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## Sleep Medicine Reviews

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## CLINICAL REVIEW

## When gender matters: Restless legs syndrome. Report of the “RLS and woman” workshop endorsed by the European RLS Study Group

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## ARTICLE INFO

## Article history:

Received 13 May 2011

Received in revised form

30 August 2011

Accepted 30 August 2011

Available online xxx

## Keywords:

Restless legs syndrome

Gender

Female

Sleep

Insomnia

Pregnancy

Estrogens

Menopause

Quality of life

## SUMMARY

Sleep is an essential human behavior that shows prominent gender differences. Disturbed sleep, in particular, is much more prevalent in females than males. Restless legs syndrome (RLS) as one cause of disturbed sleep was observed to be somewhat more common among women than men in Ekblom's 1945 seminal series of clinical cases with the disease. He, however, reported this gender difference mainly for those with more severe symptoms. Since then numerous studies have reported that women are affected by RLS about twice as often as males for mild as well as moderate to severe RLS. The present review focuses on RLS in females from the perspectives of both epidemiology and pathophysiology. RLS will generally become worse or might appear for the first time during pregnancy. Parity increases the risk of RLS later in life suggesting that pregnancy is a specific behavioral risk factor for developing RLS. Some evidence suggests that dysfunction in iron metabolism and high estrogen levels might contribute to RLS during pregnancy. But, menopause does not lower the incidence of RLS nor does hormone replacement therapy lead to an increase, suggesting a quite complex uncertain role of hormones in the pathophysiology of RLS. Therefore, further, preferably longitudinal studies are needed to unravel the factors causing RLS in women. These studies should include genetic, clinical and polysomnographic variables, as well as hormonal measures and variables assessing iron metabolism.

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## Introduction

In surveys on subjectively disturbed sleep, there is overwhelming evidence for a clear-cut preponderance of females,<sup>1</sup> particularly beyond the age of 40. The underlying causes are still under investigation, but some contributing factors are known: insomnia is tightly linked to depression which is much more prevalent in women compared to men.<sup>2</sup> Night time care of children and other family members, tasks more commonly performed by women, increases their vulnerability to disturbed night sleep.<sup>3</sup> Hormonal changes, related to the menstrual cycle, pregnancy and

ageing are prominent additional challenges to women's sleep. The influence of female steroidal sex hormones on sleep is, however, complex.<sup>4</sup> In healthy women, for example, polysomnographically recorded sleep is remarkably stable across the menstrual cycle,<sup>5</sup> whereas subjective reports of sleep disturbances are both frequent for women in the late luteal phase and associated with depressed mood, affective lability, anxiety and other emotional symptoms known as premenstrual dysphoric disorder.<sup>4</sup> Of course, the cessation of ovarian endocrine function during menopause also influences sleep and it is not surprising that during the 4th and 5th decade of life the prevalence of sleep problems in women increases to up to 25%.<sup>6</sup> However, hormonal changes are unlikely to be the only cause of this increase, because hormonal replacement therapy (HRT) is not able to entirely reverse these age-related changes.<sup>4</sup> Finally, pregnancy and delivery result in profound changes in

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**Abbreviations**

AC	active controlled
CO	crossover
CSF	cerebrospinal fluid
DB	double blind
FMT	female-to-male transsexuals
HRQoL	health related quality of life
HRT	hormone replacement therapy
IQR	interquartile range
IRLSSG	international restless legs syndrome study group
MFT	male-to-female transsexuals
MRI	magnetic resonance imaging
PC	placebo controlled
PG	parallel group
PLM	periodic leg movements
R	randomized
REST	RLS epidemiology, symptoms and treatment
RLS	restless legs syndrome
RLSQoL	restless legs syndrome quality of life
SD	standard deviation
SF-36	short form (36) health survey

hormonal secretion. Sleep problems start quite early in pregnancy indicating endocrine causes and tend to increase as the pregnancy progresses, suggesting that particularly in late pregnancy mechanical aspects might also contribute.<sup>7</sup>

The last trimester of pregnancy is also a time of increased prevalence of restless legs syndrome (RLS), which may occur in up to 30% of pregnant women. In those women affected, the typical symptoms of the disorder including unpleasant sensations in the legs and an almost mandatory drive to move, tend to further aggravate the sleep problems occurring in late pregnancy.<sup>8</sup> Additional evidence reviewed below shows that even in non-pregnant women RLS might be about twice as frequent as in males.

Hence the female side of RLS seems quite important and our effort in this paper is to review for the first time the epidemiological data and the evidence explaining the increased prevalence of RLS in general and under specific conditions in females. Of course, the interaction of hormones and RLS will be a major topic of this review, but also iron metabolism, which is closely linked to RLS and consistently affected by pregnancy, will be discussed.<sup>9</sup> The present review was endorsed by the European RLS Study Group and written by the participants of the workshop on “RLS and women” which took place in Munich, Germany (December 2009).

**Female prevalence**

In 1945, the Swedish neurologist K.A. Ekbom published his thesis “Restless legs. A clinical study of a hitherto overlooked disease in the legs”.<sup>10</sup> Thus Ekbom coined the name of this disorder and wrote what still is considered to be one of the most substantial and comprehensive works on RLS. Ekbom reported a prevalence of 5.2% of restless legs in subjects living in Stockholm. There was a female predominance noted for more severe cases.<sup>10</sup> After Ekbom’s report, there have been more than thirty published epidemiological studies focusing on RLS.<sup>11</sup>

Data on the occurrence of RLS are quite variable and this may be due to several reasons. It is important to define the study population, i.e., whether the sample studied represents a clinical patient population or harvested in the general population. Moreover, the instruments used for the diagnosis of RLS vary between different epidemiological studies.

Different strategies of data collection may influence the results. Face-to-face interviews and examinations by trained physicians are the most sensitive and specific way to acquire the data.

In 1995, the International restless legs syndrome study group (IRLSSG) published a consensus report for the diagnosis of RLS.<sup>12</sup> Data from studies performed before 1995, and some studies performed after 1995 as well, used different diagnostic instruments in order to ascertain the population defined as RLS. Thus reports on the occurrence of RLS, not using the criteria from 1995 or the revised criteria from 2003,<sup>13</sup> are not directly comparable to each other or to later studies.

