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Pregnancy as a risk factor for restless legs syndrome

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Abstract

Pregnant women have at least two or three times higher risk of experiencing restless legs syndrome (RLS) than the general population. These data come from few epidemiological studies finding an 11–27% prevalence of RLS during pregnancy. Women affected by pre-existing RLS often complain of worsening symptoms during pregnancy. This is usually a benign form of RLS, with the highest degree of severity in the third trimester and a tendency to disappear around delivery. The causes of the association between RLS and pregnancy are unknown. The most debated hypotheses are: metabolic alterations, with particular regard to iron and folate deficiency; hormonal influences related to the increase of prolactin, progesterone and estrogens during late pregnancy; and the changing motor habits and psychological state of pregnant women. The importance of folate and iron supplementation during pregnancy in preventing RLS is unclear. RLS in pregnant women is frequently unrecognized; they are often worried about the symptoms and do not receive an adequate explanation by doctors.

Keywords: Restless legs syndrome; Pregnancy; Periodic leg movements; Iron deficiency; Folati deficiency; Prolactin

1. Introduction

Until the second half of the 20th century, restless legs syndrome (RLS) was considered to be 'one of the myriad symptoms of hysteria' [1,2]. The scientific community was driven to consider RLS as a neurological disorder by several observations, most of them reported by Ekbom, clearly associating the syndrome with pathological or physiologic conditions such as: pregnancy, iron deficiency, renal failure, rheumatoid arthritis, neurological disorders and others [3]. Today the acknowledged coexistence of the above-mentioned conditions and RLS allows us to classify the syndrome as a secondary or symptomatic form.

RLS related to pregnancy was probably the first of the secondary forms to be described; Mussio-Fournier and Rawak reported this new and strange association as the presence of 'pruritus, urticaria and paresthesias' of the lower limbs appearing during rest in three subjects of the same family [4]. A member of that family referred to a characteristic aggravation of RLS symptoms during pregnancy. Later, several epidemiological studies confirmed the value of that observation [3,5–7].

Our aim is to re-examine the RLS-pregnancy relation, reviewing the literature data and presenting the preliminary results of an epidemiological study, still in progress, performed on an Italian population of pregnant women.

2. Epidemiology: literature data and personal observations

Our knowledge about the frequency of RLS occurrence during pregnancy comes from four dated epidemiological studies, performed on series of 100–500 pregnant women, which reported a prevalence rate of the syndrome ranging from 11 to 27% (Table 1) [3,5–7]. On the basis of the first large epidemiological study, performed on 486 pregnant women in 1945, Ekbom gave the first prevalence rate (11.3%) and a brief description of the clinical course of this new form of RLS [3]. Some years later, Jolivet consolidated Ekbom's data, reporting that 27 of 100 women personally examined experienced RLS symptoms

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Table 1
Frequency of RLS during pregnancy according to five epidemiological studies

Authors	Year	Population	Prevalence (%)	Hypothesis
Ekbom [3]	1945	486	11	Psycho-hormonal
Jolivet [5]	1953	100	27	–
Ekbom [6]	1960	202	12	Hormonal
Goodman et al. [7]	1988	500	19	Psychomotor-behavioral
Manconi et al. [8]	2002	200	19	Iron metabolism

during pregnancy [5]. Ekbom's son obtained similar results, continuing the epidemiological research in 1960 [6]. The latest, largest and most detailed study, performed by Goodman et al. in 1988 on a series of 500 pregnant women, found RLS prevalence around 19% [7].

The variability of these percentages may depend mainly on two factors: the above-mentioned studies are antecedent to 1995 and the existence of standard clinical inclusion criteria for the RLS [8]; the authors did not specify the threshold of symptom frequency used to define those affected by RLS. Nevertheless, it is reasonable to assume that the risk of RLS for a pregnant woman is at least two or three times higher than for other women [10,11]. The majority of affected pregnant women had not experienced RLS before, and almost all those with pre-existing RLS referred to significant worsening of symptoms during pregnancy.

The authors agree that the last trimester of pregnancy is the most critical, when the highest number of women are affected and those with pre-existing RLS usually become worse [3,7,9]. About 30% of the multipara women had similar symptomatology in previous pregnancies [7]. The main syndrome characteristics, such as anatomic sensation distribution, quality of symptoms and motor strategies for symptom relief, are similar to those of the general RLS population, and periodic limb movements (PLM) can also be observed [12].

