

# Prevalence of restless legs syndrome among pregnant women: A case–control study

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Submission: 11-07-2019  
Accepted: 07-09-2019  
Published: 02-01-2020

## Abstract:

**BACKGROUND:** This cross-sectional case–control study aimed to assess the prevalence of restless legs syndrome (RLS) and its correlates and severity among Arab (Saudi) pregnant women attending antenatal care clinics.

**METHODS:** We interviewed 742 consecutive pregnant women attending antenatal clinics face-to-face using the International RLS Study Group (IRLSSG) criteria. We assessed the severity of RLS using the IRLSSG severity scale for RLS (IRLS). A similar number of age-matched nonpregnant women were enrolled in a control group.

**RESULTS:** Among the cases, 104 (14%) were in the first trimester, 232 (31.3%) in the second trimester, and 406 (54.7%) in the third trimester. The RLS prevalence in cases and controls was 30% and 26.5%, respectively, ( $P = 0.134$ ). Among cases, severe/very severe RLS was diagnosed in 25% and mild/moderate in 75%, compared with 15% of controls having severe/very severe RLS and 85% having mild/moderate RLS ( $P < 0.001$ ). Multivariate binary logistic regression analysis identified the following parameters as independent predictors of RLS: parity (odds ratio [OR] 1.113 [confidence intervals [CI] 1.012–1.223],  $P = 0.027$ ), anemia (OR 1.452 [1.033–2.042],  $P = 0.03$ ), diabetes mellitus (OR 1.734 [CI 1.084–2.774],  $P = 0.022$ ), Vitamin D deficiency (OR 2.376 [CI 1.488–3.794],  $P < 0.001$ ), and smoking (OR 3.839 [CI 1.463–10.074],  $P = 0.006$ ). None of the cases had been diagnosed or treated for RLS in the antenatal clinics.

**CONCLUSION:** RLS is common, but underdiagnosed, among Saudi pregnant women and nonpregnant women of childbearing age. The study revealed that RLS during pregnancy is linked to parity, anemia, diabetes mellitus, Vitamin D deficiency, and smoking.

## Keywords:

Anemia, diabetes mellitus, movement disorders, parity, sleep, Vitamin D

Restless legs syndrome (RLS) is a sensory-motor disorder, which is characterized by an urge to move the legs that occur during rest or inactivity. It is usually associated with unpleasant and uncomfortable feelings in the legs that are temporary and partially relieved by movement. Smoking, alcohol, and caffeine are considered triggers of RLS.<sup>[1]</sup>

The existing data suggest that RLS may adversely affect pregnancy. Evidence suggests that women with RLS may have more complications related to pregnancy and labor, such as threatened miscarriage, threat of premature labor, complicated delivery, and intrauterine growth retardation.<sup>[2]</sup>

Previous studies have shown that RLS is common among pregnant women with a prevalence ranging from 10% to 46%,<sup>[2]</sup> compared to 2%–10% in the general public.<sup>[3]</sup> The prevalence of RLS in the

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DOI:

10.4103/atm.ATM\_206\_19

**How to cite this article:** Almeneessier AS, Alyousefi N, Alzahrani M, Alsafi A, Alotaibi R, Olaish AH, *et al.* Prevalence of restless legs syndrome among pregnant women: A case–control study. *Ann Thorac Med* 2020;15:9-14.

general population in Saudi Arabia has been reported to be 5.2%–8.4%.<sup>[4,5]</sup> A recent study assessed the prevalence of RLS among Saudi pregnant women and reported a prevalence of 21.3%; however, no control group was included.<sup>[6]</sup> No case–control study has been conducted to assess the prevalence of RLS in Arab pregnant women. New evidence indicates that RLS has a genetic origin, and it is possible that RLS may vary with race. Ethnic differences in the prevalence and predictors of RLS have been reported.<sup>[7]</sup>

This case–control study aimed to assess the prevalence of RLS and its correlates and severity among Saudi pregnant women attending Antenatal Care Clinics in King Saud University Medical City (KSUMC), Saudi Arabia, using the International RLS Study Group (IRLSSG) questionnaire.

