

# Restless legs syndrome in pregnancy: A systematic review of prevalence

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## Summary

Restless legs syndrome is a neurological disease from the spectrum of movement disorders, with psychiatric comorbid symptoms and manifestations. Women are affected twice as often as men, and the frequency in the population is 4-10%, while during pregnancy the prevalence triples. This research was conducted as a result of a search and selection of studies on the prevalence of RLS in pregnancy, which include works published in domestic and foreign journals and searches of PubMed, PubMed Central, Web of Science, Scopus and Embase. A primary search of medical databases found 316 publications. In this secondary process, due to the lack of access to the abstract or full text, and due to the poor quality of the articles, 11 relevant publications were finally found and included in this systematic review. The total number of respondents included in this research is 7033, aged 19-45. The lowest prevalence was 4.9% in Japan, and the highest prevalence was 54.7% in Saudi Arabia. In this review, the overall mean frequency of restless legs syndrome during pregnancy was 24.69%. Furthermore, in our ongoing research conducted in 2022 on restless legs syndrome, we recorded a frequency of 26.5% in a population of 266 pregnant women in the third trimester of pregnancy. The frequency of restless legs syndrome is high among the population of pregnant women, and according to its etiology, clinical manifestations and comorbid manifestation, this disorder represents a close link between psychiatry, neurology and gynecology. For this reason, pregnant women should pay extra attention to the early detection of this disorder, which can significantly affect a pregnant woman's daily energy level, poor sleep and daytime sleepiness, and more frequent symptoms of anxiety and depression.

**Keywords:** Restless leg syndrome, pregnancy, epidemiology

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## INTRODUCTION

Sir Thomas Willis gave the first known description of restless legs syndrome (RLS) 1672, writing then about a sleep disorder caused by a strong need to move the lower extremities in people with RLS. The description of the disease was originally published in Latin (*De Anima Brutorum*, 1672), and was later translated into English (*The London Practice of Physick*, 1685) (Coccagna et al., 2004). Subsequently, other descriptions of RLS were published, including Francois Boissier de Sauvages (1763), Magnus Huss (1849), Theodor Wittmaack (1861), George Miller Beard (1880), Georges Gilles de la Tourette (1898), Hermann Oppenheim (1923) and Frederick Gerard Allison (1943) (Coccagna et al., 2004; Konofal et al., 2009; Ulfberg, 2004).

However, it was not until nearly three centuries after Willis, in 1945, that Karl-Axel Ekbom (1907-1977) gave a detailed and, comprehensive account of this condition in his doctoral thesis, *Restless Legs: A Clinical Study of*

a Hitherto Neglected Disease. Ekbom coined the term “restless legs” and continued to work on this disorder throughout his career. He described important diagnostic symptoms, differential diagnosis from other conditions, prevalence, association with anemia and frequent occurrence during pregnancy (Hélio et al., 2009; Karl-Axel, 2009; Ulfberg, 2004).

The pathophysiology of RLS despite all the research carried out so far, a significant part remains controversial. Post mortem, neuroimaging and biohumoral studies suggest that brain iron deficiency (BID) may also play a role in the pathophysiology of RLS. The theory of dopaminergic dysfunction has been proposed based on the clinical improvements observed after dopaminergic treatment. More recently, the involvement of dysfunction in other neurotransmitter pathways, including GABA and adenosine, has been suggested (Jiménez Jiménez et al., 2019; Koo et al., 2016; Stefani et al., 2019).

Although the form of pregnancy-associated RLS is well described, its prevalence, natural course, and pathophysiology are not fully understood (Antelmi et al., 2022).

Recent systematic reviews have revealed that the prevalence of RLS during pregnancy ranges between 11% and 34% (Manconi et al., 2004; Neau et al., 2010; Shang et al., 2015; Sikandar et al., 2009; Suzuki et al., 2003) which is typically two to three times higher than in non-pregnant women. Furthermore, the prevalence of RLS during pregnancy has been recorded to peak in the third trimester and may be related to parity (Shang et al., 2015). These estimates were derived from obtained data from collective prevalence mainly in American, European and East Asian countries, while data from Southeast Asia are insufficient (Srivanitchapoom et al., 2014). Certain studies from Japan indicate a prevalence of RLS during pregnancy of 4-5% (Yoshimura et al., 2021).

Although the legs are most markedly affected, a significant percentage of people with restless legs syndrome also describe some sensations in the hands. Symptoms of restless legs syndrome appear and worsen at rest, mostly in the evening and at night, and are alleviated by movement of the affected limb (Turrini et al., 2018; Wang et al., 2020).

