Serum Folic Acid Level and Its Relationship to Gestational Willis Ekbom Disease (Restless Legs Syndrome)

A Pilot Study

Minesh Morker, M.D., Dana Gossett, M.D., Tacoma McKnight, M.D., Bhavita Patel, M.S., Moksha Patel, M.D., and Hrayr Attarian, M.D.

OBJECTIVE: To determine the association between folic acid levels and restless legs syndrome (RLS) in pregnancy (gestational RLS [gRLS]).
STUDY DESIGN: We checked folic acid levels during scheduled clinic visits at 24–28 weeks of gestation. We conducted a brief clinical interview to determine who met the International RLS Study Group (IRLSSG) criteria for gRLS. Those with moderate or severe RLS (IRLSSG severity scale of >10) and with symptoms occurring >3 days a week were included in the +gRLS group. The rest were included in the –gRLS (comparison) group.
RESULTS: We demonstrated a significant difference ($p<0.05$) in mean folic acid levels in women who were in the +gRLS group vs. those in the –gRLS group: 27.3±12.9 ng/mL (median, 25 ng/mL) vs. 32.2±20.6 ng/mL (median, 28 ng/mL), respectively ($p<0.03$ on two-sample independent t *test).*
CONCLUSION: Folic acid levels can be easily and inexpensively checked or supplemental folic acid can be given to women with moderate to severe gRLS. In the future we hope to build on this work with a larger comprehensive trial looking at other biomarkers and their association with folic acid levels and gRLS. (J Reprod Med 2017;62:593–597)

…women with gRLS have significantly lower folic acid levels and poorer sleep quality as compared to gestational-age matched women without gRLS.

Keywords: dysesthesia, dopaminergic effect, folic acid, gestational, insufficient sleep syndrome, paresthesia, pregnancy, pregnancy complications, restless legs, restless legs syndrome, sleep deprivation, Willis Ekbom disease.

Willis Ekbom disease/restless legs syndrome (WED/RLS) is a disorder of dopaminergic dysfunction characterized by primarily lower limb restlessness and dysesthesias occurring or worsening in the evening or at night.[1]

RLS is much more prevalent in pregnant women starting around the middle of the second trimester and is most prominent in the third trimester, with symptoms worsening as the pregnancy progresses and with a precipitous improvement, even resolution, of symptoms with delivery.[2] The prevalence of

From the Departments of Neurology and of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Address correspondence to: Hrayr Attarian, M.D., Department of Neurology, Northwestern University Chicago, 710 North Lake Shore Drive #1111, Chicago, IL 60611 (hattaria@nm.org).

Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

gestational RLS (gRLS) is between 12–38% among pregnant women, with different frequency and severity of symptoms accounting for the wide variation in prevalence.[2-7] In comparison, RLS is reported in 5–8% of the general population in North America, Japan, and Europe, with lower prevalence elsewhere.[8] Transient gRLS also increases the risk for the subsequent development of chronic RLS fourfold, and gRLS reemerges during subsequent pregnancies in about 60% of women who have previously had it.[9]

A clear pathophysiology of gRLS has yet to be established. Low ferritin levels have been strongly associated with chronic RLS. A recent study showed a significant difference in ferritin levels between women with gRLS and trimester-matched pregnant women without gRLS.[7] Other studies, however, have not shown this difference.[4,10] Furthermore, the rapid improvement of the RLS days after delivery does not support this as a primary mechanism since iron stores take up to 3 months to replenish, while improvement starts within 2 weeks postpartum.[2,11]

Since pregnancy is a state of constant hormonal changes, fluctuations in prolactin, estrogen, and progesterone have been proposed as a cause of gRLS. Prolactin has distinct antidopaminergic activity and its levels rise throughout pregnancy. In women who breastfeed, however, prolactin continues to be secreted, yet there is the same degree of improvement and often resolution of gRLS after delivery as there is among women who bottle feed.[12] Estrogen levels also fluctuate, and exogenous estrogen has been shown to correlate with risk of RLS in perimenopausal women[13] but not in younger women of childbearing age.[14] The rise of estradiol levels and their decline after delivery have been shown to correlate well with worsening and subsequent improvement in gRLS and related periodic limb movements of sleep.[15] Other larger studies, however, failed to find a relationship between estradiol levels and gRLS.[4,16] Progesterone levels do not correlate with gRLS.[4,15,16] Folic acid levels, however, have rarely been looked at as a possible correlate of gRLS.