## Methods

### Study design and setting

This cross-sectional, case–control study was conducted at KSUMC in Saudi Arabia, Riyadh, between July 2015 and July 2016. We recruited consecutive Saudi pregnant women attending Antenatal Clinics at KSUMC. Exclusion criteria comprised women with diseases that may result in symptoms that simulate RLS symptoms, such as chronic neurological diseases (e.g., multiple sclerosis), rheumatologic diseases, or psychiatric illnesses. Comorbid conditions were verified from the participants' medical records. Anemia in pregnancy and controls was defined as hemoglobin concentration  $<110$  g/L.<sup>[8]</sup> Vitamin D deficiency was considered normal if serum 25-hydroxy-Vitamin D (25OHD) was  $<25$  nmol/L and insufficient if between 25 and 75 nmol/L. Multiparity was defined as given birth more than once. The prevalence of RLS among pregnant women was compared with an age-matched group of Saudi nonpregnant women working in the University campus.

The participants were interviewed face-to-face by medical students, who also explained the study to the participants, and obtained written informed consent. Participating medical students attended a session on RLS and received training on data collection to minimize false-positive diagnoses. The study was approved by the Research Ethics Committee at King Saud University (15/0038/IRB).

### Sample size calculation

Based on previous studies, the prevalence of RLS in pregnant women ranges from 10% to 46%.<sup>[2]</sup> Therefore, a sample size that would allow the detection of an RLS prevalence of 30% with an alpha ( $\alpha$ ) of 0.05 and a precision of 1% was chosen. The minimum sample size was estimated to be 345.<sup>[2]</sup>

### Questionnaire

Data collected included demographics, comorbid conditions, and a validated Arabic version of the IRLSSG questionnaire, which is an internationally accepted assessment tool for RLS.<sup>[4]</sup> The comorbid conditions that are linked to RLS, such as anemia, diabetes mellitus, and renal failure, were documented from patients' medical records. Electronic medical records of the participants were checked to confirm the associated comorbid conditions and to check whether the participants with symptoms of RLS had been diagnosed or treated for RLS by their physician.

The diagnostic criteria recommended for RLS by the IRLSSG include<sup>[9]</sup>: “(1) an urge to move the legs, usually accompanied or caused by an uncomfortable sensation in the legs; (2) beginning or worsening of symptoms during periods of rest or inactivity; (3) partial or total relief of symptoms by movement; (4) symptoms that are worse in the evening or night compared to during the day or that occur only in the evening or night; and (5) the above symptoms are not solely explained by another medical or a behavioral condition, such as myalgia, venous stasis, arthritis, leg cramps, positional discomfort, or habitual foot tapping.”<sup>[9]</sup> The IRLSSG developed the international standard diagnostic criteria for RLS.<sup>[9]</sup> This questionnaire has been used for pregnant women.<sup>[2,10]</sup> Participants who met all IRLSSG criteria were diagnosed to have RLS.

RLS severity was assessed using a validated Arabic version of the IRLSSG severity scale for International RLS (IRLS),<sup>[4]</sup> which is a ten-question scale designed to assess the severity of RLS symptoms. It includes five items relating to symptom frequency and intensity and five other items that deal with the impact of symptoms on aspects of daily living and sleep.<sup>[4,11]</sup> The severity of RLS is categorized based on the total score with mild being  $<10$  points, moderate 11–20 points, severe 21–30, and very severe  $\geq 31$  points.

### Statistical analyses

Data were expressed as means  $\pm$  standard deviation. The Chi-square test was used to compare categorical variables. For continuous variables, Student's *t*-test was used.