In a recent substantial and comprehensive population-based survey, face-to-face home interviews were conducted in a random sample of 10,263 French adults.<sup>14</sup> The four features defined by the IRLSSG in 1995 were used to assess the prevalence of symptoms consistent with a diagnosis of RLS. The 12-month prevalence of RLS symptoms in the French adult population was estimated to be 8.5%, with a higher prevalence observed in women (10.8%) than in men (5.8%). Prevalence increased with age until 64 years and decreased thereafter in both genders. RLS was often underdiagnosed and few subjects received recommended RLS drug treatment. Accordingly, the prevalence of RLS in the Caucasian population seems so be about 5–15%. What we know from these studies is that there seems to be strong evidence for a female preponderance in the prevalence of RLS and that RLS prevalence increases with age. The female/male ratio is often 2–3/1.<sup>11</sup> Data harvested on the occurrence of RLS from countries outside Europe and USA are still few.

There are very few studies on the occurrence of RLS that did not report a female preponderance in RLS. Table 1 shows the prevalence of RLS in both genders in epidemiological surveys performed on a random sample of the population in different countries by using the IRLSSG definition to diagnose RLS.

**Quality of life in women with RLS**

One way of defining the concept of health related quality of life (HRQoL) is: “The extent to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition”. Individual patients with the same objective health status can report dissimilar HRQoL due to unique differences in expectations and coping abilities and it must be measured from the individual’s viewpoint.

Previous studies focusing on gender differences in HRQoL have reported consistently worse results for women. This has been a subject of controversy and much is written on the topic. Whether this is attributable to sociocultural, socioeconomic or biomedical factors has not been determined definitively.<sup>15</sup> It is proposed that women have a greater “inclusiveness” of various sources of

**Table 1**

Studies on the prevalence of RLS performed in random samples of the general population of different countries, using the IRLSSG criteria to assess the diagnosis.

First author, year of publication	Country	Sample size	Total RLS prevalence (%)	Prevalence (%) female/male
Ohayon, 2002 <sup>88</sup>	UK, Germany, Italy, Spain, Portugal	18980	5.5	
Sevim, 2003 <sup>a,89</sup>	Turkey	3234	3.2	
Berger, 2004 <sup>19</sup>	Germany	4310	10.6	
Bjorvatn, 2005 <sup>90</sup>	Norway, Denmark	2005	11.5	13.4/9.4
Tison, 2005 <sup>a,14</sup>	France	10263	10.3	10.8/5.8
Högl, 2005 <sup>a,53</sup>	Austria	701	10.6	14.2/6.6
Hadjigergiou, 2007 <sup>91</sup>	Greece	3033	3.9	
Ulfberg, 2007 <sup>92</sup>	Sweden	1000	5.0	5.7/3.5
Cho, 2009 <sup>a,93</sup>	South Korea	6509	0.9	1.3/0.6

<sup>a</sup> Surveys based on face-to-face interviews.

**Table 2**

Epidemiological studies published in literature on RLS prevalence that included an assessment on the quality of life.

First author, country	Year	N	HRQoL scale	RLS positives	RLS negatives	Sample group	Comments
Abetz, <sup>5</sup> USA	2004	85	SF-36	PCS 37 MCS 46	PCS 50 MCS 50	Clinically referred patients	RLS-patients had significantly lower SF-36 scores compared with the normative general US population values and similar, or worse scores than patients with hypertension, angina pectoris, diabetes and osteoarthritis. <i>No significant differences were observed between men and women in the RLS group for the SF-36 scores</i>
Allen, <sup>6</sup> USA and five European countries	2005	384	SF-36	PCS 56 MCS 66	PCS 79 MCS 75	Population based	SF-36 scores from US RLS-sufferers were below population norms, matching those of patients with other chronic medical conditions, such as type 2 diabetes and clinical depression. <i>Gender differences not reported</i>
Rothdach, <sup>3</sup> Germany	2000	36	SF-36	PCS 75 MCS 68	PCS 80 MCS 75	Population based	RLS-sufferers had lower mental and general health SF-36 scores compared with demographically matched control subjects. <i>Gender differences not reported</i>
Berger, <sup>4</sup> Germany	2004	433	SF-12	PCS 49 MCS 44	PCS 52 MCS 49	Population based	RLS-sufferers had lower mental and general health SF-36 scores compared with RLS-negatives in the study. <i>Gender differences not reported</i>
Kushida, <sup>9</sup> USA	2007	158	SF-36	PCS 3 MCS 47	PCS 48 MCS 51	Population based	After controlling for co-morbidity RLS-sufferers had a unique burden of both physical and mental aspects of HRQoL compared to US general population norms. RLS-sufferers scored lower than type-2 diabetes patients. <i>Gender differences not reported</i>
Winkelmann, <sup>7</sup> USA	2009	4.8% av 2821	SF-36	PCS 61 MCS 76	PCS 68 MCS 79	Population based	RLS-sufferers scored lower on both physical and mental domains compared to RLS-negatives in the study. Polysomnography was used. <i>Gender differences not reported.</i>
Wesström (resubmitted manuscript), Sweden	2010	536	SF-12	PCS 48 MCS 46	PCS 49 MCS 48	Population based	The study only included women. After controlling for co-morbidity RLS-sufferers had a unique burden more on mental aspects of HRQoL compared to RLS negatives in the study. <i>Gender differences could not be reported.</i>
Happe, <sup>8</sup> Germany	2008	519	EQ-5D VAS	General health 56	General health 774	Clinically referred patients	RLS-sufferers scored their health lower than the general population, as low as other chronic neurological disorders such as Parkinson's disease and stroke. <i>No significant differences were observed between men and women</i>

*Abbreviations:* EQ-5D VAS, visual analogue scale score for the EQ-5D, a quality of life questionnaire developed by the EuroQoL Group; HRQoL, health related quality of life; MCS, mental component score of the SF-36; RLS, restless legs syndrome; PCS, physical component score of the SF-36; SF-36, SF-12, short form health survey.

information when making self-assessed health judgments and that it is based on a wider range of health-related and non-health related factors compared to men.<sup>16</sup> There is, to the knowledge of the authors, no significant difference in RLS symptom severity in relation to gender.<sup>17</sup>

Impaired quality of life is most likely a consequence of RLS and there is a growing knowledge in the area. There are some methodological differences between studies. Different questionnaires measuring HRQoL among RLS-patients have been used and the quality of life has in some studies been addressed in clinical samples, in some others in the general population. In literature databases eight prevalence studies were found concerning RLS and health related quality of life (Table 2).<sup>18–25</sup>

The short form (36) health survey (SF-36) and the shorter SF-12 version are widely used questionnaires,<sup>26,27</sup> and are still the ones used most frequently for evaluating HRQoL in RLS populations. It has been suggested that a clinically meaningful difference in HRQoL is equivalent to a half standard deviation,<sup>28</sup> which would be 3–4 points in the SF scales.