The latest diagnostic criteria for RLS were updated in 2014 by the International RLS Study Group (IRLSSG) and consist of five key features that must be met for a diagnosis of RLS (Allen et al., 2014): 1) Growing uncomfortable sensations in the legs, accompanied by an irresistible need and urge to move the legs or other parts of the body; 2) Symptoms appear and worsen during periods of rest, such as lying down or sitting; 3) After moving the limbs affected by the discomfort, there is a partial or complete relief of the symptoms; 4) Appearance or worsening of symptoms in the evening or at night, and; 5) Exclusion of another primary cause of symptoms (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

According to etiology, RLS can be classified into: The primary (idiopathic) form which is characterized by an earlier onset of symptoms, a slower course of the disease, but also a better prognosis. It usually appears before the age of 40, sometimes already in early childhood when it is often misinterpreted as hyperactive child syndrome. Secondary form occurs in various conditions, such as pregnancy, iron deficiency anemia, peripheral neuropathy, kidney disease, cardiovascular disease, diabetes, migraine, hypertension, multiple sclerosis, stroke (Chen et al., 2019; Gossard et al., 2021; Kalra & Gupta, 2018; Sabic et al., 2016; Trenkwalder et al., 2016).

In clinical practice, RLS predominantly occurs in secondary form. The impact of RLS can be mild to severe, with adverse effects on sleep quality, cognitive function, mood and quality of life (Gossard et al., 2021; Liu et al., 2022; Gros & Videnovic, 2020; Lajoie et al., 2021). Because RLS has a negative effect on sleep quality, RLS

may put pregnant women at greater risk of developing complications during pregnancy and childbirth and adverse effects on fetal development (Eleftheriou et al., 2023; Goecke et al., 2020; Na et al., 2020).

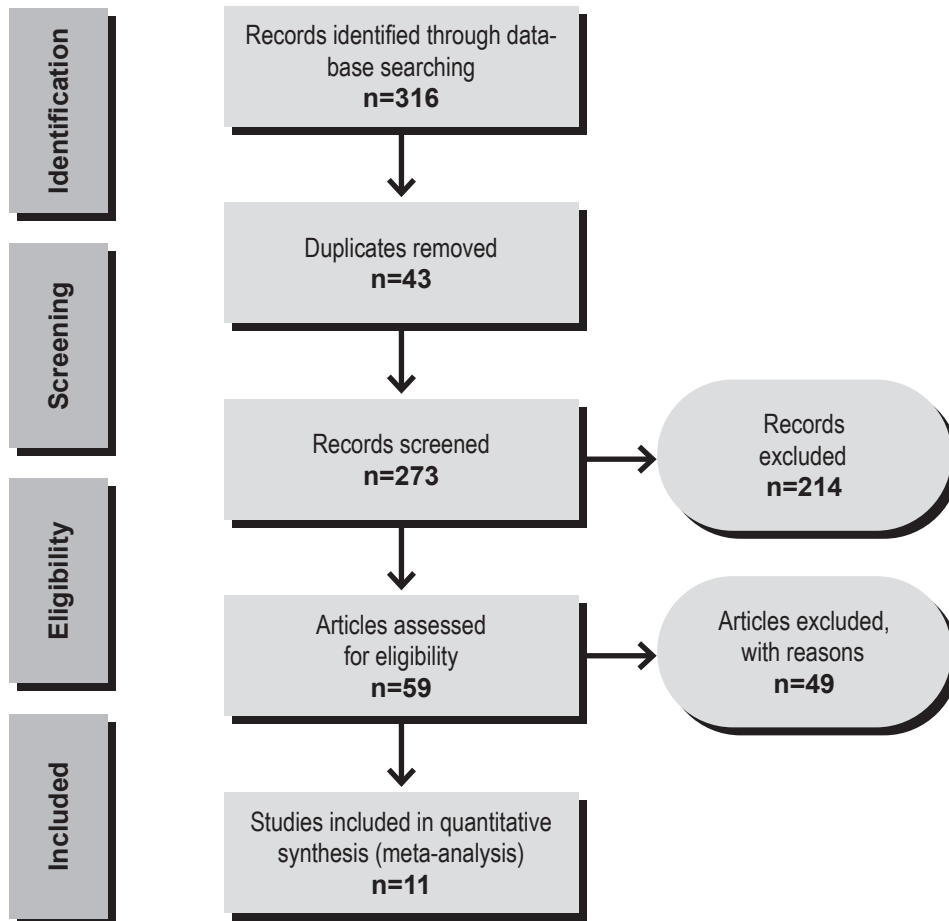
The frequency of restless legs syndrome is high among the population of pregnant women, and according to its etiology, clinical manifestations and corbid manifestation, this disorder represents a close link between psychiatry, neurology and gynecology. For this reason, pregnant women should pay extra attention to the early detection of this disorder, which can significantly affect a pregnant woman's daily energy level, poor sleep and daytime sleepiness, and increased anxiety (Kaindlstorfer, 2013; Saletu et al., 2013).

