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## Original Article

## A prospective study of Willis–Ekbom disease/restless legs syndrome during and after pregnancy

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## ABSTRACT

**Objectives:** Willis–Ekbom disease/restless legs syndrome (WED/RLS) is the most common sleep-related movement disorder in pregnancy. We designed a prospective longitudinal study to investigate the correlates of WED/RLS during and after pregnancy.**Design:** A total of 138 pregnant women with WED/RLS and a control group of 251 age-matched pregnant women were enrolled prospectively. A questionnaire was administered during a face-to-face interview at first evaluation during pregnancy and three months after delivery.**Results:** Among all women in the first trimester, 15.6% were diagnosed with WED/RLS, whereas 32.8% of those in the second trimester and 38.8% of those in the third trimester were diagnosed with WED/RLS ( $p = 0.032$ ). In regression analysis, later gestational age [ $p < 0.001$ ; odds ratio (OR) 1.054] and previous history of WED/RLS ( $p = 0.001$ ; OR 2.795) were positively correlated with the presence of WED/RLS, while ferritin levels ( $p = 0.001$ ; OR 0.956) were negatively correlated with the presence of WED/RLS. Ferritin levels were also negatively correlated with the International RLS Study Group severity index ( $p = 0.041$ ). Forty-eight patients (34.8%) experienced WED/RLS symptomatology after delivery. The ferritin levels were lower, and the mean number of pregnancies was higher, in women with residual WED/RLS ( $p = 0.008$ ). **Conclusion:** Our survey showed that WED/RLS was more common in the second and third trimesters. Emergence of WED/RLS during the second trimester was strongly associated with residual WED/RLS. Lower ferritin levels were associated with both WED/RLS in pregnancy and residual WED/RLS after delivery. A higher number of pregnancies were also associated with a greater likelihood of having residual WED/RLS after delivery.© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Willis–Ekbom disease/restless legs syndrome (WED/RLS) is a common sleep-related movement disorder with a prevalence of up to 10% in the general population [1]. In most epidemiological studies based on International Restless Legs Syndrome Study Group (IRLSSG) criteria, the prevalence of WED/RLS has been demonstrated to be about one and a half to two times greater in women [2]. It has been suggested that this gender difference may be related to the differences in either iron deficiency or hormone status [3]. The increased

prevalence of WED/RLS in pregnant women has prompted investigations into the relevance of female hormones, particularly the increased levels of estrogen found during late pregnancy [4,5]. Indeed, appearance or exacerbation of pre-existing WED/RLS symptoms during pregnancy has been reported by IRLSSG criteria-based surveys. The prevalence of WED/RLS during pregnancy is around three times greater than in the general population and is reported to vary between 15 and 35% [5–8]. It also shows a tendency to be more severe during this period [5,8].

However, factors related to the occurrence of WED/RLS in pregnant women are not well known. It has been suggested that the increased prevalence of WED/RLS associated with pregnancy may be related to iron deficiency and hormonal changes during this period [8–10]. On the other hand, well-designed studies have failed to find evidence that female hormones, or iron, and/or folate deficiencies, play a major role in the occurrence of WED/RLS during pregnancy, or have shown inconsistent results [4,5,10,11]. On this

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basis, a prospective longitudinal study was designed with the aim of investigating the correlates of WED/RLS during and after pregnancy.

## 2. Methods

### 2.1. Population and setting

A total of 138 pregnant women who had been diagnosed as having WED/RLS at any stage of their pregnancies and were aged 18 years or older were enrolled prospectively into the study. The study population was formed from the pregnant women attending routine prenatal office visits at the Gaziantep Cengiz Gökçek Obstetrics and Gynecology Hospital in Gaziantep city and at the Istanbul University Cerrahpasa Medical Faculty in Istanbul city, Turkey. Both of these clinics provide public services and have separate facilities for high-risk pregnancies. Study participants were only recruited from among those who attended these facilities for women and had no potential maternal or fetal risk. Women with eclampsia, preeclampsia, or other gestational complications that might favor or trigger WED/RLS symptoms were excluded, while women with other known causes of symptomatic WED/RLS were not. A control group of 251 age-matched pregnant women was also prospectively enrolled. The participants were not recruited consecutively, but women attending these clinics were evaluated for one year, on two days per week, and those who met the inclusion criteria and agreed to participate in the study were prospectively recruited. The study was approved by Gaziantep Clinical Research Ethical Committee. All participants were informed about the nature of the research, and informed consent was obtained from every participant.