One study of a cohort of 148 (110 controls and 38 gRLS patients) did not find a significant difference in serum folic acid levels. However, that study included all gRLS regardless of severity and did not compare mild with severe cases.[16] Another smaller trial of 21 women (16 controls and 5 gRLS patients) found a significant difference in serum folic acid levels in gRLS patients as compared to controls.[10] That smaller trial included in the gRLS group only women who had symptoms at least 3 times a week, while the prior trial included, and defined the gRLS group as, women who had symptoms 3 times per month or more. Folic acid is important in the synthesis of tetrahydrobiopterin, which is the co-factor for the hydroxylation of phenylalanine and tryptophan and is the rate-limiting step in the synthesis of dopamine.

Our goal was to compare the mean folic acid level in women with gRLS in the early third trimester to trimester-matched women without gRLS.

Materials and Methods

After obtaining approval from Northwestern University's Institutional Review Board, we consented 107 consecutive adult women (aged ≥18 years) from October 2013 to July 2015 during their scheduled clinic visit at 24–28 weeks of gestation. This is the visit during which the last routine blood work of the pregnancy is done. We (M.M., B.P., or M.P.) conducted a brief clinical interview to determine who among these women met the International RLS Study Group (IRLSSG) criteria for gRLS. Those with moderate or severe RLS (IRLSSG severity scale of >10)[1] and with symptoms occurring >3 days a week were included in the +gRLS group. The rest were included in the −gRLS (comparison) group. Table I shows the breakdown of subjects in both groups according to severity. We excluded women with current and past history of RLS. Folic acid levels were added to their routine blood work. Women who consented also filled out an Epworth Sleepiness Scale (ESS) and a Pittsburgh Sleep Quality Index (PSQI). In addition, we collected demographic information including age, parity,

Table I *Breakdown of Subjects in the Two Groups*

	−gRLS (no. of patients)
No RLS	71
Mild RLS	8
Total	79
	+gRLS (no. of patients)
Moderate RLS	14
Severe or very severe RLS	6
Total	20

and intake of prenatal vitamins prior to the onset of RLS.

Results

A total of 107 women were recruited for this study. Folic acid levels were not available for 8 women due to lab error. Out of the remaining 99 women, 20 were in the +gRLS group and 79 in the −gRLS group. Therefore, in our cohort the prevalence of first-time moderate to severe gRLS was 20.2%.

For our primary outcome, we demonstrated a significant difference ($p<0.05$) in mean folic acid levels in women who were in the +gRLS group vs. those in the −gRLS group: 27.3±12.9 ng/mL (median, 25 ng/mL) vs. 32.2±20.6 ng/mL (median, 28 ng/mL), respectively ($p<0.03$ on two-sample independent *t* test).

In the +gRLS group there was no correlation between folic acid level and the score of IRLSG severity scale score, with R^2=7E-05.

Differences Between Groups

All women were taking prenatal vitamins, and there was no difference in the mean age or mean parity between the groups. Mean age in the +gRLS group at the time of the evaluation was 34.3 years (median 35, SD 4.74, range 25–44), and that in the −gRLS group was 34.05 years (median 34, SD 4.17, range 22–43). Mean parity in the +gRLS group was 0.81 pregnancies (median 0, SD 1.17, and range 0–4) and in the −gRLS group was 0.87 pregnancies (median 1, SD 1.22, and range 0–7). Mean gestational age in both groups was 24.5 weeks.

Secondary Measures

Surprisingly, both groups had a mean ESS score that was normal (>9 indicates daytime sleepiness): +gRLS group 7.8 (SD 4.31), median of 7, and −gRLS group 5.1 (SD 3.70) with a median of 5. The difference was not significant.

The PSQI (score of ≥5 indicates poor sleep) indicated that both groups had poor sleep. The mean PSQI in the +gRLS group was 7.13 (SD 4.3) and median was 7. The mean PSQI in the −gRLS group was 5.06 (SD 3.12) and median was 5. As expected, the +gRLS women reported higher PSQI values than did the −gRLS women; this difference was statistically significant with a p value of 0.01.

