HHS Public Access

Author manuscript

Clin Ther. Author manuscript; available in PMC 2019 June 18.

Published in final edited form as:

Clin Ther. 2016 February ; 38(2): 256–264. doi:10.1016/j.clinthera.2015.11.021.

Restless Legs Symptoms and Pregnancy and Neonatal Outcomes

D. Onentia Oyieng'o, MD[1], **Kipruto Kirwa, MPH**[2], **Iris Tong, MD**[3], **Susan Martin, LDN, IBCLC**[4], **José Antonio Rojas-suarez, MD**[5], and **Ghada Bourjeily, MD**[3]

[1]Via Christi Health, Department of Pulmonary and Critical Care, Wichita, Kansas [2]Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island [3]Department of Medicine, The Warren Alpert Medical School of Brown University, The Miriam Hospital, Providence, Rhode Island [4]Women's Medicine Collaborative, Department of Medicine, The Miriam Hospital, Providence, Rhode Island [5]Grupo de Investigación en Cuidados Intensivos y Obstetricia—GRICIO, Universidad de Cartagena, Barrio Alcibia, sector Maria Auxiliadora, Cartagena, Colombia

Abstract

Purpose: Restless legs syndrome (RLS) is a commonly occurring neurologic disorder that affects up to one third of women during pregnancy. RLS has been associated with increased sympathetic tone in the nonpregnant population. We examined whether a RLS surrogate is associated with a higher prevalence of pregnancy and neonatal outcomes.

Methods: Data were analyzed from a cross-sectional survey of 1000 women interviewed soon after delivery by using an RLS surrogate question. Women were asked how frequently (0 = none, 1 = rarely [<1 time/week], 2 = sometimes [1–2 times/week], 3 = frequently [3–4 times/week], and 4 = always [5–7 times/week]) they had "experienced jumpy or jerky leg movements" in the last 3 months of pregnancy. Clinical charts were reviewed to obtain relevant demographic and clinical data, including the presence of gestational hypertensive disorders and neonatal outcomes at birth. Subjects who "always" experienced RLS were compared with subjects experiencing symptoms less frequently or not at all with respect to prevalence of gestational hypertensive disorder.

Findings: The mean ([SD]) age, prepregnancy body mass index (BMI), and BMI at delivery were 29.0 (6.1) years, 26.1 (6.2) kg/m^2, and 32.0 (6.3) kg/m^2, respectively. The overall prevalence of the RLS surrogate (jumpy or jerky leg movements) was 35.5% with the following distribution on a Likert scale: score 1 = 6.4%; score 2 = 10.2%; score 3 = 8.1%; and score 4 = 10.8%. Chronic hypertension was present in 2.1%, pregnancy-induced hypertension in 9.5%, and preeclampsia in 4.5% of respondents. Subjects who reported "always" having sensations of jumpy or jerky legs

Address correspondence to: Ghada Bourjeily, MD, The Miriam Hospital, 146 West River Street, Suite 11C, Providence, RI 02904. ghada_bourjeily@brown.edu.

Dr. Oyeing'o analyzed and interpreted the data and prepared the manuscript; Mr. Kirwa analyzed and interpreted the data and prepared the manuscript; Drs. Tong and Rojas-Suarez made significant contributions to the manuscript; Ms. Martin collected and managed the data and made significant contributions to the manuscript; and Dr. Bourjeily designed the study, implemented data collection, analyzed and interpreted the data, and prepared the manuscript.

were more likely to have gestational hypertensive disorders compared with those who reported less frequent occurrence of the symptoms. Adjusted odds ratios were 3.74 (95% CI, 1.31–10.72; $P = 0.014$) for chronic hypertension; 1.26 (95% CI, 0.65–2.46; $P = 0.487$) for pregnancy-induced hypertension; and 2.15 (95% CI, 0.97–4.75; $P = 0.060$) for preeclampsia. There was a significant association between leg movement score and neonatal birth weight (coefficient, −149.5 g [95% CI, – 276.9 to −22.5]; $P = 0.005$) and gestational age at birth (−0.7 week [95% CI, −1.1 to −0.2]; $P = 0.021$) that persisted after adjusting for preeclampsia, diabetes, and smoking.