One of the goals of this paper is to summarize the most relevant papers published in the last 5 years on the topic of the frequency of restless syndrome in pregnancy. This systematic review is important to do because of the existence of significant variation between the frequency of restless legs syndrome in pregnancy, and among different authors in studies conducted in different parts of the world.

Considering the neglect of the impact of RLS during pregnancy in terms of disturbing the quality of sleep, cognitive functions, the change in mood and decreased quality of life (Alnaaim et al., 2023; Dunitz et al., 2017), with this review article we will contribute to the awareness of the existence of more significant (more precise) mean values of the frequency of restless legs syndrome among pregnant women.

## METHODOLOGY

This research was conducted as a systematic review. It was structurally created as a result of a search and selection of studies on the prevalence of RLS in the third trimester of pregnancy, which include works published in domestic and foreign journals as well as a search of PubMed, PubMed central, Web of Science, Scopus, Embase. The search process in these databases was carried out using the keywords restless legs syndrome, pregnancy, third trimester of pregnancy in English and Bosnian. In this research, the operators (AND) and (OR) were used to combine keywords for comprehensive and complete access to published papers. Each paper was studied by two reviewers independently, and in case the paper was rejected, the reason for rejection was given, and if there was any disagreement between the two reviewers, a third reviewer would judge it. We schematically presented the methodology in Figure 1.



**Figure 1.** The flowchart on the stages of including the studies in the systematic review

According to the set criteria for the selection and evaluation of studies, articles in Bosnian and English related to the prevalence of RLS during the third trimester of pregnancy, which met the inclusion criteria, were considered. On the other hand, other review studies, observational and interventional studies were excluded from the list of papers. After that, the included studies were examined based on PRISMA 2009. The STROBE checklist was used to examine the studies. Inclusion criteria included all pregnant women over 18 years of age with RLS diagnosed according to the criteria set by the IRLSSG, while exclusion criteria were diagnosed periodic limb movement disorder not specifically diagnosed as RLS. Such subjects were excluded from our analyses.

### Statistics

Data analyzed with comprehensive meta-analysis software (SPSS version V22). Heterogeneity of the studies was examined with the I<sup>2</sup> test, and the probability of bias of the results was measured using funnel plots using Egger's test.

## RESULTS

A primary search of medical databases found 316 publications. After the primary selection, 59 publications were finally analyzed. Each publication was analyzed by two reviewers. In this secondary process, due to the lack of access to the abstract or the full text, and due to the poor quality of the articles, 11 relevant publications were finally found that were included in this systematic review.

The finally selected publications that met the required criteria are shown in Table 1. The total number of respondents included in this research is 7033, aged 19-45. The overall mean frequency of restless legs syndrome during pregnancy is 20.24%.

The lowest prevalence was in a study conducted by a group of authors in Japan (Yoshimura et al. 2021). The diagnosis was made based on the guidelines given by the IRLSSG. The subjects were aged 31.9±4.2 years, the sample size was 182 subjects, and the frequency of restless legs syndrome was recorded at 4.9%.

The highest prevalence was in a study conducted by a group of authors in Saudi Arabia (Almeneessie et al. 2020). The diagnosis was made based on the guidelines

**Table 1.** List of research studies included in the analysis

| Author (reference)     | Year of publication | Region       | Age ( $\bar{x}\pm SD$ ) | Sample | Prevalence |
|------------------------|---------------------|--------------|-------------------------|--------|------------|
| Mubeen SM,             | 2021                | Pakistan     | 33.44 ± 4.42            | 478    | 11%        |
| Nazan Tuna Oran        | 2021                | Turkey       | 28.3±5.9                | 718    | 22%        |
| Giovanna Esposito      | 2019                | Italy        | 35±3                    | 648    | 20.4%      |
| Asma S Al Shidhani     | 2022                | Oman         | 29.8±5.28               | 305    | 41%        |
| Chikara Yoshimura      | 2021                | Japan        | 31.9±4.2                | 182    | 4.9%       |
| Muzi Na                | 2020                | USA          | 30±5                    | 2704   | 18.1%      |
| Supakorn Panvatvanich  | 2018                | Thailand     | 28.60±6.52              | 214    | 11.2%      |
| Lucija Čondić Jurjević | 2022                | Croatia      | NR                      | 231    | 22.6%      |
| Aljohara S Almeneessie | 2020                | Saudi Arabia | 29.4±5.6                | 742    | 54.7%      |
| Pınar Akbaş            | 2019                | Turkey       | 28.11 ± 5.59            | 250    | 46.4 %     |
| Tamme W Goecke         | 2020                | Germany      | 32.13±4.79              | 561    | 19.3%      |

given by the IRLSSG. The subjects were aged 29.4±5.6 years, the sample size was 742 subjects, and the frequency of restless legs syndrome was recorded at 54.7%.

