

# Management Strategies for Restless Legs Syndrome/Willis-Ekbom Disease During Pregnancy



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## KEYWORDS

• Restless legs syndrome • Willis-Ekbom disease • Pregnancy • Sleep

## KEY POINTS

- Restless legs syndrome/Willis-Ekbom disease (RLS/WED) is a common sensorimotor sleep disorder, with a prevalence and severity peaking during the third trimester of pregnancy and receding around delivery.
- The exact causal mechanisms of restless legs syndrome have not been completely identified. Possible pathogenetic hypotheses include pregnancy-related endocrine and metabolic changes, and genetic factors.
- An accurate diagnosis of RLS is essential and should particularly consider other frequent complications of pregnancy that may mimic its symptoms.
- Management strategies should be personalized and based on an individual assessment of symptoms severity and impact, as well as of risks and benefits for the patient.
- Nonpharmacologic treatments should be considered first. If pharmacologic interventions are needed, medications should be used at the lowest effective dose and for the shortest duration possible.

## INTRODUCTION

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a common sensorimotor disorder characterized by a strong, nearly irresistible urge to move the limbs during rest, which improves with movement, and worsens during the evening and night.<sup>1</sup> About 70% of patients with RLS complain about sleep onset insomnia and, in 80% to 90% of the affected individuals, periodic leg movements during sleep (PLMS) can be detected, whose impact on sleep quality is still being investigated.<sup>2</sup> When periodic leg movements during sleep occur without RLS symptoms, but are associated with sleepiness and/or insomnia,

the diagnosis of periodic limb movement disorder should be considered.

Prevalence rates of periodic limb movement disorder during pregnancy are still lacking. Around 5% to 10% of the general population suffers from RLS,<sup>3,4</sup> with women being affected twice as often as men.<sup>2</sup> Pregnant women are particularly at risk to develop a new onset and often transient form of RLS, or to experience a worsening of a preexisting RLS. A recent meta-analysis found a mean prevalence of RLS during pregnancy of 21%, with variability by geographic region, ranging from 14% in the Western Pacific Region, to 20% and 22% in

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the American and European regions, respectively, and up to 30% in the Eastern Mediterranean region.<sup>5</sup> Pregnancy-related RLS peaks in the third trimester of gestation, affecting up to one-third of women, and usually remits around delivery.<sup>6-8</sup> Chen and colleagues<sup>5</sup> found prevalence rates of 8%, 16%, and 22% in the first, second, and third trimesters, respectively, and the pooled estimated prevalence of RLS after delivery was 4%.

In women already affected by RLS before pregnancy (preexisting RLS) the symptoms usually worsen in severity during pregnancy and are more likely to persist after delivery, compared with women with new-onset RLS during pregnancy.<sup>9</sup> Most pregnant women affected by RLS are unaware of the diagnosis and do not receive adequate information and reassurance by clinicians, who often tend to underestimate the problem.

### **PATHOGENETIC MECHANISMS**

The question of why pregnancy triggers or worsens RLS remains unanswered. Some pathogenetic hypotheses have been postulated, but further investigation is still needed. These include endocrine changes, iron and folate metabolism, genetics, and other factors.

#### ***Endocrine Changes***

Endocrine-related changes in pregnancy, such as an increase in estradiol, progesterone, and prolactin, all peaking in the third trimester, may play a role in inducing RLS. Estradiol and progesterone dramatically decrease around delivery, when RLS usually disappears, whereas prolactin, which is inhibited by dopamine, maintains a pulsatile secretion during lactation. Higher levels of estradiol were found in a small population of pregnant women with RLS compared to with women without RLS.<sup>10</sup> Also, the use of estrogen-based therapies in nonpregnant women may be associated with a significantly higher incidence of RLS.<sup>11</sup>

#### ***Iron and Folate Metabolism***

During pregnancy, iron, ferritin, and serum folate levels decrease, possibly because of their dilution in a greater total blood volume and due to increased fetal requirements.<sup>12</sup> Iron is an important cofactor in the synthesis of dopamine,<sup>13</sup> whose deficiency may be involved in the pathogenesis of RLS.<sup>14</sup> Low serum ferritin before or during early pregnancy has been found to be a predictor of RLS occurring during gestation<sup>15</sup> and iron supplementation may be considered in

the treatment of patients with RLS and low serum ferritin, including during late pregnancy and lactation.<sup>16</sup>

Folate also plays a role in the synthesis of dopamine via the regeneration of tetrahydrobiopterin.<sup>17,18</sup> Lee and colleagues<sup>19</sup> showed that, even before pregnancy, a decreased serum folate level, rather than indicators of iron status, was associated with RLS in pregnant women. However, because RLS symptoms rapidly decrease after delivery, whereas iron and folate levels normalize much more gradually,<sup>20</sup> the contribution of these 2 factors to the pathogenesis of RLS during pregnancy remains unclear. Moreover, oral folate and iron supplementation during pregnancy seems to be ineffective in preventing RLS symptoms.<sup>8</sup>

### ***Genetics***

The hypothesis that pregnancy may trigger the onset of symptoms in women already genetically predisposed to develop RLS is supported by 3 findings:

1. Familial RLS is a much more common trait in pregnant women with RLS than in women without the syndrome<sup>8,21,22</sup> and compared with other secondary forms of RLS;
2. Most women with a preexisting form of RLS experience a worsening of symptoms during pregnancy<sup>8</sup>; and
3. A new-onset disease during pregnancy predisposes affected women to develop a chronic, idiopathic form of RLS in the future.<sup>9,23</sup>

Although several allelic variants are known to be associated with idiopathic RLS,<sup>24</sup> further genetic analyses in women with pregnancy-related RLS are needed to better characterize the genetic component of RLS during gestation.

### ***Other Factors***

A number of other possible causal factors of RLS during pregnancy has been investigated. These factors include comorbidity with other sleep disturbances, such as respiratory disorders<sup>23</sup>; insomnia and excessive daytime sleepiness; psychological conditions exacerbating RLS symptoms, such as anxiety, stress, and fatigue; positional discomfort; and lower limb hypoxia or edema.<sup>8,15,25,26</sup>

### **CONSEQUENCES OF RESTLESS LEG SYNDROME IN PREGNANCY**

The severity of RLS/WED symptoms during pregnancy ranges from very mild to quite severe.

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