Our group is studying pregnant women, admitted in the Department of Obstetrics and Gynaecology of Ferrara University (Italy), in order to define the prevalence of the RLS on the basis of the International RLS Study Group (IRLSSG) criteria [8]. Within 2 days after delivery two medical doctors interviewed the women by means of a structured questionnaire and checked their haematological parameters; follow-up telephone interviews were conducted 3 and 6 months after the parturition. We considered a woman to be RLS affected if she experienced the four clinical diagnostic criteria at least twice in the same month during pregnancy. Women affected by specific diseases known to be causes of secondary RLS, or in chronic therapy with any drug except folate and iron supplementation, were excluded.

At present, 200 women have been included and 27% of them met the RLS criteria. Changing the minimum threshold of symptom frequency from twice a month to three times a week, the prevalence rate decreased from 27 to 12%. The majority of our subjects were experiencing RLS for the first time and indicated the third trimester as the worst for severity of symptoms. The normal and RLS groups were homogeneous in respect of age, pregnancy duration, modality of the delivery, parity and motor activity [8,10]. The two groups received the same dosage of folate and iron supplementation during pregnancy; a mild decrease in plasma iron and haemoglobin values in the RLS group was significant, considering the mean corpuscular volume. Although the intensity of restlessness was usually not severe, the RLS subjects more frequently referred to insomnia, sleepiness and difficulty falling asleep [9]. These sleep complaints did not seem to depend on other sleep disorders; in fact, nocturnal cramps, snoring, bruxism and nocturnal eating were equally distributed between the two groups. Forty-one per cent of multipara RLS women had experienced symptoms in previous pregnancies. Twenty-nine per cent of RLS women noted that one of their first grade relatives had complained of similar symptoms.

3. Prognosis and treatment

Goodman et al. noted that in the great majority of patients symptoms began to improve in the 4 weeks preceding, and disappeared after, delivery. For pre-existing RLS, the intensity of the creeping sensation was the same after delivery as before pregnancy [7]. Our follow-up is not yet complete, but the trend seems to confirm these results: three months after delivery only 5 women (of 54) continued to complain of RLS symptoms. Our experience confirms that the presence of RLS seems to have no relevant consequence to the health and weight of the newborns [9].

RLS remains practically unknown among gynaecologists and general practitioners and almost totally unknown among pregnant women, who usually do not receive an adequate explanation when they complain of symptoms. With a diagnosis of pregnancy-related RLS, before considering drug therapy, we believe doctors should reassure mothers that the nature of the syndrome is benign and the symptoms will almost certainly disappear after delivery. Moreover, these women should be informed that tiring days, caffeine, iron deficiency and anxiety might make the restlessness worse. When the symptoms are severe, producing sleep disruption and depression, these simple reassurances and behavioral rules may not suffice and drug therapy may be necessary.

No studies are available in the literature about the practical treatment of RLS during pregnancy. McParland and Pearce reported two cases of severe RLS in pregnancy in whom temazepam, diazepam and phenobarbitone had no benefit, while carbamazepine resolved the symptomatology after 2 days of therapy [13]. Carbamazepine efficacy in RLS

is well known, but no controlled studies are available as to its safety during pregnancy [14,15]. The dopaminergic agents, now considered the first choice in RLS therapy, have never been tested for the possibility of fetal harm, and these molecules may theoretically interfere with lactogenesis because of their inhibitory effect on prolactin secretion, especially for those with higher affinity to D2 receptors. We used clonazepam discontinuously in two women with good results, but it must be stressed that all these drugs, clonazepam included, are classified as category C in pregnancy (lack of controlled studies in pregnant women) [16]. Furthermore, current consensus discourages use of benzodiazepine during pregnancy [17]. If drug treatment is unavoidable, it would be best restricted to the third trimester and used only in case of need, with the lowest effective dose.

4. Pathogenetic hypothesis

The etiopathogenetic mechanism of the correlation between RLS and pregnancy is unknown. Three main hypotheses, supported by experimental data in only a few cases, have been formulated during the last 50 years: (1) hormonal, with particular reference to prolactin (PRL), progesterone and estrogens influences (2) psychomotor behavioral, with emphasis on changes in motor and sleep habits and anxiety during the last part of pregnancy (3) metabolic, ascribing RLS to the reduction in folate or iron blood levels.

