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Relationship of restless legs syndrome with number of pregnancies, duration of pregnancy and positive family history

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Abstract

Objectives: The aim of this cross-sectional study was to examine the correlation between gestational age and number of previous pregnancies in group of pregnant women with restless legs syndrome and the connection of restless legs syndrome with family history positive versus family history negative group of pregnant and non-pregnant women.

Methods: Four hundred and sixty-two women were involved in this study: 231 pregnant women and the same number of non-pregnant women of compatible age as a control group. We defined restless legs syndrome as presence of International Restless Legs Syndrome Study Group criteria. During the face-to-face interview with the researcher, respondents answered questions about duration of pregnancy, number of previous pregnancies and family history of restless legs syndrome.

Results: Before the 16th week of pregnancy, restless legs syndrome appeared in 7.1% of pregnant women and after 16 weeks of pregnancy in 22.6% of them ($t = 2.07$, $p = 0.039$). Restless legs syndrome appeared in 11.4% of pregnant women without restless legs syndrome in the family and in 74.2% of pregnant women who did have restless legs syndrome in the family ($t = 7.67$, $p < 0.001$). It was also found that among non-pregnant women with a family history of restless legs syndrome, 42.9% had restless legs syndrome, and among those without a family history of restless legs syndrome, only 4.9% had restless legs syndrome ($t = 3.49$, $p = 0.001$). No statistically significant correlation between restless legs syndrome and number of previous pregnancies in pregnant women has been found.

Conclusion: Our study confirmed a higher frequency of restless legs syndrome in women pregnant for 17 or more weeks and in both pregnant and non-pregnant women with a positive family history of this syndrome. We have not proven a connection between restless legs syndrome and multiparity.

Keywords

pregnancy, restless legs syndrome, women

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Introduction

Restless legs syndrome (RLS), or Willis-Ekbom's disease, is a movement disorder characterized by a powerful drive of the patient to move their legs due to unpleasant sensations in them. These feelings, described subjectively, are most often creeping, itching, pulling, crawling, tugging, tingling, muscle tightness and so on. International criteria for the diagnosis of RLS[1,2] were defined in 1995,[3] revised by the American National Institute of Health (NIH) in 2003 and updated by the International Restless Legs Syndrome Study Group (IRLSSG) in 2014.[2] We can distinguish between the primary (idiopathic) and secondary forms of RLS. The most common causes of secondary RLS are pregnancy, iron deficiency anemia and uremia (renal disease patients).[4] The etiology of RLS in pregnancy

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is still insufficiently investigated.[5] It is thought that reduced iron concentration in pregnant women and the existence of RLS in the family play the most important role.[6] Studies have shown that RLS occurs more frequently in the second and third trimester of pregnancy.[7] Although there is a study that showed the odds ratio for RLS was increased with the number of births among women, following a significant linear trend,[8] several other studies have not proven this connection.[9–12] This article examines the relationship between the number of previous pregnancies and pregnancy duration with the occurrence of RLS in pregnant women and the association of RLS in the family with the onset of illness in both pregnant and non-pregnant women. We chose the 16th week of pregnancy as the middle of the second trimester, when a higher incidence of RLS is expected compared to earlier stages of pregnancy.[7]

Research objectives are as follows:

- To compare the frequency of RLS in the gestational age group of up to 16 weeks, and the gestational age group of more than 16 weeks.
- To compare the frequency of RLS in women in their first pregnancy, with those who have had multiple pregnancies.
- To compare the frequency of RLS in pregnant women who have a positive family history of this syndrome with pregnant women without RLS in the family.
- To compare the frequency of RLS in non-pregnant women who have had a positive family history of this syndrome with non-pregnant women who do not have RLS in the family.