However, an RLS-specific scale was created (RLSQoL) and has been demonstrated to be a reliable tool to assess more particularly RLS impact on quality of life.<sup>29</sup>

Some studies indicate that RLS affects the physical aspects more than the mental aspects of quality of life,<sup>20,22,24</sup> but there are also studies in favor of the opposite view.<sup>18,19</sup>

Only Abetz et al.<sup>20</sup> and Happe et al.<sup>23</sup> have evaluated differences in HRQoL between men and women with RLS but no difference could be found. Five studies did not report data on gender differences.<sup>18,19,21,22,24</sup> In the last study only women were included.<sup>25</sup>

Kushida and co-workers,<sup>24</sup> controlling for the impact of age, gender and disease co-morbidity, showed that RLS-positives reported a unique burden of both physical and mental aspects of HRQoL compared with general US population norms. Similar results have also been obtained in Germany by Berger et al.<sup>19</sup> In several other previous studies RLS-positives have been shown to score their own health below population norms, similar to patients suffering from other chronic medical conditions. However, in several studies, adjustments for co-morbidities have not been made. In the German Memo-study<sup>18</sup> 36 elderly individuals with RLS had lower mental and general health SF-36 scores compared with demographically matched control subjects. The study from Abetz and colleagues provided an indication that RLS-patients had significantly lower SF-36 scores compared with the general US population and similar, or worse than, patients with hypertension, angina pectoris, diabetes and osteoarthritis.<sup>20</sup> However, the RLS-positives were not representative of the general population. In the large RLS epidemiology, symptoms, and treatment (REST) study, conducted in the United States and five European countries, Allen and colleagues reported SF-36 scores from US RLS-positives to be below population norms, matching those of patients with other chronic medical conditions.<sup>21</sup>

Similar results were recently published by Happe et al.<sup>23</sup> A study from Winkelmann and co-workers showed that subjects with RLS reported poorer HRQoL in both physical and mental domains.<sup>22</sup> In a study from Wesström et al. concerning HRQoL among women with RLS, the material was “purified” from co-morbidities and the RLS component alone was shown to significantly affect HRQoL.

Concerning the treatment effect on RLS-patients, dopaminergic treatment seems to improve HRQoL, both in short-term studies and

also in long-term ones. This improvement in HRQoL has been shown to be an important factor supporting maintenance of drug efficacy.<sup>30</sup>

In conclusion, there is an impaired self-reported well being among RLS-patients. Women often, for unclear reasons, report worse HRQoL compared to men with the same medical condition, but this has not been reported for RLS. This may reflect problems with the data in the literature but this interesting lack of HRQoL gender difference for RLS should be addressed in future investigations.

### Pregnancy-related RLS

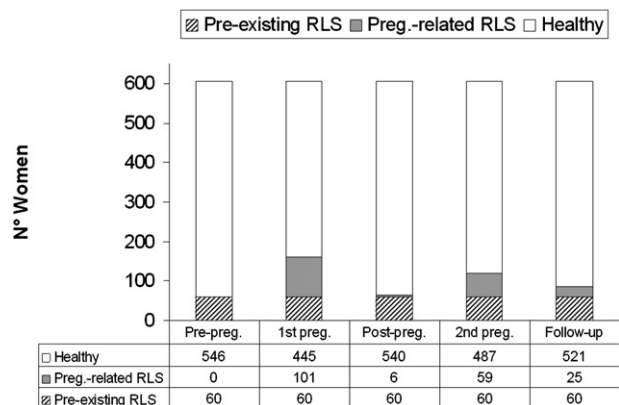
Even before the term “restless legs syndrome” was coined by Ekbom in 1945, two German physicians reported the occurrence of a strange nocturnal symptomatology characterized by “pruritus, urticaria and paresthesias” of the lower limbs, appearing during rest, in three subjects belonging to the same family. Curiously, one of the family members was a woman who suffered with symptoms mainly during pregnancy.<sup>31</sup>

The relationship between RLS and pregnancy was later confirmed by Ekbom himself, who performed the first structured epidemiological study with a prevalence of RLS of 11.3% among 486 pregnant women.<sup>10</sup> Before the diagnostic criteria for RLS were established, three other investigations explored the same topic, finding a prevalence of RLS during pregnancy ranging between 12 and 27%.<sup>32–34</sup> When the prevalence rate was assessed by using the standard diagnostic criteria for RLS, and by a face to face medical interview, the variability of the results turned out to be more narrow ranging between 26 and 30%.<sup>8,35</sup> The minimal threshold of frequency of symptoms occurrence in order to define a woman as RLS affected, the different geographic areas and racial populations considered, and the phase of the pregnancy in which the survey was assessed, represent further sources of variability. However, all the study results agree in showing pregnancy to be a significant risk factor for RLS.

Although some of the women with RLS during pregnancy are already affected by an idiopathic form of RLS, most of the women develop the symptoms only after the onset of pregnancy.<sup>36</sup> In the majority of the cases, women with a pre-existing form of RLS report a worsening of the symptoms during pregnancy.<sup>8</sup> RLS across the pregnancy period shows a progressive increase of the prevalence rate until a clear peak around the 7th and 8th month and a stabilization or a mild decrease in the last month of pregnancy.<sup>8,35</sup> Two longitudinal studies demonstrated a clear drop of the symptoms around delivery, which is maintained throughout the puerperium.<sup>8,34</sup> One long-term follow-up study, however, demonstrated that after a mean interval of about 7 years from the pregnancy, the risk to develop a chronic “idiopathic” RLS form is four-fold higher in women who experienced transient RLS in their previous pregnancy compared to those who did not.<sup>37</sup> In other words, while the immediate prognosis for the pregnancy-related RLS form remains good, the long-term one seems to be less favorable. In addition to being a risk factor for the future development of chronic RLS, pregnancy-related RLS also increases the chances for new transient symptoms in future pregnancies (Fig. 1).<sup>37</sup>

The main features of RLS during pregnancy, such as the quality of symptoms, the anatomic distribution, the circadian course and the motor activity that relieves the symptoms, resemble those of the idiopathic form.<sup>8</sup>

Women who experience RLS during pregnancy complain of longer sleep latency, excessive daytime sleepiness, shorter total sleep time, and more frequent insomnia than pregnant women free of RLS.<sup>8,38</sup> In a few cases the symptoms can be very disturbing, making evening relaxation and falling asleep almost impossible.



