development of Practice Recommendations

Two researchers trained in evidence-based medicine and possessing over ten years of clinical sleep medicine experience (FY-Z and WJ-Z) independently extracted and synthesized the evidence based on the following principles: (1) for consistent content across sources, the most specialized and concise evidence was selected; (2) for similar or complementary content, evidence was integrated into a unified statement; and (3) for conflicting evidence, priority was given to higher-quality and the most recently published evidence from authoritative evidence-based sources. Given the secondary nature of this evidence synthesis, we acknowledged the potential risk of evidence overlap and circularity—ie., different guidelines and consensus statements may draw on the same primary studies or cite one another, leading to redundant or non-independent evidence. To mitigate this, we systematically traced the reference lists of all included sources to identify shared evidentiary underpinnings. Where overlapping sources were identified, principles (1) and (2) were applied. Evidence derived exclusively from secondary sources that, after thorough tracing, could not be attributed to an independent primary study was excluded from recommendation formulation. Disagreements were resolved through discussion until consensus was reached.

The included evidence was graded using the JBI Levels of Evidence system, in which evidence is classified into Levels 1 to 5 according to study design.[22,23] Recommendations were evaluated according to the FAME (**F**easibility, **A**ppropriateness, **M**eaningfulness and **E**ffectiveness) Scale and JBI Grades of Recommendation. Through expert panel discussions, the strength of each recommendation was determined and categorized as either strong (Grade A) or weak (Grade B).[22,23]

Results

Search Results and Characteristics of Included Literatures

The database search yielded 142 records. After deduplication using EndNote, 96 records remained. After rigorous screening, nine publications were included: three CPGs, two evidence summaries, three clinical decision aids, and one algorithm. The study selection process is presented in Appendix 2. Key characteristics of the included literature, including source, evidence type, and thematic focus, are summarized in Appendix 3. Excluded records and reasons for exclusion are listed in Appendix 4.

Quality Appraisal Results

Among the three included CPGs, only one achieved standardized scores ≥60% across all six AGREE II instrument domains, warranting a Grade A recommendation.[9] The remaining two guidelines were rated Grade B.[13,24] Detailed domain-specific scores and overall appraisal results are provided in Appendix 5.

The two evidence summaries were appraised as high quality[7] and moderate quality,[25] respectively. The latter was downgraded due to "Not completely" responses to items concerning appropriate citation of recommendations, potential bias, and applicability to patients.[25] Neither evidence summary disclosed reviewer information (Appendix 6).

The two clinical decision aids[12,26] and the clinical algorithm[27] were derived from a high-quality CPG (Picchietti et al[9]) and were consequently rated as high quality (Evidence Grade A). One additional clinical decision aid[8] was based on a moderate-quality CPG (Garcia-Borreguero et al[24]) and was thus rated as moderate quality (Evidence Grade B) (Appendix 7).

Evidence Synthesis and Recommendation Formulation

Evidence was extracted and synthesized from the included literature, with key findings consolidated across five domains: "Avoidance and Management of Aggravating Factors", "Preconception Counseling and Health Education", "Iron Supplementation", "Non-Pharmacological Treatments" and "Pharmacologic Treatments". A total of 27 practice recommendations were generated, comprising 12 strong and 15 weak recommendations (see Table 1).

Table 1 Best-Practice Recommendations for the Prevention and Management of Willis-Ekbom Disease/Restless Legs Syndrome (WED/RLS) in Pregnancy

Category of Evidence	Evidence Content	Evidence Level	Recommendation Level
Avoidance and Management of Aggravating Factors	1. Limiting or avoiding the intake of caffeine, alcohol,[8] and tobacco.[12]	5c	A
	2. Treating obstructive sleep apnea when present.[12,26]	5c	A
	3. Implementing a tapering regimen for Pramipexole, Ropinirole, Rotigotine, Gabapentin Enacarbil, Pregabalin, and Gabapentin prior to planned pregnancy, or at pregnancy confirmation in unplanned pregnancies.[9]	5b	A
Preconception Counseling and Health Education	4. Informing pregnant women about the characteristic progression of WED/RLS through health education.[25]	5c	B
	5. Reviewing and reinforcing sleep hygiene rules through regular discussions with patients.[12]	5c	A
	6. Providing preconception counseling for women with preexisting WED/RLS to discuss the risks and benefits of continuing current treatments during pregnancy, assess anticipated iron status during pregnancy, and consider alternative therapeutic options for pregnancy.[9]	5c	A

(*Continued*)

Table 1 (Continued).