Implications: A higher frequency of jumpy or jerky leg symptoms, a proxy for RLS during pregnancy, was associated with a higher likelihood of gestational hypertensive disorders and neonatal outcomes such as gestational age at birth and birth weight. These findings may affect RLS treatment decisions during pregnancy.

Keywords

birth weight; gestational hypertensive disorders; limb movement; pregnancy; preterm birth; restless legs syndrome.

INTRODUCTION

Restless legs syndrome (RLS), or Willis-Ekbom disease, is a common sensorimotor disorder characterized by a circadian variation in the urge to move the legs that is worse during periods of rest or inactivity, and partially or totally relieved by movement.[1] Diagnosis of RLS is purely symptom-based and includes: (1) a compelling urge to move the legs; (2) symptoms that begin or worsen during periods of rest or inactivity; (3) symptoms that are partially or totally relieved by movement; and (4) that are worse or occur in the evening or at night.[2] Depending on the criteria used for diagnosis and reported severity based on frequency of symptoms, RLS ranges in prevalence from 4% to 29% in the general population.[3,4]

There is a growing body of literature that shows a relationship between RLS and periodic limb movements and hypertension, heart disease, and stroke,[5–9] with the risk of hypertension increasing with the burden or severity of RLS symptoms.[10,11] It is believed that the link between RLS and hypertension in the general population is mediated by increased sympathetic discharge.[7,8]

The prevalence of RLS increases with age as well as in pregnancy[12–14] and is highest in the third trimester,[15] reaching 30% in some studies.[16] Treatment of RLS in pregnancy is limited by the lack of fetal safety data of many first-line drugs used to treat RLS in the nonpregnant population.[17] The decision to treat must balance fetal safety concerns of a given drug with the risk of the untreated condition. Hence, an association between RLS and negative pregnancy outcomes may therefore strongly influence the decision to treat and the choice of medications.

Hypertensive disorders of pregnancy are important causes of fetal and maternal morbidity and mortality worldwide.[18] Preeclampsia affects immediate maternal,[19] fetal,[20] and neonatal[21] health and survival, and it is associated with long-term metabolic[22] and

cardiovascular outcomes in women.[23] Because RLS is linked to an enhanced sympathetic drive, we hypothesized that it may also be associated with a higher risk of cardiovascular complications such as gestational hypertensive disorders in the pregnant population. Similarly, because an enhanced sympathetic drive may affect placental perfusion, fetal growth and well-being may also be affected. Accordingly, the goal of the present study was to evaluate the association between RLS, hypertensive disorders of pregnancy, and neonatal outcomes, adjusting for several potential confounders. We hypothesized that a higher frequency of an RLS surrogate would be associated with a higher prevalence of hypertensive disorders of pregnancy and neonatal birth weight.

PATIENTS AND METHODS

Study Design and Study Participants

Data from 1000 women interviewed at Women & Infants Hospital, a tertiary care obstetric hospital in Providence, Rhode Island, were used to quantify the cross-sectional association between jumpy or jerky leg movements and pregnancy outcomes. A woman was interviewed if she was within 48 hours of delivery, was aged ≥18 years, proficient in English, and provided informed consent to participate in the study, as described previously.[24–26] Those who experienced fetal or neonatal demise were excluded. Participants were selected systematically from a daily list of deliveries. The institutional review board at the Women & Infants Hospital approved the study protocol.

Demographic Characteristics and Medical History

A questionnaire was used to elicit data regarding demographic characteristics, medical history, sleep-related symptoms, medications, and pregnancy-related conditions. Patient records were also searched for medical history, medication use and pregnancy outcomes, and recorded gestational age at birth and neonatal birth weight. Because prepregnancy body mass index (BMI) can be subject to significant recall bias, BMI at the time of the first prenatal visit was used as a surrogate.

Assessment of Exposure and Outcome

The independent variable was self-reported frequency of jumpy or jerky legs, a proxy for RLS. Information on RLS symptoms was obtained by using a 5-point Likert scale. Participants were asked the following question: "In the last 3 months of your pregnancy, how often did you experience jumpy or jerky leg movements?" Frequency was rated as follows: 0 = none; 1 = rarely (<1 time/week); 2 = sometimes (1–2 times/week); 3 = frequently (3–4 times/week); or 4 = always (5–7 times/week).

