Pre-pregnancy Restless Legs Syndrome (Willis-Ekbom Disease) Is Associated with Perinatal Depression

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Objectives: Both restless legs syndrome ([RLS], also known as Willis-Ekbom Disease [WED]) and depression are common during pregnancy. However, no prior studies have assessed if pregnant women with RLS have an elevated risk of depression during and/or after pregnancy.

Methods: 1,428 women who were pregnant in gestational week 16-17 were asked to participate in a longitudinal survey. They were followed by web-based questionnaires in gestational week 17 and 32, and 6 weeks after delivery. Data were also retrieved from prenatal and birth records. Two different sets of criteria were used to examine the prevalence of RLS in the cohort (International Restless Legs Syndrome Society Group standard criteria and the later developed CH-RLSQ11 questionnaire). The latter questionnaire attempts to exclude those with common "mimics" of RLS.

Results: Adjusted odds ratio for depression in gestational week 17, 32, and postpartum week 6 in relation to pre-pregnancy RLS onset and moderate to severe symptom severity were

4.74 (2.30–9.76), 3.67 (1.85–7.28), and 2.58 (1.28–5.21), respectively. No significant associations were seen in pregnant women with *de novo* RLS during pregnancy. When using the standard diagnostic RLS criteria and frequency of symptoms more than 2-3 days per week, the prevalence of RLS was 12.3%. With the CH-RLSQ11 questionnaire and the same threshold for frequency of symptoms the prevalence was 6.5%.

Conclusion: Women with RLS onset before pregnancy with moderate or severe symptoms had an increased risk of both antenatal and postnatal depression. The self-reported prevalence of RLS during pregnancy is lower when a questionnaire dealing with "mimics" is used.

Keywords: restless legs syndrome, pregnancy, depression

Citation: Wesström J, Skalkidou A, Manconi M, Fulda S, Sundström-Poromaa I. Pre-pregnancy restless legs syndrome (Willis-Ekbom Disease) is associated with perinatal depression. *J Clin Sleep Med* 2014;10(5):527-533.

Complaints of sleep disturbances are common during pregnancy, generally commencing with the onset of pregnancy and increasing in frequency and duration as pregnancy progresses, due to pregnancy-related anatomic, physiologic, and hormonal changes.¹ Sleep disturbances during pregnancy can result in excessive daytime sleepiness, diminished daytime performance, inability to concentrate, irritability, depression^{2,3} as well as obstetric complications.⁴ Subjective sleep complaints are among the most consistent symptoms associated with mood disorders, and disruption of typical sleep patterns is a core diagnostic criterion of depressive episodes.⁵

Women are at increased risk to become depressed during pregnancy and in the postpartum period, especially when they have preexisting psychiatric illnesses.⁶ During pregnancy, about 10% to 15% of women report symptoms of depression,^{6,7} and 4% to 7% suffer from major depression.^{8,9} Published estimates of the rate of major and minor depression in the postpartum period depend on the assessment method, the timing of the assessment, and population characteristics, but depressive symptoms are generally found in 10% to 12% of postpartum women.¹⁰⁻¹² Antenatal depression has been linked to premature birth, low birth weight, and disorganized sleep in the neonate.¹³ Important long-term consequences of untreated postpartum depression have been documented with increased risk for emotional, behavioral,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Both restless legs syndrome ([RLS], also known as Willis-Ekbom Disease [WED]) and depression are common during pregnancy. This study aims to assess if pregnant women with RLS have an elevated risk of depression during and/or after pregnancy.

