International Journal of Nursing and Health Care Research
OPEN ACCESS
Jagodzinski A, et al. Int J Nurs Health Care Res 6: 1446
www.doi.org/10.29011/2688-9501.101446
www.gavinpublishers.com
GAVIN PUBLISHERS
Mini Review

# The Relationship between Restless Legs Syndrome And Pre-Eclampsia: A Mini-Review

**Adam Jagodziński*, Bogusław Pałczyński†, Marek Murawski**

Department and Clinic of Gynaecology and Obstetrics at Wrocław Medical University, Poland

***Corresponding author:** Adam Jagodziński, Department and Clinic of Gynaecology and Obstetrics at Wrocław Medical University, Poland

**Citation:** Jagodziński A, Pałczyński B, Murawski M (2023) The Relationship between Restless Legs Syndrome And Pre-Eclampsia: A Mini-Review. Int J Nurs Health Care Res 6:1446. DOI: https://doi.org/10.29011/2688-9501.101446

**Received Date:** 26 June, 2023; **Accepted Date:** 07 July, 2023; **Published Date:** 12 July, 2023

## Abstract

**Introduction**: Pregnancy is associated with significant physiological, psychological, and social changes that affect normal sleep. Sleep disorders whose frequency increases significantly during pregnancy can include restless legs syndrome (RLS). The incidence of RLS in pregnancy increases with gestational age and reaches its maximum in the third trimester of pregnancy. Reduced sleep quality in pregnancy increases the incidence of hypertension and associated pre-eclampsia (PE), among other conditions. There are many hypotheses regarding the pathophysiology of RLS in pregnancy. Risk factors for RLS include a family history of RLS, low serum iron, and ferritin levels as well as high estrogen levels specific to pregnancy. **Aim:** This study aims to present the current knowledge on the association between the presence of RLS in pregnant women and the occurrence of PE. **Methods:** the study was based on scientific publications concerning the correlation between RLS in pregnancy and complications in the form of PE, extracted from PubMed, Scopus, and Web of Science databases. **Conclusions:** RLS increases the incidence of PE and thus also indirectly the risk of serious pregnancy complications such as fetal growth restriction, iatrogenic preterm birth, and increased maternal mortality among pregnant women and neonatal mortality.

**Keywords:** Restless legs syndrome; RLS, PE, Pre-eclampsia; Pregnancy

## Introduction

Pregnancy is an important risk factor for sleep disorders. Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is one of the most common sleep disorders in pregnancy. It is a condition categorized as dyssomnia and it manifests as motor and sensory complaints related to the circadian rhythm. Diagnostic criteria according to the International Restless Legs Syndrome Study Group are based on physical examination and include a compulsion to move the lower limbs combined with paresthesias and/or dysaesthesias, the compulsion to move or unpleasant sensations manifest or increase at rest, the compulsion to move or unpleasant sensations partially or completely disappear during movement, and the intensity of symptoms is most pronounced in the evening and at night. There are also criteria to support the diagnosis of RLS based on family history, response to dopaminergic therapy, and the presence of periodic limb movements during wakefulness or sleep. Validated questionnaires for the diagnosis of RLS include the Hening Telephone Diagnostic Interview (HTDI), the Cambridge Hopkins Diagnostic Questionnaire for RLS (CH-RLSq), and the RLS Diagnostic Index (RLS-DI). The incidence of RLS is higher in multiparous women compared to primiparous women, which indicates that childbearing is a risk factor for RLS. The highest symptom severity in pregnant women is observed in the third trimester of pregnancy and can affect 10 to 35% of pregnant women, depending on the source, and decreases gradually after delivery. The onset of symptoms during pregnancy increases the risk of an idiopathic form of RLS later in life. The pathogenesis of the appearance or severity of RLS in pregnancy is still unclear. Investigated causes include endocrine changes, micronutrient metabolism, or genetic predisposition.

Sleep disorders in pregnancy increase the incidence of other pathologies, with pre-eclampsia (PE) being the most serious. It is a condition characterized by the presence of hypertension and proteinuria, or hypertension and organ dysfunction with or without proteinuria. Symptoms that may occur in the course of PE include impaired vision, headache, epigastric pain, thrombocytopenia, and abnormal liver function. The pathophysiology of PE symptoms is due to microangiopathy of varying severity of target organs, including the brain, liver, kidney, and placenta. A distinction is made between maternal and fetal factors that cause PE. The key to the development of PE is the early period of pregnancy when the placental vasculature is abnormally formed and hypoperfused, resulting in the release of anti-angiogenic and pro-inflammatory factors into the maternal circulation. The symptoms of PE result from altered vascular endothelial function under the influence of the factors released due to placental hypoperfusion. The consequences of PE affect both the mother and fetus. In its course, PE can cause multiple organ dysfunction syndrome MODS), fetal growth restriction (FGR), and the need for early childbirth with all the possible complications of prematurity.