The primary outcome variable was the occurrence of hypertensive diseases of pregnancy during the index pregnancy. Hypertensive disorders in pregnancy were defined and categorized based on the definition of the American College of Obstetricians and Gynecologists, which distinguishes the following classes: (1) chronic hypertension; (2) pregnancy-induced hypertension (PIH); (3) preeclampsia; and (4) eclampsia.[27] Chronic hypertension was defined as hypertension that preceded pregnancy. Preeclampsia was defined as blood pressure ≥ 140/90 mm Hg on 2 occasions with the presence of proteinuria.

PIH was defined as hypertension that occurred in pregnancy but without proteinuria. Preterm birth was defined as birth before 37 completed weeks of gestation.

Statistical Analysis

Subjects reporting no, rare, occasional, and frequent weekly experience of jumpy or jerky legs (frequency levels 0–3 in the questionnaire) were compared with those who reported always experiencing jumpy or jerky leg movements (frequency level 4) in the last trimester of their most recent pregnancy. This choice of comparison groups was made a priori to enhance the specificity of the self-reported RLS surrogate measure (jumpy and jerky legs) because patients reporting a high frequency of symptoms are more likely to have RLS. Moreover, upon data exploration, women in categories 0–1 and 2–3 had a similar prevalence of outcomes, supporting our pre-analysis decision to combine the 2 categories. As a sensitivity check on the main analysis, a different categorization scheme was used that compared frequency levels 0–1 (reference category) versus levels 2–3 and 4, respectively. We tested for trend in prevalence of the hypertensive outcomes across RLS severity categories by assigning each category the mean outcome prevalence values within the category, including the term in a regression model as a continuous variable. The resultant P value represents the linear component of trend.

Categorical variables were compared by using the χ^2 test or Fisher's exact test in cases in which the expected cell sizes were <5. Logistic regression was used to evaluate the association between jumpy or jerky legs and hypertensive disorders of pregnancy. On the basis of previous subject matter and knowledge of their likely role as confounders in the association of leg movement with chronic hypertension, age, pregestational and delivery BMI, multiparity, multifetal gestations, renal disease, and smoking history were selected for adjustment in the multivariable regression model. Similarly, smoking, diabetes, and preeclampsia were used for adjustment in the multivariable regression model when examining the association of leg movement with neonatal outcomes. The Hosmer-Lemeshow goodness-of-fit test was used to assess model adequacy. Continuous variables were entered as linear terms in the model because polynomial terms did not suggest nonlinearity or improve model fit. Observations with missing values were excluded. All analyses were performed by using Stata version 13 (Stata Corp, College Station, Texas) and Revolution R Enterprise version 7.4 (Revolution Analytics, Redmond, Washington). P values are 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

The mean (SD) age of respondents was 29.0 (6.1) years (Table I). Nine percent of the subjects were current smokers. Mean prepregnancy BMI was 26.1 (6.2) kg/m^2, and BMI at delivery was 32.0 (6.3) kg/m^2; women had a mean weight gain of 34.7 (16.2) pounds.

Prevalence of Jumpy or Jerky Leg Movements

A total of 355 (35.5%) respondents reported symptoms of jumpy or jerky leg movements in the last 3 months of pregnancy, with varying frequency. A total of 108 participants (10.8%)

had a high burden of symptoms, reporting occurrence of jumpy or jerky leg movements 5 to 7 days per week (Likert score = 4 ["always"]). This group is referred to as the RLS surrogate group. A total of 6.4% (64) reported a symptom score of 1; 10.2% (102) reported a score of 2; and another 8.1% (81) reported a score of 3. The remaining 645 participants did not report having any jumpy or jerky leg movements (score of 0). Respondents in score categories 0 to 3 were grouped together and are referred to as the no-RLS surrogate group.

The distribution of age, BMI, parity, and prevalence of diabetes was similar between groups. The exception was that a higher proportion of participants in the RLS-surrogate group smoked before pregnancy or were current smokers (Table I). The RLS-surrogate group also reported higher mean (SD) Epworth Sleepiness Scale scores of 8.4 (3.9) compared with the no-RLS surrogate group (6.9 [3.9]; $P < 0.001$).