## DISCUSSION

In a study by a group of authors (Mubeen & Ahsan, 2021) conducted in five hospitals in Karachi, Pakistan on the population of pregnant women, the sample was 478, the mean age was 33.44 ± 4.42 years, and the frequency rate was 11%. The relationship between pregnant women with RLS and pregnant women without RLS reveals statistically significant differences with increasing age ( $p=0.01$ ), pregnancy ( $p<0.01$ ), and married ( $p<0.001$ ). RLS was significant among employed women ( $p=0.001$ ), during the third trimester ( $p=0.001$ ), with insomnia ( $p<0.001$ ), tobacco use ( $p<0.001$ ) and among women with gestational diabetes ( $p<0.001$ ), hypertension ( $p<0.001$ ).

According to a paper published by a group of Turkish authors (Oran et al., 2021), the frequency of restless legs syndrome was 22%, based on a sample of about 718 subjects. The average age was 28.3±5.9, with a range from 19 to 45. A similar study was also conducted in Turkey (Akbaş & Sözbir, 2019) in which the frequency of this syndrome was determined to be 46.4%, in a sample of 250 pregnant women.

In a study conducted in the United States (Na et al., 2020), on a population sample of 2,704 pregnant women, the cumulative incidence of RLS in pregnancy was 18.1% for all women. Broken down by race, the incidence

was 20.3% for white women, 15.4% for black women, 17.1% for Hispanic women, and 21.1% for Asian women. Among Hispanic women, older age, anemia, and greater total skinfolds of the subscapular and triceps sites, independent of body mass index, were associated with a higher risk of RLS, whereas multiparity was associated with a lower risk. In black women, larger skinfolds and waist circumference were associated with a higher risk of RLS in pregnancy, although the trends were less clear.

In a study conducted in Germany (Goecke et al., 2020), a frequency of 19.3% was found on a sample of 561 female respondents. Also, women suffering from RLS were more often affected by a psychiatric history and were more exposed to stressful life events. In the aforementioned research, the connection between RLS during pregnancy and the occurrence of gestational diabetes and hypertension was shown. Body mass index (BMI), weight gain, parity, history of childbirth, or chronic exposure to stress during pregnancy as measured by hair cortisol were not found to be associated with RLS.

According to a group of authors from Italy (Esposito et al., 2019), in a sample of 648 women with an average age of 35, with a range of 32-38, the frequency of restless legs syndrome was 20.4%. The risk of the condition was increased in women aged  $\geq 35$  years and in women who reported sleep and wakefulness disorders during pregnancy. Older age and sleep-wake disorders are the main factors associated with this condition.

In this systematic review, which included a sample of more than 7,000 subjects, from 11 relevant studies, we obtained a mean prevalence of RLS in pregnant women of 20.24% through meta-analysis.

## CONCLUSION

We can conclude that the frequency of restless legs syndrome is high among the pregnant population. Pregnant women suffering from this syndrome have a worse quality of life, and more often develop symptoms of anxiety and depression (Jahani Kondori et al., 2020). This can ultimately cause weaker cooperation during the act of giving birth, which contributes to more frequent birth complications.

RLS is a neurological disorder that can lead to the development of significant psychiatric symptoms in the form of insomnia, anxiety and depression. Given that its prevalence increases during pregnancy, according to the meta-analysis of this systematic article it is 20.24%. Pregnant women affected by RLS have a poorer quality of life due to the development of comorbid psychiatric symptoms. We can conclude that RLS is a rather neglected disease, which should be considered often during pregnancy because it affects one in five pregnant women

and, in addition to neurological manifestations, it also produces psychiatric disorders.

**Ethical Considerations:** Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

**Conflict of interest:** None to declare

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**Authors contributions:** Muhamed Lepuzanović: Design of the study, interpretation of data, manuscript writing. Osman Sinanović: Supervision of the project, manuscript writing, approval of final version. Edin Bašagić: Literature searches, and analyses. Vildana Aziraj-Smajić: Literature searches, and analyses. Dževada Kapić: Literature searches, and analyses. Mirsad Muftić: Literature searches, and analyses

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