Study Impact: This is to our knowledge the first study confirming that women with RLS onset before pregnancy has an increased risk of both antenatal and postnatal depression.

and psychological developmental difficulties in children of mothers, with postpartum depression being the most prominent ones.^{14,15} Depression is associated with a significantly increased risk for suicide; with up to 20% of all postpartum deaths in the Western world being suicides, these are among the leading causes for mortality in the postpartum period.¹⁶

Two underdiagnosed sleep-related movement disorders, commonly experienced by women in the third trimester, are leg cramps and restless legs syndrome ([RLS], also known as Willis-Ekbom Disease [WED]). Both conditions disrupt sleep and are distressing to the pregnant woman, and may mimic one another or other serious disorders.¹⁷ Nocturnal leg cramps affects up to 30% of pregnant women.¹⁸ Subjects with RLS experience a strong urge to move the limbs, usually the

legs. The classic presentation includes the onset or worsening of symptoms when at rest and a circadian pattern of symptom exacerbation at night. It is usually accompanied by unpleasant symptoms of creeping, crawling, and sometimes painful sensations in the affected limbs. The symptoms improve by movement and commonly affects sleep, which in turn, can interfere with daily role functioning and health related quality of life.^{19,20} Women are disproportionately affected by RLS, and some of this increased risk may be related to childbearing.²¹ Among women aged 25-34 years in the general Swedish population, the prevalence of RLS is approximately 11%.²² An increased prevalence of RLS has been noted during pregnancy, with numbers ranging between 10.4% and 30%.^{21,23-25}

There are two types of RLS—primary and secondary. Primary RLS, also known as idiopathic, is the most common type of RLS and can be hereditary. Primary RLS has no known cause and is accompanied by normal neurological status. Secondary or symptomatic RLS occurs as a result of an underlying medical condition or in association with the use of certain drugs. For example, some conditions that may cause secondary RLS include kidney failure, iron deficiency, and pregnancy.²¹ In most cases, RLS during pregnancy is a transient condition that often disappears around delivery. However, pregnancy-related RLS is a significant risk factor for the development of future chronic idiopathic RLS. Moreover, the recurrence rate in these women varies from 30% to 60% in subsequent pregnancies.²¹ 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 without RLS.²⁶ A number of hypothetical etiological factors for the increased risk of RLS during pregnancy have been discussed. These factors include pregnancy-related iron or folate deficiency and the influence on dopamine neurotransmission³¹ or overmodulation by the excessively elevated estrogen or progesterone serum concentrations.²⁶⁻³⁰

RLS has in many studies been associated with depressive episodes. A large prospective study suggested an increased risk of developing clinical depression and clinically relevant depression symptoms in subjects suffering from RLS.³¹ A recent study shows a bi-directional link between depression and RLS since clinically relevant depressive symptoms at baseline were associated with new-onset RLS and because RLS also predicts incident depressive symptoms.³² No information is available on the association between RLS and antenatal and postpartum depression. Hence, this nested case-control study aimed to evaluate if RLS during pregnancy increases the risk of antenatal or postpartum depression, and if so, if previously existing (idiopathic) RLS or *de novo* (secondary) RLS differ in their influence on depressive symptoms.

MATERIAL AND METHODS

The study used data from the BASIC study (Biology, Affect, Sleep, Imaging, Cognition and Postpartum depression), a longitudinal study investigating biological correlates of mood and anxiety disorders during pregnancy and in the postpartum period. All women attending routine ultrasound examination in gestational week 16-17 at Uppsala University Hospital were approached for participation in the study, enabling a

population-based sample. The present sub-study was open between January 2010 and September 2012; during this time interval, 1,686 women were included in the BASIC cohort.

Upon informed consent, women were followed by password-protected web-based surveys in gestational week 17, gestational week 32, and 6 weeks and 6 months after delivery (the 6-month assessment was not included in this study). For the purpose of the present nested case-control study, questions on RLS (see below) were included in the survey in gestational week 32 when the severity of RLS symptoms often is most pronounced.³³ In addition, questions on iron supplementation (yes/no; if yes, what type of supplementation), antidepressant use (yes/no; if yes what type), average sleep duration (> 8 h/night, 6-8 h/night, < 6 h/night) were collected in gestational weeks 17 and 32 and postpartum week 6. Data on height, first trimester weight, education level, pre-pregnancy smoking, and parity were retrieved from prenatal and birth records. Prior or ongoing somatic and psychiatric disorders were reported in the standardized maternity record at the first antenatal visit. The study was approved by the Independent Research Ethics Committee in Uppsala.