### 2.2. Study procedure

Questionnaires were administered during face-to-face interviews conducted by three clinicians with training in the diagnosis of WED/RLS (MN, RA and FB). Participants were interviewed regardless of the period of pregnancy, with a cross-sectional approach. Each interview lasted for about 30 min. All problems regarding the diagnosis were then discussed with the senior authors (AN and DK). The clinical-diagnostic interview was conducted in accordance with the criteria defined by the International RLS Study Group (IRLSSG), and the severity of WED/RLS was assessed using the IRLSSG criteria [3,12].

The questionnaire consisted of 50 questions, which included: (1) demographic characteristics such as age, height, body weight, education, income, number of previous pregnancies, gestational age for the current pregnancy; (2) habitual behaviors such as current or past history of smoking, alcohol intake, use of iron or other vitamin supplements; (3) past medical history, including the past medical records of the participants; and (4) detailed characteristics of WED/RLS, if present, such as disease duration, triggering factors, family history or use of WED/RLS treatment.

Blood samples were collected from all participants and were investigated to obtain the complete blood count, fasting glucose, blood urea nitrogen, creatine, ferritin, transferrin saturation, total iron binding capacity, urine analysis for albuminuria, and the level of estradiol.

All pregnant women with WED/RLS underwent a follow-up face-to-face interview three months after parturition, which was conducted by the same clinicians. Women who reported the presence of WED/RLS at the third postpartum month were questioned again at six months.

### 2.3. Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows was used for the statistical analysis. Descriptive variables

were expressed as percentages for categorical variables, and as mean  $\pm$  SD for continuous variables. The Chi-squared test was used in the comparisons of independent categorical variables. Student's t-test was used to compare the means of continuous variables with normal distribution; and the Mann-Whitney U test was used in the comparisons of continuous variables without normal distribution. Pearson's correlation, logistic regression or analysis of variance analysis (ANOVA) were used to analyze risk factors and interactions between non-parametric and parametric variables. The Bonferroni correction test was applied for multiple comparisons. The measure of association that was used was OR with 95% CI. All calculated *p*-values were two-tailed and considered to be statistically significant if equal to or less than 0.05.

## 3. Results

A total of 138 pregnant women diagnosed with WED/RLS had a mean score on the IRLSSG scale of  $18.5 \pm 6.0$  points. According to the gestational age, seven pregnant women (5.2%) were in the first trimester, 40 women (28.9%) were in the second trimester, and 91 women (65.9%) were in the third trimester. Among all women in the first trimester, 15.6% were diagnosed with WED/RLS, whereas 32.8% of those in the second trimester and 38.8% of those in the third trimester were diagnosed with WED/RLS ( $p = 0.032$ ). Symptoms of WED/RLS had emerged for the first time during the current pregnancy in 106 women (76.8%, 106/138); 29 of these pregnant women (27.4%, 29/106) were experiencing their first pregnancies. The number of pregnancies did not show a statistically significant relationship with the presence of WED/RLS ( $p = 0.749$ , Mann-Whitney U test). Twenty-three women (16.6%, 23/138) stated that they had had similar symptoms of WED/RLS during their previous pregnancies, but they were all free of symptoms between pregnancies. Only nine women (6.5%, 9/138) had symptoms of WED/RLS before pregnancy; all of whom had a previous diagnosis of WED/RLS. About 33.6% of pregnant women with WED/RLS reported that tiredness exacerbated their WED/RLS symptoms, and 10.5% reported stress as a triggering factor. Other than walking and/or leg movements relieving the symptoms of WED/RLS, which was the case in all women, leg massage (44.3%) and washing the legs with hot (14.8%) or cold water (12.0%) were also stated as relieving maneuvers.