## Methods

This study reviewed the literature on the correlation between RLS in pregnancy and complications in the form of PE, extracted from PubMed, Scopus, and Web of Science databases. The search process was based on the following keywords: restless legs syndrome, pregnancy, RLS, pre-eclampsia, preeclampsia, and PE in various combinations in Polish and English. Open-access publications from the last ten years were selected.

## Aim

This paper aims to present the current knowledge on the relationship between the presence of RLS in pregnant women and the occurrence of a serious pregnancy pathology such as PE.

## Discussion

### Pathogenesis and epidemiology of RLS in pregnancy

In 2020, a meta-analysis was published to determine the prevalence of RLS in the third trimester of pregnancy [1]. Ten studies involving 2,431 participants aged 25-39 were used. The prevalence of RLS in pregnancy was determined at the level of 22.9% of the participants. Restless legs syndrome is twice as common in the female population compared to men. One possible reason for the above-mentioned relationship found in research studies is the serum levels of oestradiol and ferritin, which are lower in women after puberty. In terms of the pathogenesis of RLS, dysfunction of the nigrostriatal dopaminergic pathway is under investigation. The conversion of tyrosine to dopamine occurs under the action of tyrosine hydroxylase, and iron is a cofactor in this reaction. Despite compelling evidence linking the role of iron in the pathophysiology of RLS in non-pregnant women, the resolution of RLS symptoms after childbirth is difficult to explain based on this hypothesis. There was evidence of significantly lower levels of ferritin and transferrin saturation in blood in pregnant women with RLS symptoms [2]. Iron is an important element in the biological processes of the central nervous system. Its deficiency is associated with the occurrence of some neurodegenerative diseases as well as RLS [3]. Lower cerebrospinal fluid iron and ferritin levels were observed in individuals affected by RLS symptoms, while pregnancy contributes to iron deficiency and anaemia.

Animal studies on long-term exposure of the striate body to high concentrations of 17-beta-oestradiol indicate its reduced dopaminergic responsiveness. Pregnancy is associated with a significant increase in serum oestradiol levels; however, the correlation of these levels with the incidence of RLS was not sufficiently confirmed.

In the vast majority of pregnant women, RLS symptoms are not experienced before pregnancy, and their severity and frequency increase with gestational age [4] and resolve within one month after delivery. Persistent symptoms of the syndrome were more frequently observed in correlation with lower ferritin levels, higher fertility, and onset of symptoms in the second trimester of pregnancy.

Reduced sleep quality was found in a cohort study involving 1,563 pregnant women of whom 36% presented with RLS symptoms [5]. Reduced sleep quality in pregnancy may increase the incidence of hypertension in pregnancy. Findings regarding this correlation are inconclusive. There were no significant differences in the incidence of hypertension, diabetes, or the effect of body mass index in symptomatic and asymptomatic pregnant women with respect to RLS. There were no statistically significant differences in the risk of caesarean-section birth or neonatal birth weight in the groups compared. A study involving 3,874 Chinese women revealed a higher prevalence of hypertension in pregnancy and PE in the symptomatic RLS group [6].

In 2016-2020, a study was conducted in Aachen [7], which involved 561 postpartum women surveyed in the 1$^{st}$ and 12$^{th}$ week postpartum using criteria developed by the International Restless Legs Syndrome Study Group. Furthermore, a questionnaire on RLS symptoms in pregnancy and postnatal depression (Edinburgh Postnatal Depression Scale) was used. Blood TSH and haemoglobin levels were measured, as well as hair cortisol, which is a biomarker of chronic stress [8]. Twenty-one percent of the participants experienced RLS symptoms; after delivery, they persisted in 20% of the midwives among those who manifested complaints during pregnancy. Furthermore, there was a correlation between RLS and hypertension in pregnancy. The effect of low haemoglobin levels did not prove statistically significant in that study.