Category of Evidence	Evidence Content	Evidence Level	Recommendation Level
Non-Pharmacological Treatments	7. In the absence of contraindications, moderate-intensity exercise (eg., brisk walking, water aerobics, ballroom dancing, general gardening) during pregnancy is recommended. However, such exercise should be avoided close to bedtime, as it may increase physiological arousal and interfere with sleep onset. In addition, previously inactive women or those with medical or obstetric complications should undergo systematic evaluation before initiating an exercise regimen.[9]	5c	A
	8. Practicing prenatal yoga.[26]	5c	B
	9. Avoiding contact sports[7] and activities with a high risk of falls or abdominal trauma[9] to reduce the risk of exercise-related injury; and avoiding vigorous or strenuous exercise that may induce pain, exacerbate WED/RLS symptoms, and interfere with sleep.[9]	5b	A
	10. Using warm baths to relieve WED/RLS symptoms,[7,9] while limiting exposure to intense heat sources (eg., hot tubs, very hot baths, saunas) to less than 10 minutes.[9]	5b	B
	11. Considering massage for pregnancy-related WED/RLS,[9,26] except in individuals with severe coagulation disorders or a relevant history.[26]	5b	B
	12. Considering pneumatic compression devices for the treatment of WED/RLS during pregnancy.[25,26]	5c	B
	13. Utilizing gaming devices as a distraction for WED/RLS symptoms that severely impair sleep onset.[25]	5c	B
Iron Supplementation	14. Maintaining serum ferritin levels >75 mcg/L throughout pregnancy.[9]	5b	A
	15. Recommending oral iron supplementation, in addition to prenatal vitamins, during pregnancy when ferritin is <30 mcg/L and/or transferrin saturation is <20%.[7]	5b	A
	16. Fully replenishing iron stores before pregnancy in women with a history of WED/RLS.[24,25]	5b	B
	17. Recommending once- or twice-daily oral iron supplementation (preferably as ferrous sulfate 325 mg [65 mg elemental iron] per dose) during pregnancy for individuals with significant WED/RLS symptoms and serum ferritin <75 mcg/L.[7]	5c	B
	18. Considering intravenous iron (low-molecular-weight iron dextran [eg., 100 mg over one hour]) for refractory WED/RLS during the second or third trimester of pregnancy if oral iron fails and serum ferritin is <30 mcg/L,[7,9] infusions should be performed with appropriate supervision.[7]	5b	B
	19. Monitoring ferritin levels every 6–8 weeks after initiating iron supplementation.[7,12]	5c	A

(*Continued*)

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Table 1 (Continued).

Category of Evidence	Evidence Content	Evidence Level	Recommendation Level
Pharmacologic Treatments (only in Second or Third Trimester)	20. Considering low-dose nighttime Clonazepam (0.25–0.5 mg) for refractory WED/RLS in pregnancy,[7,12,13,27] it should not be combined with antihistamines or anticonvulsants.[7,27]	5b	B
	21. Considering Carbidopa/Levodopa (25/100-50/200 mg extended release nightly) for refractory WED/RLS during pregnancy, combination of Levodopa with Benserazide should be avoided.[9]	5b	B
	22. Considering low-dose Oxycodone (5–10 mg/day) for very severe, very refractory WED/RLS,[12,27] while avoiding combination formulations containing Acetaminophen, Aspirin, or Ibuprofen.[9]	5c	B
	23. Considering Bupropion at the minimum effective dose for pregnant women with WED/RLS and comorbid depression only after reviewing its risks and exploring alternative therapies (eg., counseling).[9]	5b	B
	24. Avoiding α2δ ligands for pregnancy-related WED/RLS.[24]	5b	B
	25. Contraindicating ergot-derived dopamine agonists (eg., Pergolide, Cabergoline, Bromocriptine) for WED/RLS during pregnancy.[9]	5b	A
	26. Not recommending estrogen therapy for WED/RLS during pregnancy.[8]	5c	B
	27. Periodically reassessing the need for pharmacologic treatment in refractory cases, particularly after iron repletion and at delivery.[9]	5b	A