Leg Movement Symptom Score and Hypertensive Outcomes

The prevalence of chronic hypertension, PIH, and preeclampsia (including preeclampsia superimposed on chronic hypertension) was 2.1%, 9.5%, and 4.5%, respectively. The prevalence of chronic hypertension was significantly higher among subjects in the RLS-surrogate group compared with the no-RLS surrogate group (5.6% vs 1.7%; Fisher's exact test, $P = 0.019$). Preeclampsia was present in 8.33% in the RLS-surrogate group compared with 4.04% in the no-RLS surrogate group (Fisher's exact test, $P = 0.05$). PIH was present in 12.0% of the RLS-surrogate group and 9.2% of the no-RLS surrogate group, but this difference in prevalence was not statistically significant (Fisher's exact test, $P = 0.383$).

In the multivariable logistic regression analysis, a leg movement score of 4 was independently associated with a higher prevalence of chronic hypertension (odds ratio [OR], 3.36 [95% CI, 1.20–9.41]; $P = 0.012$), as seen in Table II. A higher frequency of leg movement score was also associated with a higher prevalence of preeclampsia (OR, 2.15 [95% CI, 0.97–4.75]; $P = 0.060$). PIH was not statistically significantly associated with frequency of jumpy or jerky leg sensations (OR, 1.26 [95% CI, 0.65–2.46]; $P = 0.487$). When comparing the trend in the odds of hypertensive outcomes with symptom severity, there seemed to be a significant upward trend with increasing severity (Table III).

Leg Movement Score and Neonatal Outcomes

Mean gestational age in the total sample was 38.6 (2.4) weeks, and mean birth weight was 3290 (649.5) g (Table I). A total of 138 (13.8%) participants had preterm births, defined as birth at <37 weeks' gestation, and 110 (11%) had infants with birth weights <2500 g. Five percent of all gestations were twin.

In the multivariable logistic regression analysis (Table IV), a leg movement score of 4 was independently associated with lower gestational age at birth (coefficient, −0.7 week [95% CI, −1.1 to −0.2]; $P = 0.005$). Leg movement score was also independently associated with lower weight at birth (coefficient, −149.7 g [95% CI, −276.9 to −22.5]; $P = 0.021$). Fisher's exact test was used to compare the prevalence of preterm births (births occurring before 37 completed weeks' gestation) between the 2 groups. Women with a leg movement score of 4 were twice as likely to have a preterm birth (21.3% vs 11.3%; $P = 0.001$). In addition, early preterm birth (birth before 34 completed weeks' gestation) occurred more commonly in

women with a leg movement score of 4 than in the no-RLS surrogate group (7.4 vs 3.7; $P = 0.07$), but this finding did not reach statistical significance at the α level of 0.05.

DISCUSSION

The present study found that the prevalence of symptoms of RLS in this population of postpartum women was elevated, with 18.9% reporting symptom occurrence at least 3 days a week in the last 3 months of the index pregnancy. Moreover, women with symptoms of RLS seemed to report significantly more daytime sleepiness, as evidenced by a higher score on the ESS, suggesting that RLS may have interfered with sleep quality. In addition, we found significant associations between these symptoms and chronic hypertension, with an association with preeclampsia that was significant at the 10% α level.

The reported prevalence of RLS in pregnancy is between 10.4% and 30% depending on the criteria used and the frequency of symptoms, the trimester of pregnancy, and the racial or geographical characteristics of the population being studied.[16,28,29] The estimated prevalence of frequently occurring jumpy or jerky leg movements in our cohort mirrors published data on the prevalence of RLS, even when the diagnosis is made using a single symptom.