Participants and Procedure

Depressive symptoms were assessed by the Edinburgh Postnatal Depression Scale (EPDS) in gestational week 17, gestational week 32, and 6 weeks postpartum. The EPDS is an internationally used 10-item self-report questionnaire, designed as a screening tool to identify depressive symptoms in the perinatal period. Murray et al. have shown that an EPDS score ≥ 12 points identifies correctly 77% of mothers experiencing a minor or major depressive episode. Test specificity is estimated at 93%.³⁴ For the present study, a threshold of 13 points was used to define cases of antenatal depression,³⁵ and 12 points was used as threshold for definition of cases with postpartum depression.³⁶

The Cambridge-Hopkins Restless Legs Syndrome Short Form 2 diagnostic questionnaire (CH-RLSQ11), developed by Allen et al., was used for assessment of RLS prevalence.³⁷ The positive predictive value (PPV) for this questionnaire has been shown to be 85.5% in population-based surveys, which is high compared to the most commonly used International Restless Legs Study Group (IRLSSG) questionnaire with a PPV in population studies < 50%.³⁸ A Swedish translation has recently been approved by the Administrative Services Agency. Based on the responses to this questionnaire, 2 different definitions were used for RLS diagnosis, according to CH-RLSQ11 (definite RLS) and according to the IRLSSG (probable RLS). The use of 2 different definitions of RLS allowed for comparison with previous studies in pregnant populations where the IRLSSG criteria predominantly have been used.

The CH-RLSQ11 questionnaire includes 7 diagnostic questions; the remaining questions are used for further characterization of the condition. The content of the questions and scoring for RLS are: (1) Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down? (yes/no); (2) Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down? (yes/no); (3) Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active? (resting/active); (4) If you get up or move around when you have these feelings do these feelings get any

better while you actually keep moving? (yes/no/don't know); (5) Which times of day are these feelings in your legs most likely to occur? (morning/midday/afternoon/evening/night/about equal at all times); (6) Will simply changing leg position by itself *once* without continuing to move usually relieve these feelings? (usually relieves/does *not* usually relieve/don't know); (7a) Are these feelings *ever* due to muscle cramps? (yes/no/don't know); (7b) If so, are they *always* due to muscle cramps? (yes/no/don't know). Scoring for definite RLS were as follows: 1 = yes, 2 = yes, 3 = resting, 4 = yes, 5 = not equal or morning, 6 = does not usually relieve, 7a = no, 7b = no.

In addition, further characterizing questions from the CH-RLSQ11 questionnaire included: (8) Do these feelings occur *only* when sitting or only when lying down? (neither/only when sitting/only when lying down/both when sitting and when lying down); (9) When you actually experience the feelings in your legs, how severe are they? (not at all/a little bit/moderately/extremely severe); (10) In the past 12 months, how often did you experience these feelings in your legs? (every day/4-5 days per week/2-3 days per week/1 day per week/2 days per month/1 day per month or less/never). For this study, only RLS cases reporting a frequency of symptoms ≥ 2 -3 days per week were included.

Probable RLS cases were defined according to the IRLSSG standardized criteria published in 1995. The RLS_{IRLSSG} criteria include: (a) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (b) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (c) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (d) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. We considered these criteria to be fulfilled if CH-RLSQ11 questions 1-5 were answered according to the scoring rules: (1 = yes, 2 = yes, 3 = resting, 4 = yes, 5 = not equal or morning). Probable RLS cases also had to report a frequency of symptoms ≥ 2 -3 days per week to be included in this study.

In addition to the CH-RLSQ11 questionnaire, we also asked for RLS onset age. If onset age was the same as the age reported by women at the first antenatal visit, cases were classified as *de novo* onset cases, whereas lower age at onset was considered as pre-pregnancy RLS.

Statistical Analysis

Differences between RLS cases and controls were analyzed with χ^2 tests or t-tests as appropriate. Differences between probable RLS, definite RLS and controls were analyzed by analysis of variance (ANOVA) or logistic regression. Joint analyses of statistical predictors for depression were analyzed with multiple logistic regression analysis. All statistical analyses were performed with IBM SPSS Statistics, version 20.