Notes: In the "Evidence Level" column, "5b" indicates that the best-practice recommendation is derived from clinical practice guidelines or expert consensus. "5c" denotes evidence originating from bench research or a single expert opinion (here representing recommendations sourced from evidence summaries, clinical decision aids, or algorithm). In the "Recommendation Level" column, "A" indicates a strong recommendation and "B" indicates a weak recommendation. All recommendations regarding pharmacological management—including the use of Clonazepam, Carbidopa/Levodopa, or Oxycodone at the lowest effective dose in severe, refractory cases, and Bupropion at the lowest effective dose in patients with comorbid depression—are classified as "weak recommendations." Before initiating pharmacotherapy, obstetricians should conduct a thorough and comprehensive evaluation of the pregnant individual to fully weigh the benefit-risk ratio, with particular attention to medication safety.

Discussion

Prevention Strategies for Women at High Risk

Identified risk factors for gestational WED/RLS include pre-pregnancy history of the condition, low hemoglobin levels, excessive daytime sleepiness, and/or muscle cramps.[28] Women with such factors—especially a pre-pregnancy WED/RLS history, which raises gestational risk approximately 7.54-fold[28]—may benefit from preventive strategies outlined in the present evidence summary (Table 1). For instance, during pre-pregnancy counseling, obstetricians should assess iron status in high-risk women and discuss potential treatment options should symptoms emerge during pregnancy.[9] Patients already using dopaminergic agents (eg., Pramipexole, Ropinirole, Rotigotine) or α2δ ligands (eg., Gabapentin Enacarbil, Pregabalin, Gabapentin) are advised to gradually taper these medications prior to a planned pregnancy or upon confirmation of an unplanned pregnancy.[9] In addition, patient education regarding WED/RLS-related knowledge[25] and ongoing reinforcement of sleep hygiene practices[12] are recommended.

Growing evidence links WED/RLS with obstructive sleep apnea syndrome (OSAS) in pregnancy. Daytime fatigue and witnessed apneas—both sleep apnea symptoms—are more prevalent in pregnant women with WED/RLS,[29] and early-pregnancy snoring may predict later WED/RLS onset.[30] Notably, in clinically significant WED/RLS cases, treatment of concomitant OSAS has been shown to alleviate WED/RLS symptoms and reduce the need for pharmacotherapy in over half of cases.[31] Thus, women planning pregnancy or already pregnant with diagnosed OSAS should be referred to sleep specialists for active management to prevent WED/RLS onset or symptom worsening.[12,26] For pregnant individuals without an established OSAS diagnosis, the need for screening and diagnostic evaluation should be guided by

risk stratification. The most recent *Consensus Guideline on the Screening, Diagnosis, and Treatment of Obstructive Sleep Apnea in Pregnancy* (issued by the SASM and the SOAP) recommends BATE Algorithm-based screening exclusively for two subgroups: women with obesity (BMI ≥ 30) and those with hypertensive disorders of pregnancy or diabetes in the current or a prior pregnancy. Screening is optimally performed in the first or second trimester (6 0/7–28 6/7 weeks).[32] Pregnant women identified as high-risk or presenting with significant symptoms should undergo further diagnostic evaluation for OSAS, either via out-of-center (home) sleep apnea testing or in-laboratory polysomnography. Universal screening is not advised, largely due to concerns regarding healthcare system burden and limited access to sleep specialty resources in certain settings.[32]

Lastly, since caffeine, tobacco, and alcohol consumption may trigger or exacerbate WED/RLS symptoms in pregnancy,[33] avoidance or limitation of these substances represents a key self-management approach for affected or high-risk women.[8,12]

Non-Pharmacological Interventions as First-Line Therapy

All included sources consistently recommend non-pharmacological interventions as primary therapeutic approach for gestational WED/RLS.