A cross-sectional study conducted by a research team from Thammasat University found an RLS prevalence of 11.2% among Tajek [9] participants, which is a lower value than among those from the European population. Averaged blood haemoglobin levels were lower in the study group (11.21±1.11 vs. 11.83±1.22 g/dl, p=0.02). Furthermore, the frequency of RLS was affected with a statistically significant frequency by hypothyroidism, a family history of RLS, and RLS during a previous pregnancy. In more than 70% of participants, the condition appeared in the third trimester and did not disappear after delivery in 33% of symptomatic cases. The sudden decrease in the incidence of RLS after childbirth may not be related to iron or folic acid deficiency but rather to the hem dilution effect that occurs during pregnancy and disappears after childbirth.

There were 742 pregnant women and a similar number of non-pregnant women from Saudi Arabia included in a cross-sectional study with additional consideration of the impact of anaemia and vitamin D deficiency on the incidence of RLS. The cut-off values were 11g/dl for haemoglobin and 25 nmol/l for 25OHD. The incidence of RLS was higher in pregnant women [10], however, the incidence among non-pregnant women is also higher than in the European population (30% and 26.5%). The correlation between hypertension and RLS symptoms was confirmed in the study group. The differences in the incidence of RLS in Arab women may be related to the higher prevalence of anaemia in women of reproductive age in this region.

### Co-occurrence of RLS and PE

Sleep disorders are common in pregnancy and are a potential cause of serious diseases during pregnancy. A systematic review and meta-analysis were performed to establish the reliability and systematise knowledge on the correlation between sleep disorders in pregnancy, including RLS, and possible pregnancy complications. Publications published up to 2020, uniform in terms of inclusion criteria for the study and control groups, were included. The disorders assessed included reduced sleep quality, altered sleep duration, insomnia, RLS, and sleep-disordered breathing in relation to the occurrence of PE, hypertension, gestational diabetes, and the need for a caesarean section. Twenty-two publications included in the meta-analysis were related to RLS and forty-three focused on PE. The correlation between RLS and PE was described in six selected articles and included a total of 5,932 pregnant women studied. The odds ratio for the occurrence of PE in pregnant women with RLS was calculated at the level of 1.83 [11]. Sleep disorders cause intermittent hypoxia, oxidative stress, and inflammatory response, which result in vascular endothelial damage and, consequently, hypertension and PE. Restless legs syndrome indirectly increases the risk of the above pathological response due to reduced sleep quality and sleep fragmentation [12,13].

For the determination of the relationship between PE and RLS, the Peruvian authors conducted a study, which included 218 pregnant women. A group of experienced neurologists identified 18.4% of women presenting with RLS symptoms in pregnancy using a questionnaire dedicated to the diagnosis of RLS. A comparison of the prevalence of PE between the study group and control group revealed a statistically significant difference, with PE occurring more frequently in the group of pregnant women diagnosed with RLS(14) A Chinese study, with 3,874 pregnant women included, was similarly designed.

The prevalence of RLS, determined by a physical examination using a questionnaire targeted at RLS diagnosis, was 12.3%. Moreover, it has been observed that there is a correlation between the increasing percentage of pregnant women suffering from the symptoms of RLS and the older age of women. In conclusion, the study found a higher prevalence of severe pregnancy pathologies, including PE, in pregnant women diagnosed with RLS [6].

In Canada, a case-control study was conducted on a group of 294 female patients, half of whom presented with symptoms of PE and the other half with uncomplicated pregnancies. In that study, 13.6% of the women met the diagnostic criteria for RLS, however, there was no statistically significant difference between the two groups [10].

The relationship between RLS and PE was also found in another systematic review, which focused on systematizing the available knowledge on the correlation between sleep disorders in pregnancy and the incidence of specific pregnancy pathologies. It was highlighted that further research is required to establish the exact pathomechanism and treatment of the disorders presented. It was found that there was a statistically significant increase in the incidence of hypertension and PE in pregnancy in women who suffered from RLS [15].

There is an emphasis on the role of metabolic abnormalities associated with RLS, which include hypertension, abnormal glucose tolerance, and obesity, which may indirectly increase the risk of PE from maternal causes. The association between PE and RLS was confirmed in another study, where the anticipated correlation was determined to be statistically significant following the analysis of the results of 498 pregnant women [16]. It should be emphasized that as a neurological disorder, RLS leads to increased metabolic disorders through reduced sleep quality, which increases the risk of PE, even in the absence of RLS symptoms in the pregnant woman.