The comparison of the pregnant women with and without WED/RLS is shown in Table 1. The mean age of the pregnant women in both groups was similar, although the mean gestational age was higher in women with WED/RLS ( $28.3 \pm 8.7$  vs  $25.9 \pm 9.7$  weeks,  $p = 0.022$ ). All other demographic variables were similar between the two groups.

Among the pregnant women with WED/RLS, 79.0% had nocturnal leg cramps, while 31.1% of the pregnant women without WED/RLS had nocturnal leg cramps ( $p < 0.001$ ). Varicose veins were present in 26.8% of the women with WED/RLS, vs 17.9% of those without ( $p = 0.040$ ). Rheumatoid complaints were reported in 6.5% of the pregnant women with WED/RLS and 2.8% of those without WED/RLS ( $p = 0.076$ ). Only one pregnant woman with WED/RLS had peripheral neuropathy (0.7%), and none of women without WED/RLS reported peripheral neuropathy. A family history of WED/RLS was present for 8.7% of the women with WED/RLS, but for 2.5% of those without ( $p = 0.006$ ).

Most of the study population had between six and eight hours of sleep per night: 46.4% among women with WED/RLS and 47.8% among women without WED/RLS. Having less than six hours of sleep per night was reported by 28.9% of women with WED/RLS and 22.3% of women without WED/RLS ( $p = 0.470$ ). Mean subjective sleep latency was also longer in pregnant women with WED/RLS: 47.1% of women with WED/RLS (compared with 31.1% of those without WED/RLS) reported that it took them more than 30 minutes to fall asleep ( $p = 0.005$ ).

**Table 1**  
Comparison of descriptive variables between women with and without Willis–Ekbom disease/restless legs syndrome.

Demographic variables	Women with Willis–Ekbom disease/restless legs syndrome (n = 138)	Women without Willis–Ekbom disease/restless legs syndrome (n = 251)	p
Age (years, mean ± SD)	27.8 ± 5.8	27.9 ± 6.0	0.854
Age groups, years, n (%)			0.442
15–19	14 (10.4)	20 (8.1)	
20–29	62 (45.9)	130 (52.4)	
30–39	59 (43.7)	98 (39.5)	
40–49	10 (7.2)	11 (4.4)	
Education, years, n (%)			0.630
<8 years	74 (53.6)	137 (54.6)	
8–12	47 (34.1)	83 (33.0)	
>12	7 (5.1)	20 (8.0)	
Current or previous smoking history, n (%)	14 (10.1)	18 (7.2)	0.307
Use of iron or other vitamin supplements, n (%)	104 (75.3)	175 (69.7)	0.073
Current BMI, kg/m <sup>2</sup> (mean ± SD)	27.6 ± 4.4	27.4 ± 4.3	0.803
Gestational history			
Gestational week (mean ± SD)	28.3 ± 8.7	25.9 ± 9.7	0.022*
Current pregnancy number, median (min–max)	3 (1–13)	2 (1–8)	0.065
Number of previous children, median (min–max)	1 (0–6)	1 (0–6)	0.970
Number of abortions, n (%)	28 (20.4)	40 (15.9)	0.265

\* p-value <0.05 indicates statistical significance.

The laboratory investigations are summarized in Table 2. Mean blood urea nitrogen ( $p = 0.040$ ), ferritin ( $p = 0.010$ ) and mean transferrin saturation levels ( $p = 0.004$ ) were significantly lower in women with WED/RLS (Fig. 1). Other measures were similar between the two groups.

All of the demographic and laboratory variables were evaluated in the regression analysis. Among them, later gestational age ( $p < 0.001$ , OR 1.054 [1.024–1.084 95% CI OR]) and previous history of WED/RLS ( $p = 0.001$ , OR 2.795 [1.560–5.005 95% CI OR]) were

**Table 2**  
Comparison of laboratory variables between women with and without Willis–Ekbom disease/restless legs syndrome.