To explore predictors of RLS in pregnancy, a univariate logistic regression model was used in a preliminary analysis; one explanatory variable was tested in the model at a time, including baseline demographics, parity, weeks of gestation, use of medication, comorbidities, and smoking. Subsequently, variables with significant *P* values were further evaluated using a multivariate logistic regression (Forward Wald method) to identify the independent predictors of RLS in pregnancy. An

odds ratio (OR) was calculated from both the univariate and the multivariable logistic regression analyses with 95% confidence intervals (CIs).

The results were considered statistically significant if the  $P \leq 0.05$ . SPSS 22.0 (IBM® SPSS® Statistics V22.0., Chicago, IL, USA) was used to analyze the data.

## Results

During the study period, a total of 742 pregnant women and a similar number of age-matched nonpregnant women agreed to participate in the study and complete the study questionnaires. Among the cases, 104 (14%) were in the first trimester, 232 (31.3%) in the second trimester, and 406 (54.7%) in the third trimester. Based on their medical records, none of them had been diagnosed or treated for RLS.

Table 1 presents a comparison between cases and controls. Diabetes mellitus, Vitamin D deficiency, and anemia were more common in pregnant women than controls. The prevalence of RLS in cases and controls was 30% and 26.5%, respectively, ( $P = 0.134$ ). The prevalence of RLS in the first, second, and third trimesters were 31.6%, 22%, and 34.2%, respectively. Diabetes mellitus and anemia were more common in cases than controls, 14% versus 2.8%,  $P < 0.001$  and 32.7% versus 25.1%,  $P < 0.001$ , respectively. However, Vitamin D deficiency was more common among controls than cases 15.2% versus 59.9%,  $P < 0.001$ .

**Table 1: Comparison between pregnant women (case) and nonpregnant women (control) groups**

Variable total (n=1484)	Mean±SD/n (%)		P
	Cases (n=742)	Controls (n=742)	
Age (years)	29.4±5.6	29.2±5.7	0.743
<20	16 (2.1)	21 (2.8)	
20-35	605 (81.5)	607 (81.8)	
>35	121 (16.3)	114 (15.4)	
BMI (Kg/m <sup>2</sup> )	29.8±6.1	26.3±10.2	<0.001
Comorbidities			
Diabetes mellitus	104 (14)	21 (2.8)	<0.001
Vitamin D deficiency	113 (15.2)	444 (59.9)	<0.001
Anemia (Hb <110 g/L)	243 (32.7)	186 (25.1)	<0.001
RLS diagnosis	223 (30)	197 (26.5)	0.134
RLS severity			
Mild	41 (18)	61 (31)	<0.001
Moderate	127 (57)	107 (54)	
Severe	53 (24)	23 (12)	
Very severe	2 (1)	6 (3)	
RLS severity			
Severe/very severe RLS	55 (25)	29 (15)	<0.001
Mild/moderate RLS	168 (75)	168 (85)	

SD=Standard deviation, BMI=Body mass index, Hb=Hemoglobin, RLS=Restless legs syndrome

The mean IRLS scores for cases and controls were  $17 \pm 6.1$  and  $13 \pm 6.8$ , respectively ( $P < 0.001$ ). Among the cases, severe/very severe RLS was diagnosed in 25% and mild/moderate in 75%, compared with 15% of controls having severe/very severe RLS and 85% having mild/moderate RLS ( $P < 0.001$ ).

Table 2 presents a comparison between pregnant women with and without RLS. Pregnant women with RLS were older ( $30.1 \pm 5.9$  years vs.  $28.8 \pm 5.3$  years,  $P = 0.006$ ) and had a higher prevalence of multiparity (18% vs. 10.9%,  $P = 0.02$ ), smoking (5% vs. 1.3%,  $P = 0.004$ ), diabetes (23.7% vs. 10%,  $P < 0.001$ ), anemia (40.3% vs. 29.5,  $P = 0.004$ ), and Vitamin D deficiency (21% vs. 12.7,  $P = 0.005$ ).

