

## COMMENTARY

## Shaking Up Perspectives of Restless Legs Syndrome in Pregnancy

Commentary on Dunietz et al. Restless legs syndrome and sleep-wake disturbances in pregnancy. *J Clin Sleep Med*. 2017;13(7):863–870.

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Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a sensorimotor disorder characterized by circadian variations of unpleasant leg sensations with an urge to move the legs. The urge is exacerbated by prolonged inactivity and improves with movement.<sup>1</sup> RLS is the most common movement disorder during pregnancy, with studies suggesting a prevalence of approximately 20% to 30%.<sup>2,3</sup> It is most frequently noted in the third trimester and a majority of cases resolve after delivery. The transience of RLS thus suggests a predominance of secondary RLS in pregnant women.<sup>3,4</sup>

The development of secondary RLS during pregnancy has been attributed to a number of pregnancy-mediated metabolic and hemodynamic changes, including (1) deficiencies in iron and folate metabolism, a consequence of the increased requirements during pregnancy; (2) dopaminergic dysregulation as a consequence of iron deficiency; and (3) hormonal changes, namely the release of prolactin during pregnancy and its depressive effect on dopamine, as well as increased neuronal activity precipitated by elevated progesterone levels.<sup>4–6</sup>

Autonomic dysfunction with predominance of sympathetic discharge has also been implicated in the pathophysiology of RLS and periodic limb movement, with a significant fraction of patients with RLS experiencing periodic limb movements. Chronic activation of the sympathetic nervous system and hypothalamic-pituitary adrenal (HPA) axis in the development of RLS are also cornerstones of cardiovascular disease (CVD), hypertension, and diabetes development, hence, the described associations between RLS, CVD, and metabolic complications<sup>7</sup> in various populations<sup>8,9</sup> including women.<sup>10</sup> These associations, however, have not always been consistent.<sup>11,12</sup>

As placental perfusion and gestational hypertension may be similarly affected by sympathetic activation during pregnancy, an obvious question would be the association of RLS with adverse pregnancy and delivery outcomes. Recent studies have examined these associations. Though some studies have shown an increased likelihood of hypertensive disorders of pregnancy,<sup>13–16</sup> other studies have failed to show an association.<sup>17</sup> Similar discrepancies have been observed in the association of RLS with neonatal outcomes.<sup>13,17</sup> These discrepancies likely relate to the definition of RLS, populations studied, study design, and sample size.

As studies about the cardiovascular outcomes of RLS in pregnancy emerge, it is equally imperative to continue investigating its effect on pregnancy and fetal outcomes.

Dunietz et al.<sup>18</sup> recruited a total of 1,563 women in their third trimester of pregnancy. The study aimed at assessing the prevalence of RLS using standardized criteria for the diagnosis<sup>19</sup> and examining the effect of RLS severity on sleep-wake disturbances using the generalized sleep disturbance scale,<sup>20</sup> as well as associations with delivery outcomes. The authors demonstrated a high prevalence of RLS in this cohort nearing 50%. In addition, the study showed a dose-response relationship between the severity of RLS and increased odds for sleep-wake disturbances such as poor sleep quality, poor daytime function, and excessive daytime sleepiness. There was no significant difference in delivery outcomes such as mode of delivery, birth weight, or Apgar scores between the group with and the group without RLS. This is an important study in that it describes a large sample of women who were evaluated using a standardized questionnaire for the diagnosis of RLS, in addition to the use of a questionnaire for the assessment of sleep disturbances that has been validated specifically in the pregnant population.<sup>21</sup> As the authors acknowledged, the study has some limitations. Importantly, it is limited by the lack of validation of some of the questionnaires used, the assessment occurring only in late pregnancy, and the inability to examine causality.

The effect of RLS on sleep and pregnancy outcomes may refocus attention on recognition and treatment of the condition, and pave the way for rigorous safety trials and registries of pharmacological interventions if the sleep disruption or the sympathetic activation of RLS consistently reveal hypertensive complications or negative effects on neonatal outcomes. Linking RLS to either adverse outcomes or precursors of adverse outcomes changes how clinicians weigh the decision of therapy in pregnancy. Many of the first-line drugs for the treatment of RLS have minimal to no safety data in pregnancy and in many cases, unfortunately, the condition is treated partially or not at all. However, if research demonstrates that the risk of the untreated condition outweighs the potential and unforeseen risk of pharmacotherapy, the choice of pharmacotherapeutic agents may be overturned. Current data suggest that poor sleep quality is associated with an enhanced proinflammatory profile<sup>22</sup>

and preterm birth<sup>23</sup> as well as an increased risk of metabolic outcomes.<sup>24</sup> Hence, conditions that result in poor sleep such as RLS, as demonstrated in this study, become critical to identify and possibly important to treat pharmacologically. The research by Dunietz et al.<sup>18</sup> and others<sup>14</sup> elevate the diagnosis of RLS in pregnancy from a self-limited condition that would likely resolve postpartum to one with potential adverse obstetric events and beg for studies evaluating the efficacy and outcome of treating RLS in pregnancy.

RLS in pregnancy remains understudied and future studies should examine temporal associations of RLS and adverse obstetric, cardiovascular, and metabolic outcomes, assess the biological and the hemodynamic effect of RLS and the consequent sleep disruption in pregnancy, and understand the risk of therapy and potential effect of therapy on these complications. Dunietz et al. should be commended on their effort to bring us closer to understanding the effect of RLS in pregnancy on sleep disturbances and delivery outcomes.

## CITATION

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## DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.