**Fig. 1.** Epidemiological results on RLS and pregnancy. Histograms show the prevalence trend of RLS in a group of 606 women surveyed at the end of pregnancy. In the period before pregnancy, 60 women already experienced RLS symptoms in their life (in a non pregnancy period) and were classified as “pre-existing RLS”. The remaining 546 women had never experienced RLS symptoms before and were classified as “healthy”. During the first assessed pregnancy (2nd histogram) 101 women, out of the 546 “healthy” ones, developed a transient RLS form strictly related to the pregnancy and were classified as “pregnancy-related RLS”. All these 101 women with a new form of pregnancy-related RLS form, except 6 women, recovered after delivery (3rd histogram). Fifty nine of the same pregnancy-related RLS group suffered again RLS symptoms during a further following pregnancy. After a mean follow up of 7 years, 25 out of the 101 women who experienced the symptoms during the first pregnancy (pregnancy-related RLS group) developed a chronic apparently idiopathic RLS form even out of pregnancy. Elaborated data from the study of Cesnik et al.<sup>37</sup>

However, it is difficult to evaluate the impact of the RLS “per se” on sleep; pregnancy is a condition that in itself induces insomnia, particularly during the third trimester when nycturia, fetal movements, gastroesophageal reflux, snoring, sleep apneas, limitations on body position in bed and anxiety about the delivery, may impair sleep quality.<sup>7</sup>

As well as for idiopathic RLS, the pathogenesis of this pregnancy-related form remains unclear. Both family history of RLS and multiparity have been recognized as independent predictors of pregnancy-related RLS.<sup>8,35</sup> Parous women have a higher prevalence of RLS compared to age-matched nulliparous women.<sup>39</sup>

Since not all women develop RLS symptoms during pregnancy, but almost all women already affected by RLS before the pregnancy report a worsening of symptoms during pregnancy,<sup>8</sup> it is plausible that there exists two different types of pathogenetic factors for this pregnancy-related RLS form: those physiologically linked to pregnancy, which lower the symptomatic threshold for RLS in all pregnant women, and those factors specific to each subject, which predispose to RLS. The first class of factors might include some pregnancy-related biological phenomena such as iron storage decline, the increase of a specific sexual hormone, the stretch or compression of lumbar nerve roots associated with the fetal growth or the physiological changes and sleep disruption typical of the late pregnancy.<sup>36</sup> The second class of factors likely includes the genetic background or the condition of iron storage before the start of the pregnancy. Compared to non-RLS women, those who develop the symptoms during pregnancy seem to have lower, though still within the normal range, iron and folate values during the time just before the pregnancy onset, and to have lower iron and iron storage indicators at the end of the pregnancy.<sup>40</sup> However, this theory is weakened by two findings: women who receive folate and oral iron supplementation during pregnancy have a similar chance to develop RLS compared with women who follow a not supplemented diet and RLS symptoms disappear just before the delivery, although the main blood and iron loss is due to the delivery, and it needs some months to be restored.<sup>8</sup> It has been suggested that the

improvement after delivery is due to the absence of the heavy iron demands of the fetus that begin to change prior to delivery (see below: Iron and RLS). Under this perspective, pregnancy can act as a strong risk factor that needs, however, a specific genetic predisposition to trigger the RLS phenotype. Future research, based on the frequency of the already known allelic variants predisposing for idiopathic RLS<sup>41,42</sup> should replicate this in this apparently “secondary” form of RLS.

Concerning a possible therapeutic approach, iron or folate deficiency must be recognized and eventually supplemented, and renal and neurological dysfunctions or other possible causes of RLS should be excluded. In addition, behavioral changes to help alleviate the symptoms, such as avoiding smoking, caffeine, prolonged erect posture and generally excessive daytime motor activity, should be suggested. No systematic studies are available about RLS pharmacological treatment in pregnancy. Dopamine-agonists, that currently are considered the first choice treatment in RLS, could theoretically interfere with the process of lactogenesis, because of their inhibition of prolactin secretion via D2 receptor agonism. It must be stressed that all the available drugs effective in RLS, clonazepam included, are classified as category C in pregnancy (lack of controlled studies in pregnant women). Therefore, pharmacological treatment of the pregnancy-related RLS is in general discouraged, and if it is unavoidable, it should be used only during the third trimester, intermittently on demand when needed and at the lowest efficacious dosage.

Correct information from physicians should be the first therapeutic step: women who experience RLS during pregnancy should be informed that symptoms will almost certainly vanish during the puerperium, but warned that they might reappear later on.

### Parity and RLS prevalence

While RLS has been studied in a large variety of settings, including clinical trials, population-based studies, patient support groups and patient registries as well as within families, only a very few studies have aimed at explaining the gender difference in RLS onset. Among these few studies, some have looked at hormonal or body changes during pregnancy since it has been known for decades that RLS symptoms often occur in the third trimester of pregnancy.

An earlier study<sup>19</sup> addressed the question if the number of children born to a woman is associated with the incidence of RLS. In this context, the number of children or parity has to be understood as a proxy measurement. It is a summary for the transient but also for the cumulative physiologic changes related to the process of pregnancy and giving birth to one or more children by a woman. Parity can be seen as a simple proxy for a very complex process. It has to be noted, however, that this process is physiologic and not pathologic. In a population-based study in North Eastern Germany,<sup>19</sup> it was found that the RLS prevalence was strongly and significantly related to the number of children born to a woman. While an increase with higher ages in the overall RLS prevalence was also observed in this study in both genders, the prevalence in women differed strongly after stratification by the number of children. Interestingly, nulliparous women had a very similar prevalence as men in all age groups up to 64 years. With each child born, the prevalence increased in women across all ages. This was the first study that suggested an association between parity and the onset of RLS. The most important finding was that the prevalence of RLS does not differ between nulliparous women and men. This result supports the hypothesis that it is not gender per se that causes the difference in RLS frequency, but puts emphasis on the effects of pregnancy and child-bearing.