Our study findings support an association between jumpy or jerky leg movements (our surrogate clinical marker of RLS) and hypertensive disorders in pregnancy. The association between jumpy or jerky leg movements and chronic hypertension was strong and remained statistically significant even after adjusting for potential confounders. The association with preeclampsia showed a trend toward statistical significance after adjusting for confounders. Although our study noted a higher prevalence of pregnancy-induced hypertension among subjects with jumpy or jerky leg movements, this finding was not statistically significant. It is possible that our study was underpowered to detect a significant difference in this outcome. RLS has been associated with hypertension in the nonpregnant population in many studies.[3,8–10,30,31] Other reports, however, have failed to show such an association.[32,33]

Similar to our study, Ramirez et al[34] observed higher Epworth Sleepiness Scale scores and a higher prevalence of preeclampsia in pregnant women with RLS (n = 40) compared with their counterparts without RLS (n = 178) in a cohort of patients presenting to a clinic in Lima, Peru. Our findings of lower birth weight and gestational age at birth in patients with a high symptom score are novel. One previous study has reported on the neonatal birth weight in women with a diagnosis of RLS and found no significant association.[35] The observed difference in findings between that study and the present one may be explained by significant differences in populations, sample size, and possibly by the method used to define the exposure. To place into context our neonatal outcomes associated with this RLS surrogate, we compared our findings versus those observed and reported with tobacco smoking, a universally accepted modifiable risk factor for birth weight reduction and prematurity. The differences observed in gestational age at birth and birth weight in our sample are within the range of reduction observed in tobacco smoking in women who smoke ~10 cigarettes per day.[36–38] In addition, our study reported a higher prevalence in preterm

births and early preterm births in women with the RLS surrogate compared with those without.

A number of possible biological mechanisms could account for the increased risk of these complications in patients with RLS. Autonomic activation with predominance of sympathetic discharge is believed to play a role in the pathophysiology of RLS and periodic limb movement, and a significant proportion of patients with RLS in the general population have periodic limb movements during sleep. Sympathetically mediated elevations in both heart rate and blood pressure result from autonomic activation that precedes or is triggered by micro-arousals in periodic limb movement.[7,8,39,40] It is believed that these repetitive blood pressure elevations at night lead to the development of daytime hypertension. EEG arousals resulting from limb movement may represent another risk factor for hypertension in persons affected by RLS through an elevated peripheral sympathetic tone.[7] Potential mechanisms for this association in pregnancy are similar and may relate to sympathetic activation, which has also been implicated in preeclampsia.[41] Furthermore, recent studies have shown that poor sleep quality and short sleep duration (which are features of RLS) are associated with an increased inflammatory response that may potentially be associated with preeclampsia.[42] Although our study did not assess sleep quality in association with RLS symptoms, the higher ESS scores are suggestive of poor sleep quality. Conversely, because preeclampsia is a multisystem disorder that also affects the central nervous system, it is possible that RLS may also be a manifestation of preeclampsia. This possibility needs to be evaluated further. The association with neonatal outcomes may also be explained by an increased sympathetic tone or an inflammatory milieu.

Our study was limited by the lack of a validated questionnaire and the use of this symptom criterion as opposed to recommended criteria, such as those by the International Restless Legs Syndrome Study Group.[2] The use of a single question may falsely increase the sensitivity (and at the expense of specificity) for a given condition.[30] A single question for the prevalence of RLS has been used and validated for screening before diagnostic confirmation by using standard criteria in adults[43] or in epidemiologic studies in adolescents.[44] However, it remains to be validated in other settings. It is noteworthy that more complex questions have been criticized because the participants are likely to retain only part of the question and answer positively to the part of the question that fits their own experience.[30] Based on a recent project by the Movement Disorders Society for the evaluation of diagnostic instruments specific to RLS, a single question is likely appropriate in large epidemiologic studies, but further validation is needed.[45] Use of this single symptom score could have limited our diagnostic accuracy of RLS, thus biasing our results.

Although within anticipated prevalence estimates, our study was restrained by a low absolute number of subjects with a diagnosis of hypertensive disorders of pregnancy. This limitation further restricted our subgroup analysis and evaluation of other maternal and fetal outcomes. We cannot exclude the possibility of residual confounding due to the broadness of some of the categories used for analysis. Because of the observational nature of the study, our data do not imply causation. Although an association of a condition with an adverse outcome does not necessarily imply that treating such condition would result in an improvement of the given outcome, the mere presence of such an association may still affect

future clinical and research decisions. Most first-line drugs for RLS do not have sufficient safety data to justify their use in the pregnant population. The demonstration of an association with an important adverse outcome could affect a decision to treat as the clinician weighs the risk of the drug and the risk of the untreated condition; it could also drive future registries and encourage trials evaluating the impact and safety of drug therapy on adverse outcomes.