Insufficient physical activity is significantly associated with an increased risk of WED/RLS,[34] whereas regular exercise appears to exert a protective effect against WED/RLS.[35] Moderate-intensity activities—such as ballroom dancing, general gardening, water aerobics, or brisk walking—are currently the preferred recommended form of exercise. Yoga has been shown to reduce muscle excitability associated with WED/RLS and promote rapid muscle relaxation.[36] Trials involving both healthy and high-risk pregnant populations suggest that yoga is safe and may improve multiple maternal and fetal outcomes;[37] thus, it is also recommended as a therapeutic option.[26] Nevertheless, previously inactive women or those with medical or obstetric complications should undergo comprehensive evaluation before initiating an exercise program.[9] Exercise should also be avoided near bedtime, as it may increase physiological arousal and delay sleep onset.[9]

Many pregnant women with WED/RLS report symptom relief through warm or hot bathing,[7,9] a finding supported by our evidence synthesis. However, exposure to intense heat sources (eg., hot tubs, very hot baths, or saunas) should be limited to less than 10 minutes,[9] as maternal hyperthermia during pregnancy (core temperature >38.3°C) has been associated with an increased risk of neural tube defects.[7,9]

In addition, massage therapy[9,26] and the use of pneumatic compression devices[25,26] may offer further symptomatic benefit for pregnancy-related WED/RLS.

Iron Status Optimization: A Cornerstone of Management

Iron supplementation is routinely recommended during pregnancy to correct iron deficiency, as stores decline due to hemodilution and increased fetal iron requirements.[38] Compared with unaffected pregnant women, those with WED/RLS exhibit significantly lower serum iron levels.[39] Disrupted iron homeostasis has also been implicated as a central mechanism in the pathophysiology of secondary WED/RLS during pregnancy.[40] Accordingly, women with a predisposition to WED/RLS should ensure adequate iron repletion prior to conception.[24]

Given the substantially increased iron demands during pregnancy,[38] iron supplementation—in addition to prenatal vitamins—is generally advised if serum ferritin is <30 mcg/L and/or transferrin saturation is <20%, even in the absence of prior WED/RLS symptoms.[7]

For pregnant women with clinically significant WED/RLS symptoms and serum ferritin levels <75 mcg/L, oral iron supplementation is recommended. Ferrous sulfate (325 mg per tablet, providing 65 mg of elemental iron) administered once or twice daily is the preferred regimen.[7] Serum ferritin should be re-assessed after approximately 6 to 8 weeks of supplementation.[7,12] Intravenous iron, such as low-molecular-weight iron dextran (eg., 100 mg infused over one hour), may be considered for refractory WED/RLS during the second or third trimester when oral iron is ineffective and serum ferritin remains <30 mcg/L.[7,9] Due to the risk of anaphylaxis, intravenous iron should be administered by trained healthcare personnel familiar with its use.[7]

Pharmacotherapy for Very Severe and Refractory Cases: A Cautious Approach

Pharmacotherapy should be reserved for severe, refractory WED/RLS cases, utilizing the lowest effective dose on an as-needed basis. To minimize the risk of congenital anomalies, initiation should be deferred until the second or third trimester.[27] This caution applies particularly to FDA Category C agents (eg., Carbidopa, Levodopa, Bupropion) and Category D agents (eg., Clonazepam, Carbamazepine).[13] In such circumstances, prescribing decisions must be grounded in a structured shared decision-making framework involving the obstetrician, sleep medicine specialist, pharmacist, and the pregnant WED/RLS patient. This process requires a comprehensive, individualized risk–benefit assessment integrating symptom severity, gestational age, potential maternal and fetal risks, and the patient's values and preferences.[41,42] Documenting this discussion in the medical record is encouraged to guarantee transparency and informed consent. Such a patient-centered, collaborative model serves as a critical pathway for balancing clinical efficacy and safety in the context of complex medication use during pregnancy, ensuring that pharmacotherapy is initiated only when the anticipated benefits clearly outweigh the potential risks.[13,41]

Clonazepam has demonstrated efficacy in promoting sleep onset and alleviating sensory symptoms of WED/RLS.[9,43] While often an adjunctive or second-line agent in non-pregnant populations,[44] substantial evidence supports its cautious use at low nocturnal doses (0.25–0.5 mg at bedtime) for refractory WED/RLS limited to the second or third trimester.[7,12,27] Although no significant teratogenic risk has been established, conservative practice advises avoidance during the first trimester.[9] Concurrent use with antihistamines or anticonvulsants during pregnancy is contraindicated.[27]