In a cross-sectional study of a German primary care population,<sup>43</sup> the association between parity and RLS was analyzed. While the overall prevalence of RLS in this population of more than 300 practices of general practitioners was higher than in the population-based studies, the same gender difference was observed. Fig. 2 shows the prevalence of RLS among the 9278 participating women, stratified in two age groups and according to the number of children born. In both age groups nulliparous women had the lowest prevalence. It increased with each subsequent child born. However, the increase was only minimal in women with more than three children.

In the interpretation of the results of the two studies several methodological issues have to be taken into account. First, the analyses were based on cross-sectional data. Thus, a clear time sequence between assessment of RLS and pregnancy cannot be given and the retrospective assessment might be influenced by recall bias. Second, the ability to give birth to a child is directly linked to female gender. Thus, disentangling the gender from parity is difficult. Both studies solved this problem by using nulliparous women as the reference. Further, while age of the mother giving birth to her first child might vary considerably, it is clear that she is older when she will have her second, third or fourth child, i.e., has become multiparous. Since RLS prevalence is related to increasing age, it is again difficult to disentangle effects of age from that of parity. In the two studies reported, this problem was addressed by stratification within age groups and by statistical adjustment. Finally, repetitive pregnancies might lead to considerable physiologic hormonal changes of long-lasting duration. These potential effects, however, can only be addressed or measured if it is known which factors to collect. Some caution should be paid to the fact that one of the principles in epidemiological studies is that replication in independent studies contributes strongly to the acceptance of study results. A more recent study has provided such a replication (see iron section), but it would be good to have further replications in large population-based studies of the association reported between parity and RLS.

The results published so far, overall, support the need for prospective cohort studies of women in their first pregnancy. Including a large number of these women in a long-term prospective study would enable identification of genetic and/or laboratory markers associated with the risk of RLS during this first pregnancy. Later follow-up would allow study of the decrease and eventual new onset of symptoms during a later pregnancy and, more generally, the risk for women to develop RLS depending upon RLS symptom status during the first pregnancy. Current evidence seems to be large enough to justify this type of study.

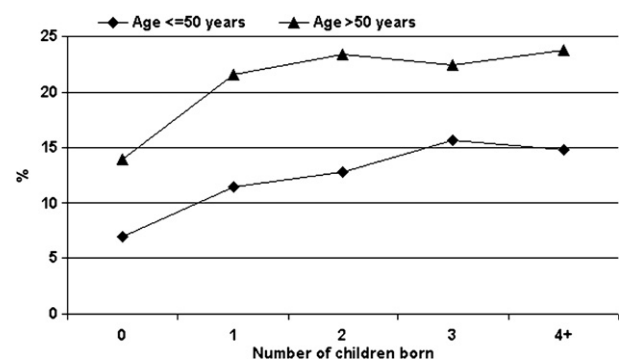


Fig. 2. Prevalence of RLS among women in two age groups and according to number of children born in the German general practitioner study.<sup>43</sup>

## Menopause and RLS

By contrast to the worsening or prompting effect of pregnancy on RLS, little is known of the effect of menopause, although it was suggested, but not yet demonstrated, that the postmenopausal intake of estrogen may play a role in the clinical manifestation of RLS in elderly women. However, if female sex hormones changes are involved, then one would expect RLS symptoms to change accordingly, as in migraines where the hormonal milestones of menstrual periods, pregnancy and menopause are often associated with changes in headache frequency and severity.

Menopause is defined by the permanent cessation of menstruation for 12 months secondary to a loss of ovarian activity with a mean age of occurrence of 51.3 years and has endocrine characteristics of elevated gonadotropin secretion and persistently low levels of ovarian steroids (estradiol, progesterone).<sup>44,45</sup> In migraines, this drop in estrogen levels seems to have a marked influence on headaches as the prevalence of both migraine and other headaches decreases markedly between 50 and 60 years.<sup>46</sup> Whether this hormonal drop has a similar influence on RLS is presently unknown but indirect cues about hormonal influence on RLS occurrence and clinical manifestation stem from the observation of a close association between migraine and RLS indicating a putative shared hormonal underlying mechanism. Indeed, RLS frequency was shown to be significantly higher in patients with migraine than in control subjects.<sup>47–49</sup> Moreover, and similarly to migraine, increase in the prevalence of RLS was found to correspond to periods of relatively high levels of estrogens<sup>50</sup> and transient increase in estradiol levels was also shown in pregnant women with RLS.<sup>51</sup> Therefore, if RLS is more prevalent in periods of high estrogen levels then one would expect a decrease in RLS prevalence starting from the fifth decade. Yet, in prevalence studies, an increase in RLS prevalence was noted between the age of 50–60 in both genders<sup>52</sup> and a clear tendency for increased RLS prevalence was noted with age in women. This is not what one would have expected if RLS expression paralleled the estrogen secretion evolution in post-menopausal women.<sup>14,18,21,53,54</sup> Furthermore, in one retrospective questionnaire-based survey among female patients with RLS, a large majority of patients (69%) admitted an increase in the severity of their RLS symptoms following menopause, regardless of the use of hormonal replacement therapy.<sup>55</sup> Based on the available epidemiological data, the menopausal drop of estrogens levels is not associated with a decrease in prevalence of RLS. On the other side, since men also complain of worsening severity and frequency of RLS symptoms over time, the roles of menopausal condition per se and underlying hormonal status contributing to the increased prevalence of RLS in women, need to be clarified.<sup>21,54</sup> A possible confounding factor in the assessment of the RLS prevalence across the ages and its relationship with menopause might be represented by the increase in age-related co-morbidity.

## The role of estrogens

In women RLS symptoms fluctuate with changing levels of estrogens. During the menstrual cycle, pregnancy and menopause estrogen levels vary considerably and RLS-patients reported that RLS symptoms worsened at time of menses, during pregnancy or post-menopausal.<sup>55</sup> Since this associated temporal fluctuation is at best circumstantial evidence, a more direct test of the role of estrogens in RLS could come from studies involving hormone replacement therapy (HRT).