RESULTS

Of the 1,686 women who participated in the BASIC study while the RLS substudy was open, 1,428 (84.7%) filled out the RLS questions in gestational week 32 (**Figure 1**). Seven hundred ninety-two women did not report any uncomfortable

Figure 1—Flow chart of the study population

and unpleasant sensations in the legs *or* any urge to move the legs and served as controls in the analyses; 192 women who reported one of these items were excluded from the analyses. Among the remaining 1,236 women, 264 (18.5%) fulfilled the IRLSSG criteria, and 176 (12.3%) of these had symptoms ≥ 2 -3 days/week. When RLS criteria according to the stricter CH-RLSQ11 were applied, 134 (9.4%) fulfilled the criteria for RLS. Of these, 94 (6.6%) women had symptoms ≥ 2 -3 days/week. Hence, the final study population consisted of 792 controls, 82 (5.7%) women who fulfilled RLS criteria according to IRLSSG (including frequency of symptoms) but not according to CH-RLSQ11 (denoted as probable RLS), and 94 women who fulfilled criteria according to CH-RLSQ11 and had frequent symptoms (denoted as definite RLS; **Figure 1**). EPDS scores were available from 886 (91.5%), 966 (99.8%), and 675 (69.7%) women in gestational week 17, gestational week 32, and postpartum week 6, respectively.

RLS during pregnancy was significantly associated with multiparity, pre-pregnancy tobacco use, prior psychiatric history, and antidepressant treatment (**Table 1**). Probable RLS was also associated with hypothyroidism (**Table 1**). In gestational weeks 17 and 32, RLS cases more often reported < 6 h sleep per night, but in the postpartum period, no difference in sleep duration was evident between RLS cases and controls. Anemia during pregnancy was not more common in RLS cases; however, RLS cases used iron supplementation less often (**Table 2**). Women with definite RLS reported an earlier onset age and had preexisting RLS more often than women with probable RLS. However, reported frequency and severity of symptoms did not differ between probable and definite RLS cases, (**Table 3**).

Prior psychiatric history was reported by 160 (16.5%) women in the study population. Anxiety and depressive disorders were most common and were reported by 146 (15.1%) women, of whom 4 (0.4%) women had bipolar disorder. Other psychiatric disorders reported by the women included eating disorders ($n = 18$), attention deficit hyperactivity disorder ($n = 4$), alcohol or drug abuse ($n = 2$), borderline personality ($n = 1$), and autism spectrum disorder ($n = 1$).

EPDS scores were higher in RLS cases in gestational week 17, gestational week 32, and at 6 weeks postpartum. Similarly,

the proportion of women who were classified as depressed was significantly greater among RLS cases than controls in gestational weeks 17 and 32. However, these differences were predominantly driven by women with definite RLS, who had higher depression scores than controls at all assessments, and

likewise, greater proportions of women classified as depressed at all time-points (**Table 2**).

Following adjustment for parity, pre-pregnancy smoking, and psychiatric history, multiple regression analyses revealed that women with definite RLS, but not probable RLS, were at

Table 1—Differences in pre-pregnancy demographic and clinical variables between probable RLS cases, definite RLS cases, and controls

	All RLS cases n = 176	Probable RLS (IRSSSG) n = 82	Definite RLS (CH-RLSQ11) n = 94	Controls n = 792
Age, years	31.4 ± 4.7	30.9 ± 4.7	31.9 ± 4.8	31.1 ± 4.4
BMI, kg/m ²	24.5 ± 4.2	24.3 ± 4.2	24.7 ± 4.2	24.0 ± 4.3
Two or more children, n (%)	36 (20.5) ^b	16 (19.5)	20 (21.3) ^a	100 (12.6)
Pre-pregnancy tobacco, n (%)	39 (22.4) ^c	19 (23.8) ^c	20 (21.3) ^c	74 (9.4)
Hypertension, n (%)	1 (0.6)	1 (1.2)	0	2 (0.3)
Hypothyroidism, n (%)	12 (6.8)	9 (11.0) ^a	3 (3.2)	43 (5.4)
Prior psychiatric history, n (%)	40 (22.7) ^a	17 (20.7)	23 (24.5) ^a	120 (15.2)
SSRI use, n (%)	13 (7.4) ^b	7 (8.5) ^b	6 (6.4)	21 (2.7)

Statistical analyses by one-way ANOVA or binary logistic regression. ^ap < 0.05, ^bp < 0.01, ^cp < 0.001.