Dopamine agonists constitute first-line therapy for WED/RLS in non-pregnant patients.[45] However, among the nine reviewed literatures, only one explicitly suggests considering Carbidopa/Levodopa (25/100 to 50/200 mg extended-release in the evening or at night) for refractory pregnancy-related WED/RLS.[9] This cautious stance likely reflects limited safety data regarding its use during pregnancy,[46] as well as evidence of augmentation—a treatment-related worsening of WED/RLS symptoms—in a subset of patients.[47]

Opioid therapy during pregnancy is rarely indicated. Low-dose Oxycodone may be considered only in cases of very severe, refractory WED/RLS (defined as an IRLS score >30 with inadequate response to at least one non-pharmacological intervention, iron supplementation [when ferritin <75 mcg/L], and one non-opioid medication) after the first trimester.[9] Combination products containing Oxycodone plus Acetaminophen, Aspirin, or Ibuprofen should be avoided, as these additional agents may pose pregnancy-related risks.[9]

A Japanese study linked higher IRLS scores, including subscale scores, to depression in pregnant women, suggesting that severe WED/RLS symptoms may facilitate early detection of depression during pregnancy.[48] Given the frequent comorbidity of depression with WED/RLS, routine brief screening for depression is suggested in the clinical management of pregnant women with WED/RLS. Screening should particularly target high-risk subgroups, including those with: (1) unintended pregnancy; (2) maternal anxiety or significant life stress; (3) prior depression; and/or (4) lack of social support, interpersonal conflict, or experience of domestic violence.[49] The EPDS-3 or the PHQ-9 are recommended as screening tools;[50] those scoring above the scale cutoffs should be promptly referred to mental health professionals for further evaluation and diagnostic confirmation.[51] There is evidence that treatment of WED/RLS may alleviate depressive symptoms;[52] therefore, Bupropion at the minimum effective dose may be considered during the second or third trimester for women with comorbid WED/RLS and depression, following careful discussion of alternative therapies (eg., counseling) and potential risks associated with Bupropion use.[9]

Contextual Adaptation and Implementation Considerations

In summary, this study proposes a stepped-care pathway for the management of gestational WED/RLS, spanning prevention, health education, non-pharmacological interventions, iron supplementation, and pharmacotherapy (Figure 1). Given substantial regional variation in healthcare resources, implementation strategies should be tailored to local contexts to bridge the evidence–practice gap.[53] For instance, primary care facilities serving community-dwelling pregnant women with WED/RLS but lacking capacity to administer intravenous iron should establish timely, structured referral linkages with higher-level medical centers. In sleep specialist-scarce settings, task-shifting strategies—such as training midwives or general practitioners to deliver WED/RLS education, perform rapid screening for comorbid OSAS and depression, and offer non-pharmacological management guidance—represent a pragmatic approach to extending service coverage under resource constraints.