On a population level, two large-scale, epidemiological studies,<sup>18,50</sup> failed to find a more frequent use of HRT in women with RLS (Table 3). This might be different in a sleep lab population,

as one study of subjects with a chief complaint of sleep initiation insomnia found that HRT consisting of estrogens alone or in combination with progesterone was significantly more frequent in patients with RLS (74%) than in patients without RLS (48%).<sup>56</sup>

RLS symptoms are not routinely included in the assessment during HRT trials and it is therefore unknown what would be the incidence of new-onset RLS in subjects undergoing HRT. In a one-year trial of estradiol or estradiol plus norethisterone acetate in 73 healthy post-menopausal women, one of the 73 (1.4%) women dropped out because of the new onset of RLS, which would suggest a low incidence of RLS during HRT.<sup>57</sup>

A closer look at sleep disorders and RLS could be expected in studies that have evaluated the effect of HRT on sleep with polysomnography (Table 3). From the 13 studies that have measured sleep in relation to HRT, six did not mention RLS and did not record leg movements.<sup>58–65</sup> In three further studies subjects with periodic leg movements (PLM) and arousals were excluded at baseline and RLS was not mentioned<sup>66</sup> or subjects with RLS were excluded and PLM were not recorded<sup>67</sup> or subjects with RLS or PLM were excluded.<sup>68</sup> In the remaining four studies, one of them a case report, PLM were recorded during HRT (Table 3).

In the double blind, placebo-controlled, cross-over study of Polo-Kantola and co-workers a total of 62 post-menopausal women were randomized to either receive HRT or placebo.<sup>69</sup> In women younger than 56 years active medication was estradiol (2.5 g/day) and the older were treated with patches (estradiolhemihydrate, 50 mg/day). None of the subjects had RLS but PLM were recorded with the static-charge-sensitive bed at the end of the 3 months hormone or placebo treatment. Nearly half of the subjects had some PLM (48%), but there was no significant difference in percentage with PLM index greater than 5 per hour during placebo vs. estrogen therapy (27% vs. 31% respectively). In addition, for the complete group median number of PLMs was low (0–0.45) both during estrogen and placebo treatment. The study therefore failed to find an effect of estrogen on PLM.

In an active comparison study Montplaisir and co-workers<sup>70</sup> studied the effect of six months estrogen and progesterone treatment in 21 post-menopausal women (Table 3). All subjects received estrogen (0.625 mg) and were randomized to additional oral micronized progesterone (200 mg,  $n = 10$ ) or medroxyprogesterone acetate (5 mg,  $n = 11$ ). Specific sleep disorders, presumably including RLS, were excluded. Combined estrogen and progesterone treatment had no effect on the PLM index during sleep and the PLM index did not exceed 20/h in any subject.

In 2007, Hachul and colleagues<sup>71</sup> reported the case of a 62 year old woman with insomnia, RLS and a PLMS index of 31, who reported an improvement of insomnia, a disappearance of RLS and PLMS (PLMS index 1) after 2 months of transdermal estrogenic replacement treatment. Based on this case report, the group initiated a randomized study on the effect of estrogen and progesterone on sleep in 33 post-menopausal women.<sup>72</sup> In the first, parallel-group part of the study, subjects were randomized to receive either 0.625 mg conjugated equine estrogen or placebo for 12 weeks. In the second, cross-over part, both groups received additional 5 mg medroxyprogesterone allowing for the comparison of estrogen vs. estrogen and progesterone and placebo vs. placebo plus progesterone. Sleep disorders were not specifically excluded and 50% in the estrogen treated group and 42.1% in the placebo group complained of RLS symptoms (Table 3). At the same time, average PLM index at baseline was below 10 in both groups. After 12 weeks, the number of subjects with RLS complaints had slightly but non-significantly increased in both groups and PLM indices did not change significantly. Interestingly, in the estrogen treated group the number of RLS complaints significantly decreased after progesterone was added (from 62.1% to 38.4%) and this was

**Table 3**

Studies exploring the role of estrogens in RLS.

Study	Design/population	Finding
<i>Use of HRT in women with RLS</i>		
Rothdach et al. 2000 <sup>18</sup>	Epidemiological study /385 elderly from German population; 14% of the women had RLS	No difference in the use of HRT in women with RLS (9.4%, 3 32) vs. women without RLS (3.8%, 10 290)
Wesström et al. 2008 <sup>50</sup>	Epidemiological study/3516 women (18–64 years) from the Swedish population; 15.7% had RLS	No difference in the use of HRT in women with RLS (11.6%, 64 551) vs. women without RLS (6.8%, 200 2950)
Brown et al. 2005 <sup>56</sup>	Retrospective chart review/200 consecutive sleep lab patients with a chief complaint of sleep initiation insomnia; 57% of the women had RLS	Significantly higher use of HRT in patients with RLS (74%, 29 39) vs. patients without RLS (48%, 39 81)
<i>Effect on HRT on periodic leg movements (PLM) in women</i>		
Polo-Kantola et al. 2001 <sup>69</sup>	DB PC CO 3 months HRT vs. placebo, 1 month placebo wash-out, 3 months HRT vs. placebo; 62 post-menopausal women; none had RLS	No difference between HRT and placebo in number of women with PLM index > 5 (31% vs. 27%) No difference in median PLM index (IQR) Group 1 (HRT first): HRT: 0 (0–21); P: 0 (0–20) Group 2 (P first): P: 0.45 (0–32); HRT 0 (0–37)
Montplaisir et al., 2001 <sup>70</sup>	AC R PG 6 months estrogen (0.625 mg Premarin) + oral micronized progesterone (200 mg Prometrium, n = 10) vs. estrogen (0.625 mg Premarin) + medroxyprogesterone acetate (5 mg Provera, n = 11); 21 post-menopausal women, none had RLS	No difference in average PLM index (SD) between drug-free baseline and 6 months HRT: Pramarin + Prometrium: 8.4 (11.8)–7.4 (10.6) Pramarin + Provera: 1.7 (2.3)–2.6 (4.6)
Hachul et al., 2008 <sup>72</sup>	DB PC AC PG CO 12 weeks estrogen followed by 12 weeks estrogen + progesterone (n = 14) vs. 12 weeks placebo followed by 12 weeks placebo + progesterone (n = 19); 33 post-menopausal women, 15 had RLS complaints	No difference in the percentage of women with RLS complaints or mean PLM index (SD) between drug-free baseline and 12 weeks estrogen or placebo treatment: Estrogen: RLS complaints: 50%–62.5% PLM index: 4.3 (4.6)–8.1 (10.8) Placebo: RLS complaints: 42.1%–50% PLM index: 6.2 (7.7)–3.7 (6.0)
<i>Frequency of RLS in transsexuals treated with estrogen or testosterone</i>		
Fulda et al. 2007 <sup>74</sup>	Observational survey / 30 estrogen treated male-to-female transsexuals and 43 testosterone treated female-to-male transsexuals	Prevalence of RLS did not differ between male-to-female transsexuals (MFT) and female-to-male transsexuals (FMT): MFT: 20% FMT: 9.3%

Abbreviations: AC, active controlled; CO, crossover; DB, double blind; HRT, hormone replacement therapy; IQR, interquartile range; PC, placebo controlled; PG, parallel group; PLM, periodic leg movements; R, randomized; SD, standard deviation.

mirrored by a reduction in the PLM indices (from 8.1 (10.8) to 2.8 (3.7), mean (SD)). No such change was observed when progesterone was added to the placebo treatment. Taken together, the treatment trials do not support a major role of estrogens in the aetiology of PLM or RLS.