Table 2—Differences in pregnancy-influenced variables and EPDS scores between probable RLS cases, definite RLS cases and controls

	All RLS cases n = 176	Probable RLS (IRSSSG) n = 82	Definite RLS (CH-RLSQ11) n = 94	Controls n = 792
Hb < 110 g/L, n (%)	41 (23.4)	15 (18.3)	26 (28.0)	196 (24.8)
Iron supplementation, n (%)	91 (51.7) ^a	44 (53.7)	47 (50.0)	477 (60.2)
Sleep < 6 hours gw 17, n (%)	12 (7.3) ^a	5 (6.5)	7 (8.0)	23 (3.0)
Sleep < 6 hours gw 32, n (%)	25 (14.2) ^c	13 (15.9) ^b	12 (12.8) ^a	50 (6.3)
Sleep < 6 hours ppw 6, n (%)	64 (53.3)	34 (55.7)	30 (50.8)	303 (54.9)
EPDS score gw 17	6.5 ± 5.0 ^c	5.8 ± 4.8	7.2 ± 5.1 ^c	4.8 ± 3.9
EPDS score gw 32	6.7 ± 4.9 ^c	5.9 ± 4.4	7.5 ± 5.2 ^c	5.3 ± 4.2
EPDS score ppw 6	6.8 ± 4.9 ^a	6.5 ± 4.8	7.2 ± 5.0 ^a	5.7 ± 4.4
Depressed cases gw 17, n (%)	21 (13.5) ^c	8 (10.7) ^a	13 (16.2) ^c	36 (4.9)
Depressed cases gw 32, n (%)	22 (12.5) ^a	6 (7.3)	16 (17.0) ^b	60 (7.6)
Depressed cases 6 ppw, n (%)	22 (18.0)	8 (12.9)	14 (23.3) ^a	65 (11.8)

Frequencies are reported in relation to number of given responses. Depressed cases were defined as EPDS score > 12 during pregnancy and as EPDS score > 11 in the postpartum period. gw, gestational week; ppw, postpartum week. Statistical analyses by one-way ANOVA or binary logistic regression.

^ap < 0.05, ^bp < 0.01, ^cp < 0.001 in comparison with controls.

Table 3—Differences and description of probable and definite RLS

	Probable RLS (IRSSSG), n = 82	Definite RLS (CH-RLSQ11), n = 94	Test statistic, p-value
RLS onset age	28.9 ± 6.4	25.8 ± 6.4	F = 4.4, p = 0.04
RLS onset			$\chi^2 = 9.4$, p = 0.002
before pregnancy, n (%)	25 (32.9)	52 (56.5)	
during pregnancy, n (%)	51 (67.1)	40 (43.5)	
RLS frequency			$\chi^2 = 4.6$, p = 0.1
2-3 days/week	53 (64.6)	46 (48.9)	
4-5 days/week	16 (19.5)	29 (30.9)	
every day	13 (15.9)	19 (20.2)	
Symptom severity			$\chi^2 = 1.4$, p = 0.3
Non or minor, n (%)	20 (20.4)	16 (17.2)	
Moderate or severe, n (%)	63 (75.6)	77 (82.8)	

Frequencies are reported in relation to number of given responses.

Table 4—Risk for depression in gestational week 17, gestational week 32, and postpartum week 6

	AOR (95% CI)
Gestational week 17	
Probable RLS (IRSSSG)	1.97 (0.86–4.53)
Definite RLS (CH-RLSQ11)	2.87 (1.40–5.90)
Prior psychiatric history	2.62 (1.43–4.82)
Gestational week 32	
Probable RLS (IRSSSG)	0.80 (0.33–1.94)
Definite RLS (CH-RLSQ11)	2.03 (1.09–3.79)
Prior psychiatric history	2.32 (1.38–3.90)
Postpartum week 6	
Probable RLS (IRSSSG)	1.00 (0.44–2.24)
Definite RLS (CH-RLSQ11)	1.94 (0.99–3.81)
Prior psychiatric history	2.46 (1.46–4.15)

Multiple logistic regression, adjusted for parity and pre-pregnancy smoking.

increased risk of being depressed in gestational weeks 17 and 32. There was also a trend toward increased risk of depression in postpartum week 6 (AOR 1.94, CI 0.99–3.81, **Table 4**).