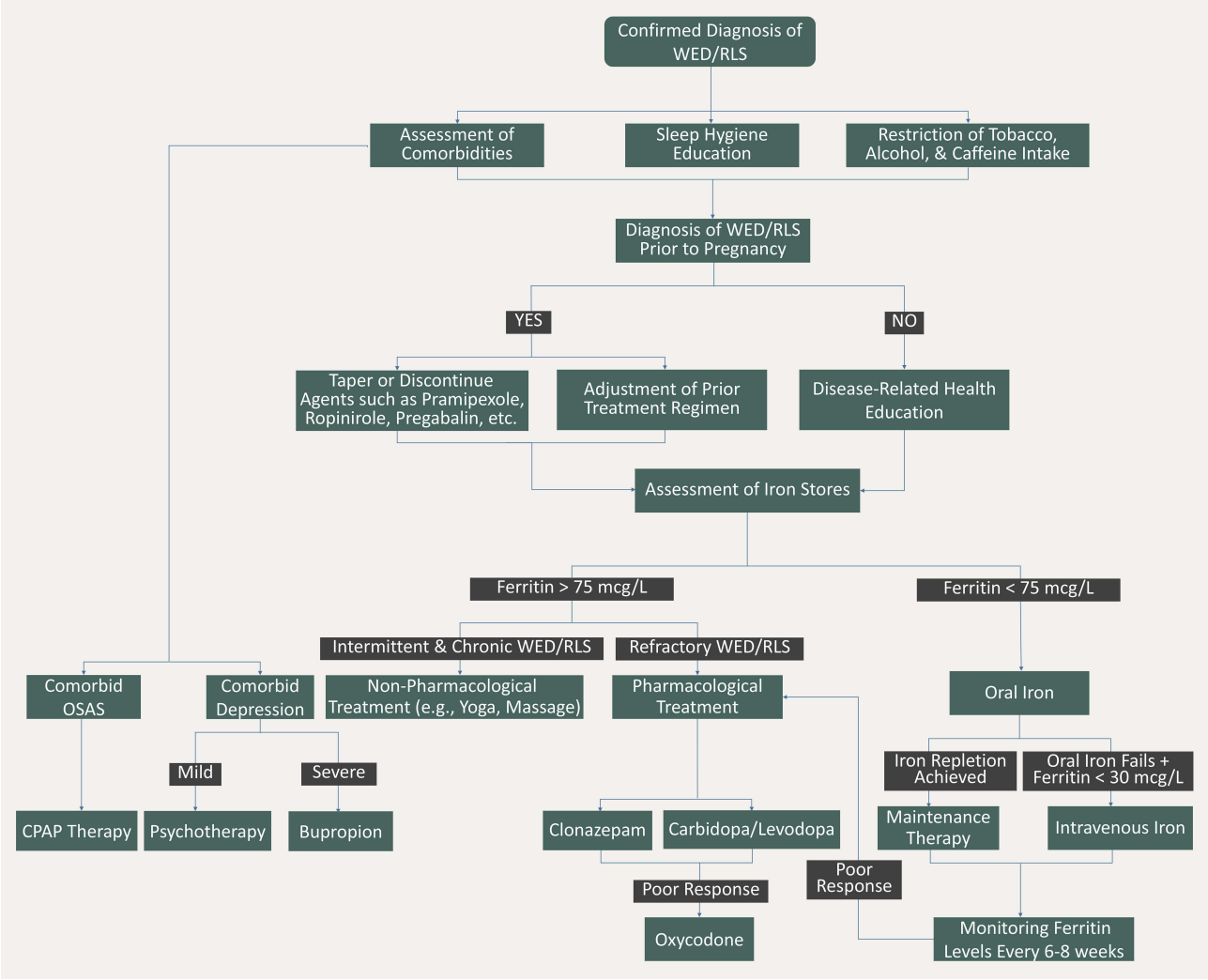

Figure 1 Stepped-Care Pathway for Managing WED/RLS during Pregnancy.
Abbreviations: CPAP, Continuous Positive Airway Pressure; OSAS, Obstructive Sleep Apnea Syndrome; WED/RLS, Willis-Ekbom Disease/Restless Legs Syndrome.

Future research should prioritize effectiveness-implementation hybrid designs to evaluate the feasibility, fidelity, and cost-effectiveness of this pathway across diverse healthcare contexts.[54] Such studies should integrate quantitative metrics (eg., symptom improvement and medication use rates) with qualitative inquiries (eg., women's acceptance of and adherence to non-pharmacological interventions and underlying reasons, and providers' perceived facilitators and barriers to implementing this care pathway). These efforts would facilitate the translation of this evidence base into sustainable, equitable, and patient-centered clinical practice globally.

Strengths and Limitations

Compared with existing CPGs, decision aids, and algorithms, this study offers several key contributions: (1) Systematic Integration – Recommendations on gestational WED/RLS management, previously dispersed across multiple sources, were consolidated into five clearly defined domains (Table 1). (2) Structural Reconstruction – A stepped-care pathway was developed, providing a decision-making framework that progresses sequentially from prevention to therapeutic intervention. (3) Heterogeneity Reconciliation – Variations in medication dosage thresholds and suggestions prioritization across sources were systematically resolved using quality appraisal tools and the JBI grading system, leading to the formulation of best-practice recommendations. (4) Transparent Grading – Each recommendation is explicitly assigned a strength level (strong/weak), facilitating rapid selection of contextually appropriate strategies tailored to individual patient characteristics.