## Conclusions

Normal sleep plays an important role in the well-being of pregnant women. Sleep disorders can have a negative impact on women's health. An important aspect of obstetric practice is to perform a

thorough physical examination to increase the accuracy of sleep disorder detection. An interdisciplinary therapeutic approach reflecting the complexity of sleep disorders is essential to reduce their adverse effects on pregnant women's health. The observed link between a seemingly innocuous condition, RLS, and PE, which is associated with higher morbidity and mortality rates among expectant mothers and new-borns, encourages intensified efforts to pinpoint the precise pathophysiological foundations of RLS. The presented study of available knowledge on the correlation between PE and RLS does not sufficiently cover the topic, and further research is needed to better understand the pathophysiological basis of the above relationship.

## References

1. Darvishi N, Daneshkhah A, Khaledi-Paveh B, Vaisi-Raygani A, Mohammadi M, et al. (2020) The prevalence of Restless Legs Syndrome/Willis-ekbom disease (RLS/WED) in the third trimester of pregnancy: A systematic review. BMC Neurology. 20: 1-7.
2. Neyal A, Senel GB, Aslan R, Nalbantoglu M, Acikgoz S, et al. (2015) A prospective study of Willis-Ekbom disease/restless legs syndrome during and after pregnancy. Sleep Med 16: 1036-1040.
3. Telarović S, Čondić L (2019) Frequency of iron deficiency anemia in pregnant and non-pregnant women suffering from restless legs syndrome. Hematology. 24: 263-267.
4. Umeno S, Kato C, Nagaura Y, Kondo H, Eto H (2020) Characteristics of sleep/wake problems and delivery outcomes among pregnant Japanese women without gestational complications. BMC Pregnancy Childbirth. 20: 179.
5. Dunietz GL, Lisabeth LD, Shedden K, Shamim-Uzzaman QA, Bullough AS, et al. (2017) Restless Legs Syndrome and Sleep-Wake Disturbances in Pregnancy. J Clin Sleep Med 13: 863-870.
6. Liu G, Li L, Zhang J, Xue R, Zhao X, et al. (2016) Restless legs syndrome and pregnancy or delivery complications in China: a representative survey. Sleep Med 17: 158-162.
7. Goecke TW, Schnakenberg P, Frensch M, Chechko N (2020) Restless Legs Syndrome During Pregnancy and 12 Weeks Postpartum and Its Links to Cardiovascular Diseases, Stressful Life Events, and Psychiatric History. J Clin Med 9: 3046.
8. Stalder T, Steudte-Schmiedgen S, Alexander N, Klucken T, Vater A, et al. (2017) Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. Psychoneuroendocrinology. 77: 261-274.
9. Panvatvanich S, Lolekha P (2021) Restless legs syndrome in pregnant Thai women: Prevalence, predictive factors, and natural course. J Clin Neurol 15: 97-101.
10. Almeneessie A, Alyousefi N, Alzahrani M, Alsafi A, Alotaibi R, Olaish A, et al. (2020) Prevalence of restless legs syndrome among pregnant women: A case-control study. Ann Thorac Med 15: 9-14.
11. Lu Q, Zhang X, Wang Y, Li J, Xu Y, Song X, et al. (2021) Sleep disturbances during pregnancy and adverse maternal and fetal outcomes: A systematic review and meta-analysis. Sleep Med Rev 58: 101436.
12. Picchietti DL, Hensley JG, Bainbridge JL, Lee KA, Manconi M, McGregor JA, et al. (2015) Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev 22: 64-77.
13. Phan K, Pamidi S, Gomez YH, Gorgui J, El-Messidi A, Gagnon R, et al. (2022) Sleep-disordered breathing in high-risk pregnancies is associated with elevated arterial stiffness and increased risk for preeclampsia. Am J Obstet Gynecol 226: 833.e1-833.e20.
14. Ramirez JO, Cabrera SAS, Hidalgo H, Cabrera SG, Linnebank M, Bassetti CL, et al. (2013) Is preeclampsia associated with restless legs syndrome? Sleep Med 14: 894-896.
15. Steinweg K, Nippita T, Cistulli PA, Bin YS (2020) Maternal and neonatal outcomes associated with restless legs syndrome in pregnancy: A systematic review. Sleep Med Rev 54:101359.
16. Innes KE, Kandati S, Flack KL, Agarwal P, Selfe TK (2016) The Relationship of Restless Legs Syndrome to History of Pregnancy-Induced Hypertension. J Women Health 25: 397-408.