Laboratory variables	Women with Willis–Ekbom disease/restless legs syndrome (n = 138)	Women without Willis–Ekbom disease/restless legs syndrome (n = 251)	p
Fasting glucose (mg/dL), mean ± SD	82.7 ± 16.8	80.9 ± 18.9	0.265
Blood urea nitrogen (mmol/L), mean ± SD	10.5 ± 5.2	12.0 ± 6.1	0.040*
Creatinine (mg/dL), mean ± SD	0.5 ± 0.09	0.5 ± 0.1	0.468
Ferritin (ng/mL), mean ± SD	17.5 ± 33.4	23.0 ± 19.0	0.010*
Transferrin saturation (%), mean ± SD	23.3 ± 15.2	52.9 ± 29.2	0.004*
Total iron binding capacity (µg/dL), mean ± SD	438.1 ± 64.6	421.9 ± 66.7	0.161
Hemoglobin (g/dL), mean ± SD	11.8 ± 1.2	12.4 ± 8.5	0.590
Hematocrit (%), mean ± SD	35.5 ± 3.3	35.9 ± 3.7	0.242
Presence of albuminuria, n (%)	25 (18.1)	36 (14.5)	0.344
Estradiol levels (pg/mL), mean ± SD	4446.7 ± 5728.6	4532.4 ± 6185.9	0.154

\* p-value <0.05 indicates statistical significance.

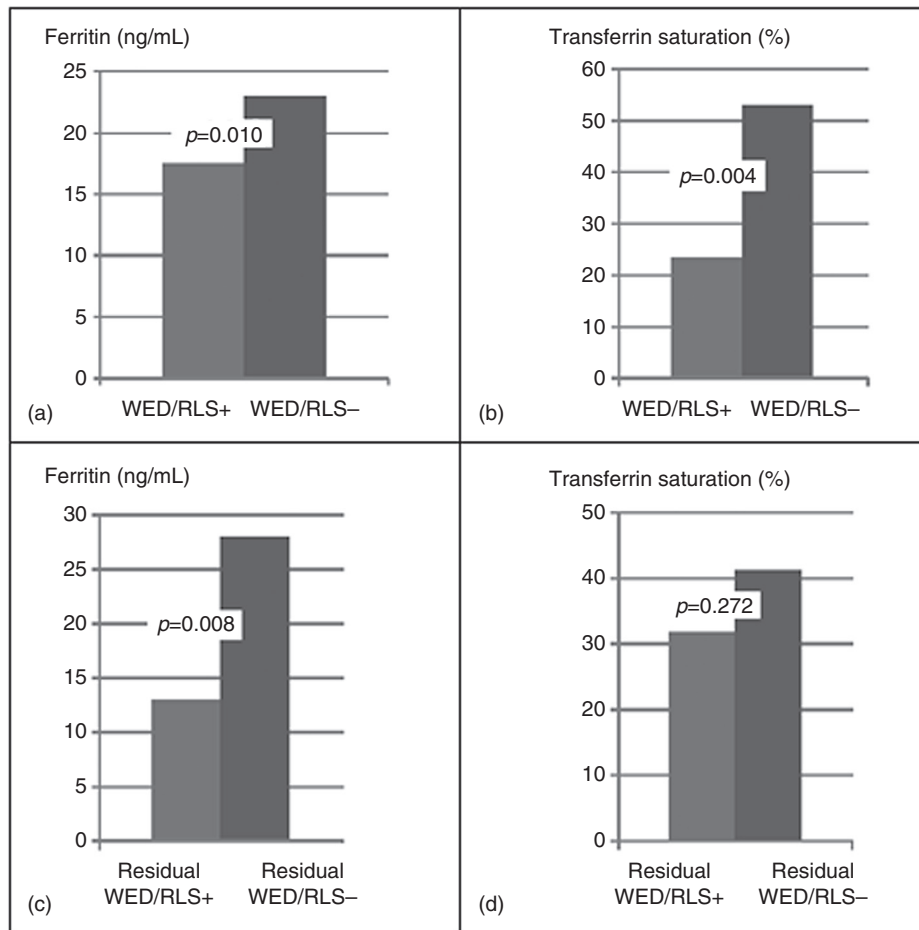
positively correlated with the presence of WED/RLS, whereas ferritin levels ( $p = 0.001$ , OR 0.956 [0.932–0.980 95% CI OR]) were negatively correlated with the presence of WED/RLS. Ferritin levels were also negatively correlated with the IRLSSG severity index ( $p = 0.041$ , linear regression analysis and ANOVA). Comparison of women with WED/RLS that recurred during their pregnancies ( $n = 23$ ) and those who experienced WED/RLS symptoms continuously ( $n = 9$ ) showed that ferritin levels were lower in those with continuous WED/RLS, although not significantly ( $24.4 ± 16.1$  ng/mL vs  $21.6 ± 15.8$  ng/mL,  $p = 0.167$ ).