Discussion

To our knowledge, this study is the largest series where a significant difference between folic acid levels among pregnant women with and without gRLS has been demonstrated. Lee et al demonstrated a similar difference in a very small cohort in 2001. Unlike ours, most of the women in their study were not on prenatal vitamins with folic acid (91%), and mean folic acid levels in both groups were much lower than the levels in the current study.[10] Nevertheless, our study showed a similar difference in folic acid levels in +gRLS in a larger cohort.

Tunc et al in 2007 did not demonstrate a significant difference in folic acid levels in a cohort similar in size to ours. They, however, included all gRLS subjects regardless of severity, even patients with only mild occasional symptoms. Moreover, they commented that not taking prenatal vitamins was a risk factor for gRLS, hence indirectly suggesting a possible relationship between folic acid levels and gRLS.[16]

A third study, by Hubner et al, from 2013 did not compare folic acid levels between women with gRLS and those without. They merely commented that folic acid levels were normal by their laboratory standards.[4] This was indeed the case with our cohort as well. All 99 had normal folic acid levels, but those with gRLS had significantly lower mean folic acid levels than did those without gRLS.

This is not the first time that a laboratory measure has been shown to be significantly lower in people with RLS than in those without the condition, even if the specific measure is within the laboratory range of normal. Ferritin is one such example where normal levels of <50 μg/L are associated with RLS[17] despite the fact that levels <50 μg/L may still be normal.

The prevalence of gRLS in our cohort was 20.2%, which is consistent with previously reported statistics. Two recent studies reported different prevalences. Hubner et al showed a prevalence of only 12% but included women in all 3 trimesters,[4] while we included only those at ≥24 weeks of gestation. It is well known that the risk of RLS increases as pregnancy progresses. Neyala et al in 2015 demonstrated a much higher prevalence of 32.8%[7] at the same gestational age as our cohort, but they included mild, moderate, and severe cases as well as those who had had gRLS in previous pregnancies, while we included only first-time gRLS sufferers with moderate or severe symptoms.

Neither maternal age nor parity impacted the prevalence of gRLS.

Those with gRLS, not surprisingly, had significantly poorer sleep on the PSQI than did women without gRLS. Poor sleep quality has been associated with number of negative outcomes including increased risk of premature delivery, cesarean sections, and postpartum depression.[18-21] Recently, gRLS has also been associated with pregnancy-induced hypertension (PIH) in a large Chinese cohort. Out of 3,876 women who participated, 453 had gRLS. PIH was found in 11.5% of the gRLS group vs. 7.7% of those without gRLS. After controlling for all other factors, gRLS remained a risk factor for PIH with odds ratio (95% CI) of 1.68 (1.27, 2.23).[22]

Presence of gRLS also significantly increases the risk of subsequent gRLS and RLS.[9] We therefore believe that supplementing women with gRLS with additional folic acid may not only improve quality of sleep and prevent other complications associated with poor sleep in pregnancy, but may even potentially reduce the risk of RLS in the future. Currently there are no good treatment options for gRLS as most drugs are category C, and the only medication that is not category C is oxycodone, which has a high risk of tolerance and abuse.[23]

The ESS scores were normal in both groups, indicating lack of daytime sleepiness despite poor sleep quality at night. This is a novel finding as most, but not all, other studies both in gRLS and idiopathic RLS show an abnormal ESS, indicating excessive daytime sleepiness.[22,24,25] Although ESS is internally validated in women, the cutoff for normal may be different in younger women.[26,27]

Ours is a pilot study and has many limitations, primarily due to lack of resources. First, we could not follow the subjects postpartum with further folic acid levels to explore changes in folic acid levels in those women whose gRLS resolved. Second, we did not have the resources to check iron studies, blood pressure, glucose levels, or other vitamin levels. Third, and perhaps most importantly, we were unable to screen for other, undiagnosed, sleep disorders such as obstructive sleep apnea, periodic limb movement disorders, or chronic insomnia. Lastly, our sample size was relatively small.

In conclusion, our pilot study demonstrates that women with gRLS have significantly lower folic acid levels and poorer sleep quality as compared to gestational-age matched women without gRLS. Despite the size limitations and inability to do correlations with other biomarkers of anemia, gestational complications, and sleep disorders, we suggest that supplementation with folic acid, in addition to prenatal vitamins, may be an important therapeutic intervention for gRLS. In the future we hope to build on this work with a larger comprehensive trial looking at many other variables mentioned above so we can make more definitive recommendations regarding folic acid supplementation in gRLS.

Acknowledgments

We would like to thank Tanya Simuni, M.D., and Phyllis Zee, M.D., Ph.D., for their help in making the trial possible.