CONCLUSIONS

In this cross-sectional study, we found that jumpy or jerky leg movements, a surrogate of RLS, were associated with a higher prevalence of hypertensive disorders in pregnancy and lower gestational age at birth and birth weight. Our findings raise important observations that require clarification in further prospective studies using diagnostic criteria of RLS rather than surrogate questions. Such studies are key, as they would strongly affect clinical decision-making in weighing the fetal safety risk of pharmacotherapy against the maternal and fetal risk of untreated RLS.

ACKNOWLEDGMENTS

Dr. Bourjeily is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (1R01HL130702–01A1 and National Center for Complementary and Integrative Health 5R01AT008393).

CONFLICTS OF INTEREST

Dr. Bourjeily has received research equipment support from Respironics; this support is not related to the current study does not impact the findings in this study or their interpretation. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Hening WA. Restless legs syndrome: a sensorimotor disorder of sleep/wake motor regulation. Curr Neurol Neurosci Rep. 2002;2:186–196. [PubMed: 11898486]
2. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15:860–873. [PubMed: 25023924]
3. Ulfberg J, Nystrom B, Carter N, Edling C. Restless legs syndrome among working-aged women. Eur Neurol. 2001; 46:17–19. [PubMed: 11455178]
4. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16:283–295. [PubMed: 21795081]
5. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32:589–597. [PubMed: 19480225]
6. Walters AS, Rye DB. Evidence continues to mount on the relationship of restless legs syndrome/periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. Sleep. 2010;33:287. [PubMed: 20337185]
7. Pennestri MH, Montplaisir J, Colombo R, et al. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007;68:1213–1218. [PubMed: 17420405]
8. Siddiqui F, Strus J, Ming X, et al. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol. 2007;118:1923–1930. [PubMed: 17588809]

9. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. Chest. 2006;129:76–80. [PubMed: 16424415]
10. Batool-Anwar S, Malhotra A, Forman J, et al. Restless legs syndrome and hypertension in middle-aged women. Hypertension. 2011;58:791–796. [PubMed: 21986505]
11. Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome–theoretical roles of inflammatory and immune mechanisms. Sleep Med Rev. 2012;16:341–354. [PubMed: 22258033]
12. Suzuki K, Ohida T, Sone T, et al. The prevalence of restless legs syndrome among pregnant women in Japan and the relationship between restless legs syndrome and sleep problems. Sleep. 2003;26:673–677. [PubMed: 14572119]
13. Manconi M, Govoni V, De Vito A, et al. Pregnancy as a risk factor for restless legs syndrome. Sleep Med. 2004;5:305–308. [PubMed: 15165540]
14. Tunc T, Karadag YS, Dogulu F, Inan LE. Predisposing factors of restless legs syndrome in pregnancy. Mov Disord. 2007;22:627–631. [PubMed: 17285614]
15. Pavlova M, Sheikh LS. Sleep in women. Semin Neurol. 2011;31:397–403. [PubMed: 22113512]
16. Sikandar R, Khealani BA, Wasay M. Predictors of restless legs syndrome in pregnancy: a hospital based cross sectional survey from Pakistan. Sleep Med. 2009;10:676–678. [PubMed: 19110469]
17. Oyiengo D, Louis M, Hott B, Bourjeily G. Sleep disorders in pregnancy. Clin Chest Med. 2014;35:571–587. [PubMed: 25156772]
18. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. Hypertens Pregnancy. 2003;22:203–212. [PubMed: 12909005]
19. Roberts JM, Pearson G, Cutler J, Lindheimer M. NHLBI Working Group on Research on Hypertension During Pregnancy. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension. 2003;41:437–445. [PubMed: 12623940]
20. Odegard RA, Vatten LJ, Nilsen ST, et al. Preeclampsia and fetal growth. Obstet Gynecol. 2000;96:950–955. [PubMed: 11084184]
21. Basso O, Rasmussen S, Weinberg CR, et al. Trends in fetal and infant survival following preeclampsia. JAMA. 2006;296:1357–1362. [PubMed: 16985227]
22. Smith GN, Pudwell J, Walker M, Wen SW. Risk estimation of metabolic syndrome at one and three years after a pregnancy complicated by preeclampsia. J Obstet Gynaecol Can. 2012;34:836–841. [PubMed: 22971452]
23. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366:1797–1803. [PubMed: 16298217]
24. Bourjeily G, Raker CA, Chalhoub M, Miller MA. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. Eur Respir J. 2010;36:849–855. [PubMed: 20525714]
25. Bourjeily G, El Sabbagh R, Sawan P, et al. Epworth sleepiness scale scores and adverse pregnancy outcomes. Sleep Breath. 2013;17:1179–1186. [PubMed: 23420179]
26. Bourjeily G, Raker C, Chalhoub M, Miller M. Excessive daytime sleepiness in late pregnancy may not always be normal: results from a cross-sectional study. Sleep Breath. 2013;17:735–740. [PubMed: 22872283]
27. ACOG Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33. Obstet Gynecol. 2002;99:159–167. [PubMed: 16175681]
28. Chen PH, Liou KC, Chen CP, Cheng SJ. Risk factors and prevalence rate of restless legs syndrome among pregnant women in Taiwan. Sleep Med. 2012;13:1153–1157. [PubMed: 22854259]
29. Alves DA, Carvalho LB, Morais JF, Prado GF. Restless legs syndrome during pregnancy in Brazilian women. Sleep Med. 2010;11:1049–1054. [PubMed: 20947424]
30. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002;53:547–554. [PubMed: 12127170]
31. Chhabra A, Aronow WS, Ahn C, et al. Incidence of new cardiovascular events in patients with and without peripheral arterial disease seen in a vascular surgery clinic. Med Sci Monit. 2012;18: CR131–CR134. [PubMed: 22367123]

32. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006;7:545–552. [PubMed: 16740407]
33. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008;70:35–42. [PubMed: 18166705]
34. Ramirez JO, Cabrera SA, Hidalgo H, et al. Is preeclampsia associated with restless legs syndrome? Sleep Med. 2013;14:894–896. [PubMed: 23891236]
35. Sharma SK, Nehra A, Sinha S, et al. Sleep disorders in pregnancy and their association with pregnancy outcomes: a prospective observational study. Sleep Breath. 2015 [Epub ahead of print].
36. Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. Am J Obstet Gynecol. 1957;73:807–815. [PubMed: 13411046]
37. Andriani H, Kuo HW. Adverse effects of parental smoking during pregnancy in urban and rural areas. BMC Pregnancy Childbirth. 2014;14:414. [PubMed: 25551278]
38. Bernstein IM, Mongeon JA, Badger GJ, et al. Maternal smoking and its association with birth weight. Obstet Gynecol. 2005;106:986–991. [PubMed: 16260516]
39. Izzi F, Placidi F, Romigi A, et al. Is autonomic nervous system involved in restless legs syndrome during wakefulness? Sleep Med. 2014;15:1392–1397. [PubMed: 25266501]
40. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep. 2007;30:755–766. [PubMed: 17580597]
41. Schobel HP, Fischer T, Heuszer K, et al. Preeclampsia–a state of sympathetic overactivity. N Engl J Med. 1996;335:1480–1485. [PubMed: 8890098]
42. Palagini L, Gemignani A, Banti S, et al. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Med. 2014;15:853–859. [PubMed: 24994566]
43. Ferri R, Lanuzza B, Cosentino FI, et al. A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. Eur J Neurol. 2007;14:1016–1021. [PubMed: 17718694]
44. Zhang J, Lam SP, Li SX, et al. Restless legs symptoms in adolescents: epidemiology, heritability, and pubertal effects. J Psychosom Res. 2014;76:158–164. [PubMed: 24439693]
45. Walters AS, Frauscher B, Allen R, et al. Review of diagnostic instruments for the restless legs syndrome/Willis-Ekbom Disease (RLS/WED): critique and recommendations. J Clin Sleep Med. 2014;10:1343–1349. [PubMed: 25348242]

Clin Ther. Author manuscript; available in PMC 2019 June 18.

Table I.

Demographic and clinical characteristics of 1000 postpartum women. Unless otherwise indicated, values are number (%).