Follow-up examinations three months after parturition, with face-to-face interviews conducted by the same clinicians, revealed that 48 women (34.8%) still experienced WED/RLS symptoms. Of these, nine women had WED/RLS continuously (18.7%, 9/48), four women had had WED/RLS temporarily during their previous pregnancies (8.3%, 4/48), and 35 women (70%) were experiencing WED/RLS symptoms for the first time in their lives. Twenty-seven out of the latter 35 women had symptoms that started during the second trimester (77.1%). Among these 35 women, 19 were primiparous (54.2%, 19/35), while 16 had had more than one pregnancy (45.8%, 16/35). The mean number of pregnancies was higher in women with residual WED/RLS symptoms ( $4.0 ± 1.4$  between three and six pregnancies) when compared with those with no symptoms following delivery ( $2.2 ± 1.1$  between one and four pregnancies,  $p = 0.050$ ). The mean gestational age for women with residual WED/RLS was also higher than in those with no residual symptoms ( $32.0 ± 9.2$  vs  $29.4 ± 7.5$  years), but this difference was not significant ( $p = 0.434$ ). Ferritin levels were significantly lower in women with residual WED/RLS symptoms when compared with those with no residual symptoms ( $13.7 ± 7.0$  ng/mL vs  $28.6 ± 10.4$  ng/mL,  $p = 0.008$ ) (Fig. 1). All other demographic and laboratory data, including estradiol levels, failed to show statistically significant differences between the two groups.

#### 4. Discussion

Willis–Ekbom disease/restless legs syndrome is the most common movement disorder of pregnancy. The appearance of symptoms is most commonly reported in the last trimester of gestation [2,8] and has been reported to generally disappear in the month following delivery [4,7]. In a Brazilian study [8], 94.4% of pregnant women with WED/RLS were in the second or third trimester. An earlier onset of WED/RLS during pregnancy, around the 20th week, has also been reported [13]. The present survey replicated the finding that WED/RLS usually started by the second trimester of pregnancy and was more common in the second and third trimesters. In addition, it was observed that the emergence of WED/RLS symptoms during the second trimester was associated with residual WED/RLS after delivery.

A follow-up study performed about 6.5 years after delivery showed that women who had transient WED/RLS during their pregnancy had a four-fold increased risk of developing chronic WED/RLS [14]. Another recent study reported that 38.5% of pregnant women who experienced symptoms for the first time during the index pregnancy developed chronic WED/RLS [6,14]. In the present study, 34.8% of pregnant women still experienced WED/RLS symptoms after parturition; 70% of these were experiencing WED/RLS symptoms for the first time in their lives, and half of them were multiparous. Studies have reported conflicting results as to whether the number of pregnancies is a risk factor for WED/RLS [6,7,15]. Berger et al. reported data from a large epidemiological study showing that parous women had a significantly greater prevalence of WED/RLS than nulliparous women, and that nulliparous women had the same incidence of WED/RLS as men [15]. The present study found that the number of pregnancies did not show a statistically significant relationship with the presence of WED/RLS; on the other hand, the mean number of pregnancies was higher for women with residual WED/RLS symptoms after delivery.



**Fig. 1.** Ferritin (a) and transferrin saturation levels (b) in pregnant women with and without WED/RLS; ferritin (c) and transferrin saturation levels (d) in postpartum women with and without residual Willis–Ekbom disease/restless legs syndrome. WED/RLS = Willis–Ekbom disease/restless legs syndrome; WED/RLS+ = present; WED/RLS- = absent.