References

1. Allen RP, Kushida CA, Atkinson MJ: Factor analysis of the International Restless Legs Syndrome Study Group's scale for restless legs severity. Sleep Med 2003;4:133-135
2. Manconi M, Govoni V, De Vito A, et al: Restless legs syndrome and pregnancy. Neurology 2004;63:1065-1069
3. Alves DA, Carvalho LB, Morais JF, et al: Restless legs syndrome during pregnancy in Brazilian women. Sleep Med 2010;11:1049-1054
4. Hubner A, Krafft A, Gadient S, et al: Characteristics and determinants of restless legs syndrome in pregnancy: A prospective study. Neurology 2013;80:738-742
5. Neau JP, Porcheron A, Mathis S, et al: Restless legs syndrome and pregnancy: A questionnaire study in the Poitiers District, France. Eur Neurol 2010;64:268-274
6. 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
7. Neyala A, Benbir Senelb G, Aslana R, et al: A prospective study of Willis-Ekbom disease/restless legs syndrome during and after pregnancy. Sleep Med 2015;16:1036-1040
8. Ohayon MM, O'Hara R, Vitiello MV: Epidemiology of restless legs syndrome: A synthesis of the literature. Sleep Med Rev 2012;16:283-295
9. Cesnik E, Casetta I, Turri M, et al: Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology 2010;75:2117-2120
10. Lee KA, Zaffke ME, Baratte-Beebe K: Restless legs syndrome and sleep disturbance during pregnancy: The role of folate and iron. J Womens Health Gend Based Med 2001;10:335-341
11. Pavord S, Myers B, Robinson S, et al: UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2012;156:588-600
12. Neau JP, Marion P, Mathis S, et al: Restless legs syndrome and pregnancy: Follow-up of pregnant women before and after delivery. Eur Neurol 2010;64:361-366
13. Budhiraja P, Budhiraja R, Goodwin JL, et al: Incidence of restless legs syndrome and its correlates. J Clin Sleep Med 2012;8:119-124
14. Kamsheh L, Ambrogi I, Rambally C, et al: Restless legs syndrome in combined hormonal contraception users. Acta Obstet Gynecol Scand 2013;92:727-729
15. Dzaja A, Wehrle R, Lancel M, et al: Elevated estradiol plasma levels in women with restless legs during pregnancy. Sleep 2009;32:169-174
16. Tunc T, Karadag YS, Dogulu F, et al: Predisposing factors of restless legs syndrome in pregnancy. Mov Disord 2007;22:627-631
17. Sun ER, Chen CA, Ho G, et al: Iron and the restless legs syndrome. Sleep 1998;21:371-377

18. Okun ML, Luther J, Prather AA, et al: Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. J Affect Disord 2010;130:378-384

19. Okun ML, Kiewra K, Luther JF, et al: Sleep disturbances in depressed and nondepressed pregnant women. Depress Anxiety 2011;28:676-685

20. Ko H, Shin J, Kim MY, et al: Sleep disturbances in Korean pregnant and postpartum women. J Psychosom Obstet Gynaecol 2012;33:85-90

21. Chang JJ, Pien GW, Duntley SP, et al: Sleep deprivation during pregnancy and maternal and fetal outcomes: Is there a relationship? Sleep Med Rev 2009;14:107-114

22. Ma S, Shang X, Guo Y, et al: Restless legs syndrome and hypertension in Chinese pregnant women. Neurolog Sci 2015;36:877-881

23. Picchietti DL, Hensley JG, Bainbridge JL, et al: Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev 2015;22:64-77

24. Civelek GM, Ciftkaya PO, Karatas M: Evaluation of restless legs syndrome in fibromyalgia syndrome: An analysis of quality of sleep and life. J Back Musculoskelet Rehabil 2014;27:537-544

25. Chavoshi F, Einollahi B, Sadeghniat Haghighi K, et al: Prevalence and sleep related disorders of restless leg syndrome in hemodialysis patients. Nephrourol Mon 2015;7:e24611

26. Baumgartel KL, Terhorst L, Conley YP, et al: Psychometric evaluation of the Epworth sleepiness scale in an obstetric population. Sleep Med 2013;14:116-121

27. Beaudreau SA, Spira AP, Stewart A, et al: Validation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older black and white women. Sleep Med 2012;13:36-42