Table 3 presents the univariate and multivariate binary logistic regression analyses to predict RLS among pregnant women. The independent predictors of RLS were parity (OR 1.113 [95% CI 1.012–1.223],  $P = 0.027$ ), anemia (OR 1.452 [95% CI 1.033–2.042],  $P = 0.03$ ), diabetes mellitus (OR 1.734 [95% CI 1.084–2.774],  $P = 0.022$ ), Vitamin D deficiency (OR 2.376 [95% CI 1.488–3.794],  $P < 0.001$ ), and smoking (OR 3.839 [95% CI 1.463–10.074],  $P = 0.006$ ).

## Discussion

This is the first case-control study to assess RLS in pregnancy in Saudis and Arabs in general. The study revealed that RLS is common among pregnant women. However, an interesting finding of this study is the high prevalence of RLS among childbearing nonpregnant women (the control group), which could be related to the high prevalence of anemia and Vitamin D deficiency in this group. This finding needs future studies. The diagnosis of RLS was higher in the third trimester, which is consistent with previous studies.<sup>[12]</sup>

The prevalence of RLS among pregnant women in this study is within the reported prevalence in previous studies in different countries; however, the trend is toward the high prevalence rate. A recent meta-analysis that included 51,717 pregnant women revealed that the pooled overall prevalence of RLS across all three trimesters was 21%; however, the prevalence of RLS in different regions varied.<sup>[12]</sup> The analysis showed that the prevalence of RLS during pregnancy in the European Region, Western Pacific Region, Eastern Mediterranean Region, and Region of the Americas was 22%, 14%, 30%, and 20%, respectively.<sup>[12]</sup> The finding of the current study is consistent with this recent meta-analysis, which showed a higher prevalence of RLS in the Eastern Mediterranean Region (30%). Ethnic differences in the prevalence of RLS has long been proposed and has been systematically verified by Kutner and Bliwise who reported a lower

**Table 2: A comparison between pregnant women with and without restless legs syndrome**

Variable total (n=742)	Mean±SD/n (%)		P
	No RLS (n=519)	RLS (n=223)	
Age (years)	28.8±5.3	30.1±5.9	0.006
BMI (kg/m <sup>2</sup> )	29.6±6.4	30.1±5.8	0.211
Smoking	7 (1.3)	11 (5)	0.004
Educational level			
Illiterate	11 (2.1)	4 (1.9)	0.384
General education	209 (40.3)	101 (45.3)	
High education	299 (57.6)	118 (53)	
Parity	1.4±1.6	1.8±1.9	0.01
Primigravida (0)	188 (36.3)	67 (30.2)	0.02
Grand (1-3)	274 (52.7)	116 (52)	
Multiparty (>3)	57 (11)	40 (18)	
Anemia (Hb <110 g/L)	153 (29.5)	90 (40.3)	0.004
Vitamin D deficiency	66 (12.7)	47 (21)	0.005
Diabetes mellitus	52 (10)	52 (23.3)	<0.001
None	467 (90)	171 (76.7)	0.002
Type I	4 (0.7)	1 (0.4)	
Type II	5 (1)	7 (3.1)	
Gestational	43 (8.3)	44 (19.7)	
Hypertension	11 (2.6)	12 (3.7)	0.388
Hypothyroidism	32 (7.6)	18 (5.6)	0.275
Medications			
Iron	361 (69.5)	172 (77.1)	0.02
Multivitamin	232 (44.8)	11 (49.3)	0.2
Folic acid	189 (36.4)	93 (41.7)	0.128
Calcium	286 (55.2)	141 (63.2)	0.026
Vitamin D	59 (11.4)	45 (20.2)	0.001

SD=Standard deviation, BMI=Body mass index, Hb=Hemoglobin, RLS=Restless legs syndrome

**Table 3: Univariate and multivariate binary logistic regression analyses\* to predict restless legs syndrome among pregnant women (n=742)**