Methods

Respondents

Four hundred and sixty-two women were involved in this observational cross-sectional study. The sample size was calculated according to a precision of 5%, prevalence of 20% for pregnant women and 5% for non-pregnant women[5] and 95% confidence interval (CI), while the minimum required sample size was 384 pregnant and 384 non-pregnant women. Interviews with the pregnant women were conducted by the researcher, at the outpatient clinic of the Department of Gynaecology and Obstetrics, after a scheduled gynecological appointment. A total of 231 non-pregnant women of compatible age were also included in this study as a control group; they were recruited through relatives and friends of the clinic staff. The duration of the study and the gathering of participants lasted 16 weeks (from 9 January 2017 to 30 April 2017). Researcher (neurologist) established the diagnosis of RLS after conducting a first interview with participants and after a clinical examination. Those pregnant women who met the criteria for RLS after the first interview and clinical examination were included in the research, after which they participated in another interview with the researcher and completed a sociodemographic questionnaire. We defined RLS as presence of IRLSSG criteria confirmed in 2014,[2] with symptoms occurring $\geqslant$5 days/month and associated with at least moderate distress.[13,14] We evaluated level of distress through a sociodemographic questionnaire completed by the respondents. Since our sociodemographic questionnaire is not validated, we stated this as one of the limitations in our study. During the first interview with the researcher (neurologist), a diagnosis of RLS was established with consideration of differential diagnoses and exclusion of mimicking conditions, such as leg cramps, swelling (venous stasis, leg edema), positional discomfort, arthritis, myalgias and numbness (neuropathy).[2] The inclusion criteria were being aged between 18 and 50 years and being healthy at the time of recruitment. Woman who had underlying diseases such as diabetes mellitus, renal failure and neurological disorders (all other secondary possible causes of RLS) or women with a complicated pregnancy (pre-eclampsia, eclampsia and gestational diabetes mellitus) were excluded. Over a period of 16 weeks, interviews were conducted daily for 3–4 hours per day. All research was performed in accordance with ethical principles and approved by the relevant Ethics Commissions. The participants were made familiar with the goals of the research, potential benefits and risks and have given their written consent.

Questionnaire

During the face-to-face interview with the researcher, respondents answered questions about duration of pregnancy, number of previous pregnancies and family history of RLS.

No standard validated questionnaire was used; the researcher created it specifically for this study.

The questionnaire for pregnant women consisted of questions about number of their prior pregnancies, duration of their pregnancies, sleep quality (graded 1–5) and level of distress, RLS in the family, iron deficiency anemia, kidney diseases as well as use of medicines during pregnancy. As the control group consisted of non-pregnant women, questions about pregnancy were omitted from their questionnaires. All methods were carried out in accordance with relevant guidelines and regulations. We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cross-sectional checklist when writing our report.[15]

Statistical analysis

Four hundred and sixty-two subjects, in total, were classified according to RLS and pregnancy (Table 1). The statistical methods used are inferential (chi-square test

Table 1. Number of respondents surveyed for the presence of RLS in the family and according to the presence of restless legs syndrome and pregnancy.

Characteristic	NO RLS N (%)	RLS N (%)	Total N (%)
RLS in the family			
Yes	20 (5)	32 (44)	52 (11)
No	360 (92)	31 (43)	391 (85)
Doesn't know	10 (3)	9 (13)	19 (4)
Pregnant			
Yes	181 (78.4)	50 (21.6)	72 (15.6)
No	209 (90.5)	22 (9.5)	390 (84.4)

Table 2. Descriptive indicators of pregnancy duration and previous pregnancies, in the surveyed pregnant women (N=231).

Indicator	Number of respondents (N)	Arithmetic mean (x)	Median (Me)	Standard deviation (σ)
Duration of pregnancy				
No RLS	181	32.3	36.0	8.25
RLS	50	37.2	38.5	5.23
Total	231	33.4	37	7.95
Previous pregnancies				
No RLS	181	2.1	2.0	1.21
RLS	50	2.0	2.0	1.01
Total	231	2.1	2.0	1.17

and t-test difference proportions for independent samples) and descriptive (relative numbers, mean values, dispersion measures, graphical representations). Conclusions were made based on the differences and correlations between variables, taken at the usual significance level of 0.05 ($p < 0.05$), that is, with a confidence of 95%.

Results

Descriptive indicators of pregnancy duration and previous pregnancies

Pregnancy duration varied between 4 and 41 weeks, averaging 33.4 weeks. In Table 2, descriptive indicators of pregnancy duration and previous pregnancies are broken down into two subgroups of respondents: those with RLS and those without it. Higher values of pregnancy duration prevailed in both women who have RLS and in those who do not have it. Of the 231 pregnant women, 14 (6%) were pregnant for 16 weeks or less, and the remaining 217 (94%) were pregnant for 17 or more weeks. Distributions of previous pregnancies were L-shaped, that is, fewer values prevailed (first pregnancy), both for women who had RLS and those who had not. The dispersion was increased (the coefficients of variation are 51% and 58%). In conclusion, 39% of women have been pregnant once, and 61% have had multiple pregnancies.