Hormonal hypothesis. The plasma levels of estrogens, progesterone and prolactin increase during pregnancy, peaking in the third trimester, with a sudden fall after delivery of estrogen and progesterone, and prolactin secretion assuming a circadian pulsatile trend [18]. There is evidence that progesterone increases neuronal activity; for example, there is increased respiratory center sensitivity to CO_2 [19] and common hyperreflexia during late pregnancy [20]. According to Santiago et al. PLM and RLS could be another manifestation of this nervous hyperexcitability [15]. Estrogens increase the turnover of brainstem noradrenaline [21], possibly interfering indirectly with dopaminergic transmission. Progesterone and estrogen influences may explain the higher prevalence of RLS in the female gender reported by some epidemiological studies [22,23]. Considering that dopamine is the most important PRL inhibitor, some authors suggest that the PRL increase during pregnancy could be related to a decrease in dopamine action, with consequent promotion of RLS symptoms. The same mechanism is also postulated for RLS in general because PRL secretion has the same circadian rhythmicity as the RLS symptomatology [24]. Wetter et al. failed to support this theory, finding no differences in PRL secretion between RLS patients and controls, but did not study pregnant women [24].

Psychomotor behavioural hypothesis. Anxiety, stress and tiring days are often referred to by patients as causes of RLS symptom exacerbation [25]. Pregnancy, especially in the last trimester, is a condition often associated with tension, insomnia and easy fatigue. Goodman et al. concluded that the decrease in RLS prevalence during the last weeks of pregnancy could depend on a voluntary or enforced period of reduced activity that limits stress [8]. However, recent studies found no differences in motor habits during late pregnancy between RLS and non-RLS women [10].

Metabolic hypothesis. Iron and folate requirements during normal pregnancy are, respectively, 3–4 and 8–10 times higher compared to the non-pregnant state. The increase of fetal demand and the strong hemodilution, especially in the second half of gravidity, could partially explain the fall in serum folate, iron and other iron indicators (ferritin, haemoglobin, mean corpuscular volume). The majority of occidental women receive iron and folate supplementation during pregnancy, significantly increasing plasma serum levels compared to those without supplementation [26]. Iron and folate deficiency are well known conditions correlated with RLS [27]. Botez and Lambert found RLS prevalence of 9% in pregnant women receiving folate supplementation compared to a prevalence of 80% in women without supplementation [28].

Our group, similar to Goodman et al. [25] and others who examined a large series [8,10], found plasma iron and haemoglobin values to be comparable between RLS and healthy pregnant women receiving folate and iron supplementation. However, we could not confirm Phillips et al.'s finding of a mean corpuscular volume that is significantly lower in the RLS group [10]. Lee et al., who recently followed 30 pregnant women, found that the seven who had RLS during pregnancy had lower folate levels before and during gravidity compared to the non-RLS women, while iron storage indicators were lower only in the pre-pregnancy period [27]. In both cases folate and iron indicators remained within normal range values.

This well done study should be repeated using a larger series. A number of aspects need to be considered concerning the influence of iron on RLS pathogenesis: RLS patients could have normal serum iron storage indicators but low CSF concentrations of ferritin and transferrin [29]; the gut-blood barrier, which strongly limits iron adsorption of oral supplementation, may be bypassed by intravenous route [30]; oral iron absorption depends on serum ferritin values, and subjects with very low values may absorb 35–40% of their dietary iron compared to subjects with high values who absorb less than 2% of oral supplementation [31].

5. Conclusion

Pregnancy may be considered a risk factor for initial or worsening RLS symptoms. Larger epidemiological studies, using IRLSSG criteria, are needed to verify the amount of risk. Pregnancy-related RLS is usually mild, transitory

and more accentuated during the third trimester. Because of the benign nature of this form of RLS, the use of drug therapy is to be discouraged. RLS is not well known among doctors and patients and should be divulged by educational programs, especially for pregnant women. Why is RLS so strongly associated with pregnancy? We need further experimental studies in order to evaluate the relevancy of hormonal, psychomotor/behavioral and metabolic factors.

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