Variables in the equation	OR (95% CI)	P
Univariate analysis		
Age (years)	1.043 (1.016-1.071)	0.002
Parity (multiparty >3)	1.984 (1.234-3.188)	0.005
Gestational age (weeks)	1.019 (1.002-1.037)	0.026
Anemia (Hb <110 g/L)	1.553 (1.129-2.135)	0.007
Diabetes mellitus	2.146 (1.407-3.274)	0.001
Vitamin D deficiency	1.96 (1.307-2.94)	0.001
On iron supplement	1.495 (1.071-2.087)	0.018
On calcium supplement	1.401 (1.041-1.886)	0.026
On Vitamin D supplement	1.96 (1.307-2.94)	0.001
Multivariable analysis		
Parity	1.113 (1.012-1.223)	0.027
Anemia (Hb <110 g/L)	1.452 (1.033-2.042)	0.032
Diabetes mellitus	1.734 (1.084-2.774)	0.022
Vitamin D deficiency	2.376 (1.488-3.794)	<0.001
Current smoking	3.839 (1.463-10.074)	0.006

\*Multicollinearity=No, Overall accuracy=63%, Sensitivity=38.2%, Specificity=82.3%, Area under the curve=62.6%, Omnibus tests of model=P<0.001, Hosmer–Lemeshow goodness of fit=P=0.851, Nagelkerke R<sup>2</sup>=8.3%. OR=Odds ratio, CI=Confidence interval, Hb=Hemoglobin

prevalence of RLS in older African-American compared to older Caucasian patients on chronic hemodialysis.<sup>[13]</sup>

Ethnic variations in the prevalence remained, even after adjusting for confounding factors, such as age, sex, education, and health status.<sup>[13]</sup> It has been suggested that racial differences may also affect the prevalence of RLS in pregnancy because pregnancy is considered a secondary condition associated with RLS, such as anemia and renal impairment.<sup>[12,14,15]</sup>

Possible explanations for the differences in the prevalence of RLS in pregnancy among different studies include different assessment methods, different populations, and the gestational age during the assessment.<sup>[2]</sup> Moreover, studies that relied on medical records to obtain the diagnosis of RLS may have underestimated the prevalence of RLS during pregnancy, as RLS is frequently underdiagnosed or misdiagnosed.<sup>[14]</sup> This shortcoming has been overcome in studies that used face-to-face interviews using standardized diagnostic criteria as has been done in the current study. However, none of the interviewed cases with RLS had been diagnosed or treated for RLS during antenatal follow-up, suggesting that this disorder is underrecognized and undertreated. The current study identified several independent predictors of RLS during pregnancy, including parity, anemia, diabetes mellitus, Vitamin D deficiency, and smoking.

It has been shown that multiparous women are affected up to three times more often than nulliparous women.<sup>[16]</sup> A proposed explanation for the increased prevalence of RLS in multiparous women includes the influence of parity on iron status.<sup>[2]</sup> Iron content in the body tends to decrease with pregnancy if not restored between pregnancies. This is a possible cause of the increased prevalence of RLS during multiparity.<sup>[17]</sup>

In the Arab Gulf countries, anemia during pregnancy, mainly iron deficiency anemia, has been reported to have a high prevalence ranging from 22.6% to 54.0%.<sup>[18]</sup> Iron deficiency anemia has been identified previously as a risk factor for the development of RLS.<sup>[17,19-21]</sup> In a pregnant woman with chronic moderate-to-severe RLS and low ferritin levels, intravenous iron therapy administered before pregnancy resulted in a complete remission of RLS symptoms until 5 months postpartum.<sup>[22]</sup> Moreover, anemia is very common among childbearing nonpregnant Saudi women. A recent study of 683 nonpregnant women aged between 18 and 40 years reported a prevalence of iron deficiency anemia of 41.6%.<sup>[23]</sup> This is consistent with the current study findings and may explain the high prevalence of RLS in the control group. Nevertheless, further studies are needed to explore RLS in Saudi women of childbearing age.