A final piece of evidence concerning the role of estrogen in the pathology of RLS stems from another patient group that is treated with sex steroids: transsexual patients. The prevalence of transsexualism is estimated to be 1:100,000 in females and 1:30,000 in males and the aetiology remains uncertain.<sup>73</sup> Cross-sex hormonal treatment is part of the treatment plan and life long in most patients. Treatment regimens for female-to-male transsexuals (FMT) consists of testosterone and for male-to-female transsexuals (MFT) includes estrogens, progestins, and anti-androgens. Fulda and co-workers<sup>74</sup> found that the prevalence of RLS was higher in female-to-male transsexuals (20%) than in male-to-female transsexuals (9.3%), but this difference was not statistically significant. Furthermore, there was no conclusive association between the onset of RLS and the start of the hormonal treatment.

Therefore at the present moment, the available evidence does not argue convincingly for a role of estrogens in the pathophysiology of RLS.

## The role of iron

Iron status has to be considered as a primary neuropathological factor of RLS in any evaluation of factors affecting RLS, especially for gender where iron status differs markedly. Reduced brain iron status for RLS, particularly for the substantia nigra and the striatum, has been documented,<sup>75</sup> and is consistent with the cerebrospinal fluid (CSF) findings.<sup>76,77</sup> Moreover, the well-established relation between serum ferritin and CSF ferritin shows both decreased slope and intercept for RLS-patients compared to healthy controls. These indicate brain iron is not only low in RLS-patients but also becomes extraordinarily low when peripheral iron status is low. Thus, very low serum ferritin exacerbates or even engenders RLS symptoms.<sup>78,79</sup> The gender differences in peripheral and brain iron provide an interesting, informative and somewhat surprising window on the role of iron in the pathology of RLS.

### Peripheral and brain iron status: gender differences

Serum ferritin reflects mostly bone marrow iron status supporting erythropoiesis and unfortunately is not a very accurate measure of body iron stores. In addition ferritin is phase reactive

increasing in response to inflammatory processes. Serum ferritin, nonetheless, remains the single best serum measure of peripheral iron status.

Population averages for the United States indicate low serum ferritin during childhood with only a small increase from average values of about 15–20 mcg/l at ages 1–2 years to about 25–35 at age 13. There are no gender differences before age 15, but after that genders diverge. Serum ferritin rapidly increases for males to an average of about 150–200 mcg/l by ages 30 to 50 and then may decrease slightly to 125–175 mcg/l by age 70. Females, in contrast, show little change in ferritin from ages 15–49 with average values remaining at about 35–40 mcg/l during the pre-menopausal adult life. The serum ferritin values post-menopause (ages over 50) increase to 75–125 mg, slightly lower than males, and generally remain at that level thereafter (Fig. 3).

The relation between CSF and serum ferritin would suggest that the lower serum ferritin for adult women would occur with lower CSF ferritin and accordingly lower brain iron status. But this somewhat oversimplifies the peripheral – central iron relationship. The poorly understood transfer of iron into and out of the brain has been recently documented to include a 24-h cycle with active transport into and out of the brain across the blood brain barrier. There must be some general body store supporting this activity.<sup>80</sup> Moreover, iron content in the brain shows regional variation partly but certainly not entirely related to cell types.<sup>81,82</sup> Magnetic resonance imaging (MRI) and autopsy studies show that some brain areas, particularly the iron-rich dopaminergic areas such as the nigrostriatal system, increase iron content during adult life. Two MRI studies evaluating the gender differences in brain iron reach somewhat different conclusions. One study using a well validated field-dependent relaxation-rate-increase measurement

showed significantly lower brain iron for adult women than men.<sup>83</sup> A different MRI technique using susceptibility-weighted magnetic resonance corrected phase images without autopsy validation failed to find any gender differences.<sup>84</sup> The studies of brain iron unfortunately did not report prior pregnancy history of the women, the peripheral iron status, or any clinical information about RLS. Lacking these data complicates evaluation of the significance for RLS.

#### Gender differences in RLS in relation to iron status

The age-related gender differences in prevalence of RLS have often been attributed to the gender differences in serum ferritin developing after childhood. It, however, deserves note that the prevalence of RLS shows no significant gender difference until after age 30, about 15 years later than the development of the significant gender differences in serum ferritin (Figs. 3 and 4).<sup>21,85</sup> The gender differences in RLS may represent effects of pregnancy occurring more commonly after age 25 increasing the risk of RLS, as noted above.<sup>19,40</sup> This raises the interesting possibility that gender differences have less immediate effects on RLS status than the more acute effects of pregnancy including the associated iron deficiency. The large gender differences in iron status do not suffice to increase the risk of RLS unless another factor further stresses the iron stores. The only source of iron for the developing fetus must come from the mother. In addition the fetal hemoglobin has gamma rather than the adult beta chain complementing the alpha chain. The gamma chain has a higher affinity for oxygen giving priority to the fetus for placental oxygen delivery. Thus both general cellular and erythropoietic iron needs of the fetus place heavy priority demands on the maternal iron status. These demands start early in pregnancy leading to a rapid decline in iron stores with decreasing serum ferritin indicating serious iron problems by the second trimester. This process is so extreme that if the maternal iron stores are low at the beginning of this iron-stress state of pregnancy catching up with oral iron is apparently not possible.<sup>86</sup> Given peripheral priority for bone marrow iron, other iron stores, including those for the brain, become depleted in order to maintain iron for erythropoiesis. Low serum ferritin before or during early pregnancy is the best and most consistently reported predictor of RLS occurring during the pregnancy.<sup>87</sup> During the last few weeks of pregnancy fetal iron demand decreases somewhat. The fetus then begins the change over from gamma to beta hemoglobin chains and also decreases general cellular demand. The iron demand, of course, changes abruptly with delivery when the heavy iron demands of the fetus are suddenly removed. The blood loss at delivery represents less a blood volume to be replaced and much more an overall decrease