The frequency of RLS in the families of surveyed women

The results of the chi-square test showed that there is a statistically significant association between RLS in the family and the occurrence of the disease in the respondents ($\chi^2 = 115{,}482$, df=2, N=462, $p < 0.001$). In a group of women with RLS, 44% had RLS in the family, while among women who do not have RLS, only 5% had RLS in the family.

Results of t tests of difference between ratios

For the purpose of estimating the correlation between the number of pregnancies and pregnancy duration with the occurrence of RLS in pregnant women and the correlation of RLS in the family with the onset of the disease, t tests of difference between ratios for independent samples were performed. The results showed that before the 16th week of pregnancy, RLS appeared in 7.1% of pregnant women, and after 16 weeks of pregnancy, in 22.6% of them. This difference is not random but is statistically significant ($t = 2.07$, $p = 0.039$). RLS was present in 22.5% women pregnant for the first time and 21.1% of women with multiple pregnancies. This difference is small, random and not statistically significant ($t = 0.24$, $p = 0.810$). RLS appeared in 11.4% of pregnant women without RLS in the family and in 74.2% of pregnant women who did have RLS in the family. This difference was large and statistically significant ($t = 7.67$, $p < 0.001$). Among the 227 non-pregnant women for whom family history was known, 21 had a family history of RLS. Among those with a family history of RLS, 42.9% had RLS, and among those without a family history of RLS, only 4.9% had RLS. This difference was also statistically significant ($t = 3.49$, $p = 0.001$). Nineteen women did not know if they have RLS in the family (4 non-pregnant and 15 pregnant), so they were not taken into consideration when proving the connection between a positive family history of RLS and the occurrence of the syndrome. Figure 1 shows the percentage of RLS in pregnant and non-pregnant subgroups.

Discussion

In this article, we wanted to investigate the association of several risk factors with the occurrence of RLS. We analyzed the relationship between pregnancy duration and the number of previous pregnancies with RLS in pregnant women, and the association of RLS in the family with the onset of the illness in pregnant and non-pregnant women. The analysis of the frequency of RLS in pregnant women before gestational week 16 showed that RLS appeared in

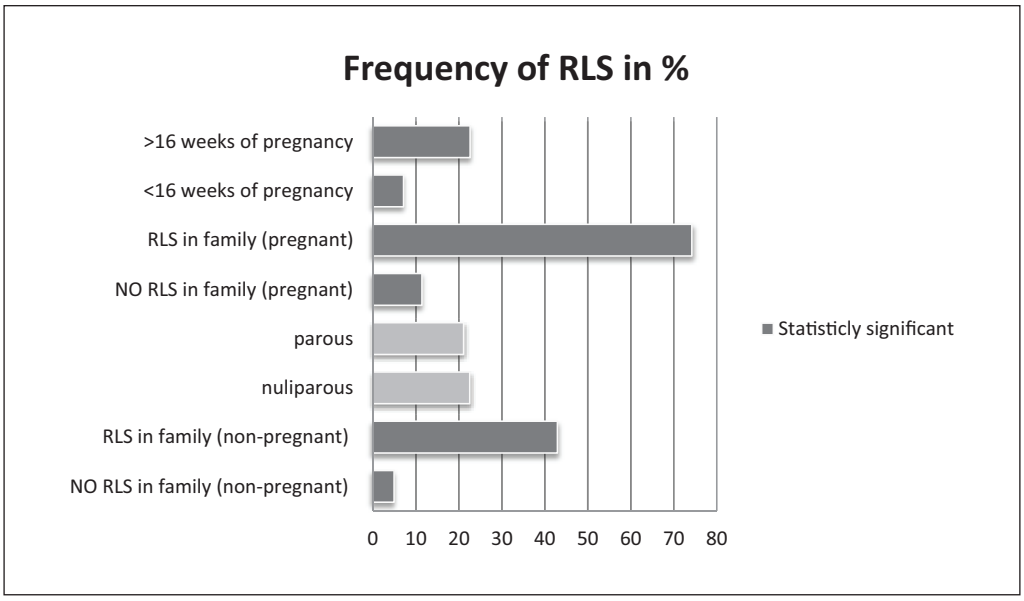

Figure 1. Frequency of RLS in pregnancy subgroups (first three pairs of columns) and in the subgroup of non-pregnant women (the last pair of columns) in %.