Among all RLS cases, those with pre-pregnancy RLS and moderate or severe symptoms were more often depressed in gestational week 17, gestational week 32, and postpartum week 6 than controls (**Table 5**). In contrast, RLS cases with *de novo* onset during pregnancy and moderate or severe symptoms were not more often depressed than controls (data not shown).

DISCUSSION

This is the first study observing a significant relationship between RLS and antenatal depression and possibly postpartum depression. More specifically, women with RLS onset already before pregnancy (idiopathic RLS) who also reported moderate or severe symptoms during pregnancy, had an increased risk of both antenatal and postpartum depression, whereas this was not the case in women with *de novo* onset of RLS during the present pregnancy.

RLS outside of pregnancy in women's lives is associated with an increased risk of developing depression.^{22,31,39} One possible mechanism by which RLS could lead to perinatal depression is obviously the disturbed sleep associated with RLS. Besides RLS, disturbed sleep is a well-established and independent risk factor for development of depression.^{40,41} Indeed, a growing body of evidence suggests that disturbed sleep is not just a symptom of depression, but that it may actually precede onset of the depression.⁴² Among pregnant women with preexisting RLS, pre-pregnancy sleep disturbances may worsen during pregnancy, thus increasing the vulnerability to depression. Alternatively, the relationship between RLS and perinatal depression could be due to increasing RLS symptomatology. It is known that symptom severity of RLS increases during pregnancy.²¹ Besides influencing sleep, it is plausible that the overall burden of the disease may render women more susceptible to depression. This is particularly important

Table 5—Risk for depression in gestational week 17, gestational week 32, and postpartum week 6 in relation to RLS onset and symptom severity

	AOR (95% CI)
Gestational week 17	
Pre-pregnancy RLS with severe symptoms	4.74 (2.30–9.76)
<i>De novo</i> RLS with severe symptoms	1.76 (0.67–4.61)
Gestational week 32	
Pre-pregnancy RLS with severe symptoms	3.67 (1.85–7.28)
<i>De novo</i> RLS with severe symptoms	0.84 (0.30–2.70)
Postpartum week 6	
Pre-pregnancy RLS with severe symptoms	2.58 (1.28–5.21)
<i>De novo</i> RLS with severe symptoms	1.37 (0.57–3.30)

Multiple logistic regression, adjusted for parity, pre-pregnancy smoking, and psychiatric history.

during pregnancy, when efficient treatment for RLS is generally advised against.

Iron deficiency with or without anemia is common during pregnancy and is generally thought to influence the risk of RLS in pregnancy.^{43,44} Similarly, iron deficiency in itself may contribute to depression, especially in the perinatal period. Preliminary findings suggest that infusion of ferric carboxymaltose, which is not contraindicated after the first trimester, may be effective in reversing RLS in pregnant women with iron deficiency or anemia.⁴⁵ Together these findings emphasize the role of iron deficiency in RLS and the significance of iron status assessment during pregnancy. However, it is yet unknown if iron treatment also improves depressive symptoms during pregnancy or the postpartum period. A final possible mechanism by which RLS may influence antenatal depression (specifically) resides in the interaction between pregnancy hormones, predominantly estradiol and progesterone, and their influence on dopaminergic neurotransmission.^{29,30} During pregnancy, estradiol serum concentrations increase a hundred-fold, whereas progesterone levels are approximately 50 times increased. In non-pregnant women, it is generally thought that estradiol increases dopaminergic neurotransmission in the ventral striatum.⁴⁶ However, recent evidence has suggested that estradiol influence on dopamine may be dose-dependent,⁴⁷ but few studies have in fact assessed the effect of extremely high estradiol levels, such as during pregnancy. Possibly, the increased prevalence of RLS and depression during pregnancy are epiphenomenon, representing the final pathway for ovarian steroid-dopaminergic interactions.⁴⁸