Among other demographic factors, no difference between pregnant women with and without WED/RLS was reported in previous studies for age, ethnicity or education [7,13]. In the present study, mean gestational age was significantly higher in women with WED/RLS; it was also higher in those with residual WED/RLS than in those with remission, although not significantly.

A positive family history has been reported as one of the predictors of WED/RLS in pregnancy, as has the occurrence of WED/RLS in a previous pregnancy [13,15]. In the present study, a family history of the condition was also significantly more common in pregnant women with WED/RLS. However, a family history of WED/RLS was not significantly associated with the presence of residual WED/RLS symptoms after delivery.

There are different hypotheses for the higher prevalence of WED/RLS in pregnancy. Among them, associations with hormone levels, such as estrogen alterations, and metabolic changes, such as iron deficiency, have been investigated in many studies. In the third trimester of gestation, elevated levels of estradiol, which counteracts the action of dopamine, occur at the core time for development of the pathophysiology of transient WED/RLS in pregnancy [10]. However, many analyses have failed to show significant differences in estrogen levels between pregnant women with and those without WED/RLS, challenging the hypothesis that estrogen levels may play an important role in the pathophysiology of WED/RLS in this context [13]. In the present study, estradiol levels were also similar between pregnant women with and those without WED/RLS. They were also similar in postpartum women with or without residual symptoms.

Although there is convincing evidence for a major role of iron (which is required for the function of tyrosine hydroxylase in dopamine synthesis) in the pathophysiology of WED/RLS in non-pregnant individuals, this relationship is not well established in pregnant women. Disturbances in iron transport, metabolism and storage in pregnancy might play a role in aggravating WED/RLS symptoms in pregnant women [4,16]. However, the rapid improvement in symptoms in the postpartum period is difficult to account for by changes in total iron stores, which typically remain low postpartum [5,10]. In addition, many studies have failed to show a difference in hemoglobin and ferritin levels between pregnant women with and without WED/RLS [5,13]. In the present survey, however, it was possible to demonstrate that pregnant women with WED/RLS had significantly lower ferritin levels, transferrin saturation, and blood urea nitrogen levels. Moreover, pregnant women with WED/RLS had a slightly, but significant, higher mean gestational age than those without, and ferritin levels showed a progressive decrease during pregnancy. Low ferritin levels during pregnancy were also significantly associated with residual WED/RLS symptoms after delivery, supporting the ferritin hypothesis.

Another hypothesis related to the development of WED/RLS in pregnancy involves water retention in the lower extremities secondary to increased peripheral venous distension and decreased peripheral vascular resistance, which in turn increase the pressure in the tissues surrounding the peripheral somatosensory system receptors and thus enhance their stimulation [17]. This hypothesis has not been supported by other studies [13], although in the



present study, the presence of varicose veins was found to be significantly more common in pregnant women with WED/RLS. A recent study indicating a possible association between the occurrence of WED/RLS in pregnancy and preeclampsia may provide indirect evidence to support this hypothesis [18].

The present study had some limitations: (1) the limited number of women included during their first trimester did not allow for speculation about this period of pregnancy; (2) the apparently high numbers of pregnant women with WED/RLS – this probably occurred because the participants were not consecutively recruited and no randomization was used; (3) although estimation of the prevalence of WED/RLS was beyond the scope of this study, this finding may attract attention to a social issue related to differences among geographical areas in iron status and the response to iron loss.

The present survey showed that WED/RLS was more common in the second and third trimesters, and the emergence of WED/RLS symptoms during the second trimester was strongly associated with residual WED/RLS after delivery. The data also confirmed that later gestational age, previous history of WED/RLS, and positive family history were significantly correlated with the presence of WED/RLS in pregnancy. In addition, lower ferritin levels, transferrin saturation, and blood urea nitrogen levels were shown to be associated with WED/RLS in pregnant women. Lower ferritin levels were also associated with residual WED/RLS symptoms after delivery. Finally, a higher number of pregnancies were associated with a greater likelihood of having residual WED/RLS symptoms after delivery.

#### Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2015.01.026>.

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