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Despite these strengths, several limitations warrant consideration. This synthesis primarily drew upon secondary sources, including CPGs, evidence summaries, and decision-support materials, without conducting formal appraisal of the primary studies cited within them. While this methodology is suitable for generating practice-oriented guidance, it may not fully capture recent findings from primary research. Furthermore, the literature search was restricted to publications in Chinese and English, potentially introducing language bias. Finally, as the evidence was drawn from multicenter summaries, it may reflect the specific background conditions, regional variations, and demographic characteristics of the participating centers. Consequently, clinicians should consider patients' cultural background, lifestyle, socioeconomic status, and local healthcare resources when applying these recommendations to ensure contextually appropriate management.

Conclusions

This study synthesized best-practice evidence across five domains for the prevention and management of pregnancy-related WED/RLS, anchored in a stepped-care framework. The proposed hierarchy proceeds sequentially from (1) preventive counseling, lifestyle modification, and iron homeostasis optimization in high-risk individuals; to (2) upon diagnosis, prioritized non-pharmacological interventions alongside indicated iron supplementation; and (3) pharmacotherapy—restricted to the lowest effective dose for minimal duration in second or third trimester—only for severe, refractory cases. The resulting set of 27 graded recommendations provides an integrated, evidence-based guide to enhance care safety and efficacy.

Notably, as most evidence derives from international sources, contextual adaptation is imperative. Successful implementation requires evaluating each recommendation's feasibility within local healthcare systems, resource availability, and congruence with patient preferences. A deliberately contextualized approach thus ensures that clinical practice aligns best-practice evidence with individual patient needs and local care realities, advancing sustainable, patient-centered care.

Abbreviations

AASM, American Academy of Sleep Medicine; AGREE II, Appraisal of Guidelines for Research and Evaluation II; ACPG, Australian Clinical Practice Guidelines; ACOG, American College of Obstetricians and Gynecologists; AHRQ, Agency for Healthcare Research and Quality; BATE, BMI, Age, and Tongue Enlargement; BMI, Body Mass Index; CASE, Critical Appraisal for Summaries of Evidence; CPG(s), Clinical Practice Guideline(s); CPG Infobase, Canadian Clinical Practice Guidelines Infobase; EBP, Evidence-based Practice; EPDS-3, Edinburgh Postnatal Depression Scale-3; FDA, U.S. Food and Drug Administration; GIN, Guidelines International Network; GSS, German Sleep Society; IRLS, International Restless Legs Syndrome Study Group Rating Scale; IRLSSG, International Restless Legs Syndrome Study Group; JBI, Joanna Briggs Institute; NGC, National Guideline Clearinghouse; NICE, National Institute for Health and Care Excellence; OSAS, Obstructive Sleep Apnea Syndrome; PHQ-9, Patient Health Questionnaire-9; RLS, Restless Legs Syndrome; RNAO, Registered Nurses' Association of Ontario; SASM, Society of Anesthesia and Sleep Medicine; SIGN, Scottish Intercollegiate Guidelines Network; SOAP, Society for Obstetric Anesthesia and Perinatology; SOGC, Society of Obstetricians and Gynecologists of Canada; WED, Willis-Ekbom Disease.

Data Sharing Statement

Data availability is not applicable as no new data was generated or analyzed for this article.

Author Contributions

Fei-Yi Zhao: Conceptualization, Investigation, Formal analysis, Funding acquisition, Writing – original draft. Li-Ping Yue: Investigation, Formal analysis, Writing – review & editing. Russell Conduit: Investigation, Formal analysis, Writing – review & editing. Yan-Mei Wang: Investigation, Formal analysis, Writing – review & editing. Wen-Jing Zhang: Investigation, Formal analysis, Writing – review & editing. Peijie Xu: Data curation, Writing – review & editing. Yuen-Shan Ho: Conceptualization, Formal analysis, Writing – review & editing. Qiang-Qiang Fu: Validation, Formal analysis, Writing – review & editing. Chin Moi Chow: Formal analysis, Project administration, Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests.

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