Clearly, women with *de novo* RLS during pregnancy, even though symptoms were severe, were not at increased risk of developing antenatal or postpartum depression. In contrast to women with pre-pregnancy RLS, *de novo* pregnancy RLS most often remit after delivery.³³ For women affected by *de novo* pregnancy RLS, the RLS symptoms may appear as typical somatic pregnancy symptoms which are bound to disappear after pregnancy. For the clinician, it is thus important to establish if RLS symptoms during pregnancy is a preexisting disorder or newly developed, particularly as pre-pregnancy RLS has a greater

influence on the psychiatric well-being of women. In addition, other reasons why the RLS history is important to establish include recent findings suggesting that women with idiopathic RLS have less sleep duration during pregnancy and decreased birth weight of neonates compared to pregnant women with *de novo* RLS.⁴⁹

The present study confirms prior studies of RLS during pregnancy, showing that multiparity and pre-pregnancy tobacco use are associated with RLS during pregnancy. As mentioned, previous studies have reported a wide range of pregnancy RLS prevalence rates. Some of this variation is likely dependent on whether frequency of symptoms has been taken into account in the RLS definition, but other factors such as age, number of prior pregnancies, and nutritional status and iron status before pregnancy in the study population presumably influence the results. In our data, the prevalence of RLS during pregnancy, corresponding to the IRLSSG standard criteria, was 18.5%, and 12.3% had symptoms more often than two to three days/week. These numbers fit well with previous findings in pregnant populations but is in the lower range.²¹ The most likely reason why we found a lower prevalence than the majority of previous studies is the high cutoff used for frequency of symptom occurrence requested for RLS diagnosis in this study. The even lower prevalence found by the CH-RLSQ11 questionnaire is primarily due to the exclusion of leg cramps and positional discomfort, which are common pregnancy complaints.⁵⁰ In a review of nearly 50 community-based studies, RLS prevalence rates declined by half when a threshold for frequency and/or severity of symptoms was added to the standard IRLSSG criteria. In addition, when “mimics” were considered, the prevalence estimates became even lower.⁵¹ Over time it has become clear that the positive predictive value of many RLS screening questionnaires may be fairly low; the four questions in the IRLSSG tool for RLS diagnosis is calculated to have 50% false-positive identification of RLS. Many individuals who are identified by these screening questionnaires have other conditions that can mimic the features of RLS, thus satisfying the four diagnostic criteria.³⁸ The CH-RLSQ11 was designed to be more specific and somewhat less sensitive; its error rate is lower, with false positives in general populations of 7% to 10%.³⁷

It has been discussed if leg cramps, positional discomfort, and RLS simultaneously affect pregnant women, why questionnaire-based discrimination may be difficult. Interviews are of course recommended whenever possible. For this reason, one weakness of our study is that RLS cases might have been excluded by the coincident occurrence of leg cramps and positional discomfort. Another important limitation of the study was that pre-pregnancy depression was not systematically assessed by psychiatric interviews. However, it should be emphasized that Swedish maternity records are standardized and include specific questions on prior somatic and psychiatric health. Nevertheless, it is possible that some women had pre-pregnancy depression that continued throughout the pregnancy and postpartum period.

In summary, women with RLS onset before pregnancy and moderate or severe symptoms had an increased risk of both antenatal and postpartum depression. Currently, few treatment options are available in pregnant women for both RLS and depression, and it remains to establish if RLS treatment also

has a positive impact on the depressive symptoms. A further potential therapeutic problem might be represented by the pharmacological treatment for depression, which often worsen RLS. Finally, the presence of idiopathic RLS before pregnancy might be useful as an early predictor of perinatal depression and can suggest a more careful psychological assessment and management in these women. Given the impact of RLS on the psychological well-being of pregnant women, further intervention studies in pregnant populations should not only address RLS symptoms but also depressive symptomatology.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2013

Submitted in final revised form December, 2013

Accepted for publication January, 2014

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.