Another predictor of RLS during pregnancy in this study was Vitamin D deficiency. Vitamin D deficiency has been linked to an increased risk of RLS.<sup>[24]</sup> Moreover,

an inverse correlation between Vitamin D levels and severity of RLS has been reported.<sup>[24,25]</sup> Vitamin D deficiency is common in pregnant women.<sup>[26,27]</sup> A recent study in Saudi Arabia conducted on 160 pregnant women during the first trimester of pregnancy revealed that serum 25OHD deficiency (25(OH)D <50 nmol/L) and insufficiency (25[OH]D = 50–74 nmol/L) were reported in 50% and 43.8% of the study samples, respectively.<sup>[28]</sup> Moreover, a cross-sectional study of 465 Saudi nonpregnant women aged 19–40 years attending primary health-care centers revealed that 100% of the participants had Vitamin D deficiency (25[OH]D <25 nmol/L).<sup>[29]</sup> This may partially explain the high prevalence of RLS among the control group. Vitamin D deficiency has been linked to impaired dopaminergic neurotransmission.<sup>[30]</sup> The role of Vitamin D in the development of RLS was further supported by the higher concentration of Vitamin D binding protein in the cerebrospinal fluid of patients with RLS.<sup>[31]</sup> However, it is not proven yet whether treatment with Vitamin D can improve RLS symptoms. A recent randomized controlled trial of 35 patients with RLS who received either Vitamin D (50,000 IU caplets) or a placebo revealed that Vitamin D supplementation does not improve RLS symptoms.<sup>[32]</sup>

It has been suggested that smoking may trigger RLS symptoms during pregnancy.<sup>[2,10]</sup> In the current study, active smoking was an independent predictor of RLS in pregnancy. Diabetes mellitus presented as an independent predictor of RLS in pregnant women in this study. Previous studies have suggested a positive relationship between RLS and diabetes, with increased risk estimates ranging from 1.6 to 4.7.<sup>[33]</sup> Moreover, two previous studies revealed that adults with RLS, but without diabetes mellitus, had an increased likelihood of impaired glucose tolerance and elevated glycemia levels compared to those without RLS.<sup>[34,35]</sup> In a study that assessed the association of RLS with a history of gestational diabetes mellitus in a sample of older women (aged  $\geq 40$ ), prior history of gestational diabetes mellitus was strongly associated with RLS.<sup>[36]</sup> The investigators reported that women who have a history of gestational diabetes mellitus were approximately three times as likely to meet the criteria for RLS.<sup>[36]</sup>

The current study has strengths and limitation. Strengths include the fact that a proper sample size calculation was performed and being the first case-control study to assess RLS in pregnancy in Saudis and Arabs in general. Limitations include the shortcoming of questionnaires-based studies such as recall bias and the fact that there is less space for respondents to provide answers, which reflect their true feelings.

In summary, this is the first case-control study to report RLS in Saudi (Arab) women during pregnancy. RLS is

common and underdiagnosed among Saudi pregnant women and childbearing nonpregnant women. The study revealed that RLS during pregnancy was linked to parity, anemia, diabetes mellitus, Vitamin D deficiency, and smoking. It is possible that pregnancy unmasks RLS in susceptible women via several mechanisms, including factors identified in this study. Since RLS may adversely affect pregnancy outcome, increasing the awareness among physicians and the public about this disorder is important.

### Acknowledgment

We thank the following students who participated in data collection: Mohammed Alangari, Abdulmalik Aldubayan, Abdulrahman Alsharidah, and Aamer Altaki.

### Financial support and sponsorship

This study was funded by a grant from the Strategic Technologies Program of the National Plan for Sciences and Technology and Innovation in the Kingdom of Saudi Arabia (08-MED511-02).

### Conflicts of interest

There are no conflicts of interest.

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