Characteristic	Total Sample (N = 1000)	RLS Surrogate Group (n = 108)	No-RLS Surrogate Group (n = 892)
Age, mean (SD), y	29.0 (6.1)	29.3 (5.8)	29.0 (6.1)
Race/ethnicity			
White non-Hispanic	682 (68.2)	84 (77.8)	598 (67.0)
Other races	318 (31.8)	24 (22.2)	294 (33.0)
BMI, mean (SD), kg/m^2			
Prepregnancy	26.1 (6.2)	26.5 (6.3)	26.0 (6.3)
At delivery	32.0 (6.3)	32.0 (6.7)	32.0 (6.3)
Smoking			
Never smoker	762 (76.3)	66 (61.1)	696 (78.1)
Current or past smoker	237 (23.7)	42 (38.9)	195 (21.9)
Diabetes	95 (9.5)	13 (12.04)	82 (9.19)
Kidney disease	14 (1.4)	3 (2.8)	11 (1.23)
Prenatal vitamin intake			
Iron or folate	160 (16.0)	13 (12.0)	147 (16.5)
None or missing	840 (84.0)	95 (88.0)	745 (83.5)
Mode of delivery			
Vaginal	527 (52.8)	48 (44.9)	479 (53.7)
Cesarean delivery	333 (33.3)	41 (38.3)	292 (32.7)
C after failed V	139 (13.9)	18 (16.8)	121 (13.6)
Gestational age at birth, mean (SD), wk	38.6 (2.4)	37.9 (3.1)	38.7 (2.3)
Birth weight, mean (SD), g	3290.0 (649.5)	3117.0 (751.9)	3311.0 (751.9)

BMI = body mass index; C after V = Cesarean delivery after failed vaginal delivery.

Table II.

Frequencies, unadjusted and adjusted odds ratios (ORs), and 95% CIs of hypertensive disorders of pregnancy associated with leg movement score in the last trimester of the index pregnancy.

	Frequency of Jumpy/Jerky Legs		Unadjusted Effect Estimate		Adjusted* Effect Estimate	
Variable	**No RLS Surrogate, No. (%)**	**RLS Surrogate, No. (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Chronic hypertension	15 (1.68)	6 (5.56)	3.44 (1.31–9.06)	0.012	3.36 (1.20–9.41)	0.021
PIH	82 (9.19)	13 (12.04)	1.35 (0.73–2.52)	0.343	1.26 (0.65–2.46)	0.487
Preeclampsia	36 (4.04)	9 (8.33)	2.16 (1.01–4.62)	0.047	2.15 (0.97–4.75)	0.060

PIH = pregnancy-induced hypertension; RLS = restless legs syndrome.

*Adjusted for age, prepregnancy body mass index, vitamin intake, diabetes, race, and smoking.

Table III.

Odds (95% CIs) of hypertensive disorders and severity of symptom score.

	Severity of Jumpy/Jerky Legs			
Outcome	**None or Rarely (n = 709)**	**Sometimes or Frequently (n = 183)**	**Always (n = 108)**	***P* for Trend**
Chronic hypertension	1.00 (Ref)	0.61 (0.09–2.35)	3.06 (1.00–8.57)	0.018
PIH	1.00 (Ref)	1.04 (0.57–1.83)	1.30 (0.64–2.48)	0.448
Preeclampsia	1.00 (Ref)	0.95 (0.37–2.12)	2.10 (0.89–4.55)	0.061

PIH = pregnancy-induced hypertension.

Clin Ther. Author manuscript; available in PMC 2019 June 18.

Table IV.

Unadjusted and adjusted coefficients and 95% CIs of neonatal characteristics associated with the restless legs syndrome surrogate in the last trimester of the index pregnancy.

	Unadjusted Effect Estimate		Adjusted* Effect Estimate	
Neonatal Characteristic	**Coefficient (95% CI)**	***P***	**Coefficient (95% CI)**	***P***
Gestational age, wk	−0.8 (−1.3 to −0.3)	0.001	−0.7 (−1.1 to −0.2)	0.005
Birth weight, g	−194.3 (−323.7 to −65.0)	0.003	−149.7 (−276.9 to −22.5)	0.021

*Adjusted for smoking, preeclampsia, and diabetes.