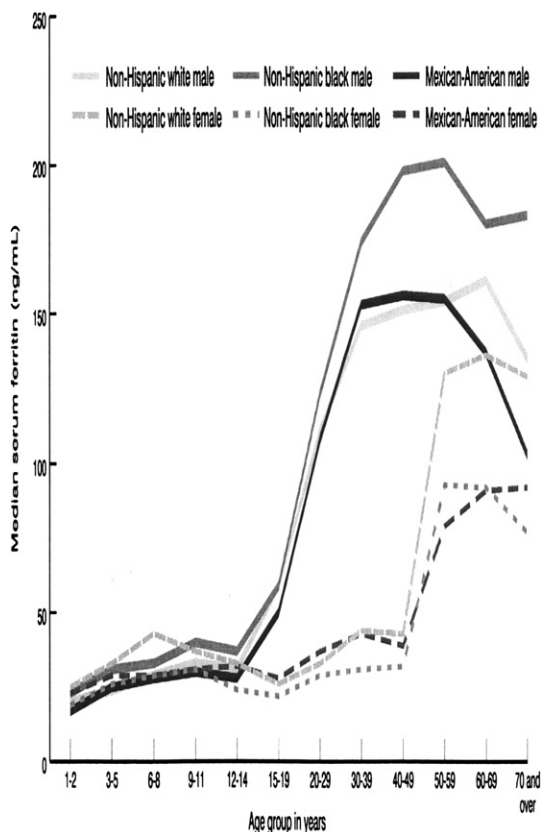


Fig. 3. Median serum ferritin by age for major USA gender and population groups.

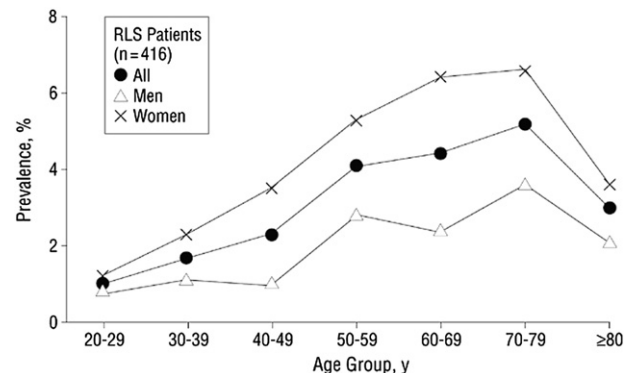


Fig. 4. Prevalence of clinically significant RLS by gender and age from large European and United States population-based samples. (Slightly modified from Allen et al.)<sup>21</sup>

in blood volume supported by the mother. RLS prevalence and severity during pregnancy would thus be expected to change with the brain iron status, increasing as pregnancy continues with some decrease toward the end of pregnancy and a marked decrease very shortly after delivery.

Pregnancy thus provides an interesting insight into the iron-RLS relationships. RLS appears to occur more when vulnerable persons with already low body iron stores have some life event that significantly depletes the iron stores. The changes in iron stores in pregnancy appear to be largely reversible, but for unknown reasons there occurs a lasting increase in any vulnerability for developing RLS later in life. This may reflect a general process where any relatively acute severe challenge to an already marginal iron status produces some lasting biological change, possibly in iron management or storage, increasing the risk of RLS. The relatively low levels of iron storage for children and young adult women puts them most at risk for such an experience. This putative relation of peripheral iron status to RLS suggested by the gender and pregnancy effects on iron, however, remains to be evaluated.

## Conclusions

The available evidence clearly indicates that RLS is roughly twice as prevalent in females than in males. Women's quality of life is considerably impaired by RLS, but these impairments, in contrast to many other disorders, seem not to exceed those seen in males, although more studies on this issue are needed. Pregnancy is an important factor as it may precipitate the disorder or considerably aggravate RLS if it is pre-existing. Although just prior to and after delivery symptoms seem to alleviate, women with an incidence of RLS in pregnancy are highly likely to develop the chronic idiopathic form. Hormones, particularly estrogens, might be an important factor linking RLS to pregnancy, as might be reduced iron stores and folate levels. Surprisingly RLS prevalence increases with age, including post-menopausal women, and estrogen replacement therapy has no clear cut effect. These data question a causative role of estrogens, but this might also be masked in elderly women by other yet unknown effects of ageing. To further elucidate the peculiarities of female RLS, controlled longitudinal studies are needed starting in young women before the first pregnancy. These studies should include genetic, clinical and polysomnographic variables, as well as measurements of the hormonal status and iron metabolism.

## Practice points

1. Most of the studies show a female/male ratio in the prevalence of RLS around 2-3/1.
2. RLS-patients report impaired quality of life, similar or worse than patients suffering from other chronic medical conditions, without solid differences between males and females.
3. Pregnancy is a significant risk factor for transient RLS, which in turn is a risk factor for the development of a future chronic idiopathic RLS, and for a new transient symptomatology in a future pregnancy.
4. Unlike migraine, there is no evident role of female sex hormones in the pathophysiology of RLS.
5. Although possible, currently there is no solid evidence for a pathogenetic role of estrogens in RLS.
6. Iron metabolism remains a major factor associated with occurrence of RLS in women and during pregnancy.

## Research agenda

1. Further improve the knowledge of the effect of gender on quality of life in RLS in the health care system and among patients.
2. Prospective studies on the evolution of RLS symptoms according to the hormonal milestones of menstrual periods, pregnancy and menopause are needed.
3. Assessment of RLS symptoms should be included in prospective HRT trials to explore the incidence of RLS due to HRT.
4. The frequency of the already known allelic variants predisposing for idiopathic RLS (loci: MEIS1, BTBD9, MAP2K5) should be replicated in large populations of women with pregnancy-related RLS.
5. Taking this into account, further replications of the association reported between parity and RLS are needed.
6. Changes in iron status and iron management during and after pregnancy should be more carefully evaluated.

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