7.1% of pregnant women, and after gestational week 16 in 22.6% of them. We can conclude that RLS more often occurs after the 16th week of pregnancy, which is comparable with the results of similar studies.[16–18] Some of the assumed mechanisms for the frequent occurrence of RLS in later stages of pregnancy include a reduced level of folates and ferritin in the serum of women before conception and during pregnancy,[19] increased iron demand and consequent decrease in its concentration, a positive family history, a disturbed circadian rhythm of dopamine with decreasing concentrations in the evening and hormonal changes, primarily the rise in estradiol in the third trimester, which acts inhibitively on the dopaminergic system.[20] Studies did not confirm that a higher number of previous pregnancies was associated with a higher frequency of RLS among pregnant women.[9–12] Our study did not prove this association as well. It is certain that, along with pregnancy, many other factors also affect the symptoms of RLS, such as renal disease, antidepressant consumption, antipsychotics, anti-nausea drugs and other drugs that reduce the levels of dopamine, age, lifestyle (smoking, alcohol consumption and caffeinated beverages etc.), social status,[21] which could explain the results obtained. Today, we know that RLS is a complex disease, and its manifestation is determined by environmental and genetic interactions.[22] The results of this study show that there is a correlation between the existence of RLS in the family and the onset of illness in the participants, that is, that RLS occurs more often in both pregnant women and non-pregnant women with cases of RLS in the family. Numerous studies reveal more and more genetic loci associated with RLS,[23,24] which provides a starting point for further research and the development of new therapeutic options. Some comorbidities associated with RLS are pain disorders, insomnia, depressive and anxiety disorders.[25] Differential diagnosis is particularly important, as some of the medications used to treat insomnia and depression may exacerbate RLS symptoms. It has been shown that RLS is associated with different pathologies, not only neurological diseases, but also cardiovascular diseases, hypertension and diabetes. Multiple factors may contribute to the interplay between RLS and vascular disease: high blood pressure and heart rate, high sympathetic drive, nondipping blood pressure, sleep deprivation and inflammation.[26] Treatment of some comorbid conditions may reduce RLS symptoms, and treatable conditions (iron deficiency anemia, diabetes or hypertension) should be optimized first.[27] It is necessary to recognize the illness and begin treatment as early as possible, in order to alleviate symptoms and, in some cases, also lessen comorbid disease burden. Our study has several strengths, including the large size, the standardized assessment of RLS according to the diagnostic criteria of the International Restless Legs Study Group and inclusion of a control group of non-pregnant women in the study. Limitations of this study are also several. Information regarding potential confounders such as age, lifestyle (smoking, alcohol consumption and caffeinated beverages), social status that might be associated with RLS was not systematically assessed, so we could not investigate whether this influenced our results. Also, we used a sociodemographic questionnaire that was created specifically for this study and was not validated.

Conclusion

Our study confirmed a higher frequency of RLS in pregnant women for 17 or more weeks and in both pregnant and non-pregnant women with a positive family history of this syndrome. We have not proven a connection between RLS and multiparity. It is important to educate patients about the existence of this syndrome, explain the nature of their illness and advise them to change their life habits (moderate physical activity, relaxation exercises, reduction of caffeinated and alcoholic drinks, smoking cessation, going to bed and waking up at about the same time, avoiding sleep during the day etc.). The secondary form of the illness can be prevented by treating the underlying disease, most often by oral or intravenous iron replacement, but also by compensating folic acid, stopping drug therapy that reduces dopamine levels and so on. If the mentioned treatment measures do not help, consideration is given to the introduction of appropriate medication therapy, but only to non-pregnant women. Due to the harmful effects of some drugs on unborn children, primarily the risk of congenital fetal malformations, it is necessary to estimate the risk–benefit ratio of medication therapy for each patient. Due to the limitation of medication therapy in pregnant women, additional efforts are needed for education about and prevention of RLS.

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Author contribution(s)

Lucija Čondić Jurjević: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Writing—original draft; Writing—review & editing.
Srđana Telarović: Conceptualization; Formal analysis; Supervision; Writing—review & editing.

Consent to participate

All participants provided written informed consent prior to enrollment in the study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Central Ethics Committee, University of Zagreb, School of Medicine (20.12.2016, ID: 380-59-10106-16-5981) and Ethics Committee University Hospital Centre Zagreb, Clinic for Women's Disease (20.10.2016, ID: 021-1/127-16).

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Supplemental material

Supplemental material for this article is available online.

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