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Original article

The effects of dietary folate and iron supplementation on restless legs and preeclampsia in pregnancy

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Summary. *Introduction:* RLS in pregnant women at the beginning of the condition increases the risk of reduced sleep quality, systemic arterial pressure increase, iron and folate deficiency anemia. The most common causes are thought to be physical changes, decreased sleep quality, or organic factors (decreasing folate and iron level). *Aim:* The aim of this study was to evaluate the role of RLS and its interaction with preeclampsia, anemia, folate deficiency, and low sleep quality. *Methods:* Our study was conducted between July 2018 and February 2019 in Trakya University Medical Faculty Hospital, Obstetrics Department. Pregnant women with symptoms related to RLS were investigated in terms of sleep quality and preeclampsia. An interview form was completed with the pregnant women during face-to-face interviews. Sociodemographic characteristics were questioned in this form. The IRLSGG criteria were used for RLS evaluations. The sleep quality of the participants was assessed using the PSQI. The iron status of pregnant women was questioned. Pregnant women were asked whether they received prophylactic iron medication. *Results:* Three hundred twenty-four volunteer pregnant women who presented to the obstetrics clinic of Trakya University Medical Faculty Hospital were included in the study. The mean age of the pregnant women in the study was 29.18±6.19 years. There was no statistically significant difference when we compared pregnant women with and without RLS when asked about their BMI in pre-gestational periods. The average use of iron medication of the women with RLS was 3 days or less per week. There was a significant difference between women with and without RLS regarding iron prophylaxis. The evaluation of the relationship between RLS, sleep quality, and preeclampsia in the pregnant women showed that RLS and PSQI levels had statistically significant differences according to trimesters. *Discussion:* Our study evaluated the frequency of RLS, the relationship between RLS and preeclampsia, and the relationship between RLS and sleep quality in pregnant women. RLS is more common in pregnant women who do not receive iron support. Low iron levels contribute to the development of RLS. Clinical and laboratory (hemoglobin) analysis revealed some differences between the groups. As the hemoglobin levels and iron supplementation decreased, the incidence of RLS symptoms was found to increase. For the treatment of RLS, non-pharmacologic treatments in pregnant women should be considered first; however, the use of iron medication is usually recommended. After the iron requirement is met, additional treatment planning should be made by investigating whether the RLS symptoms have regressed. Therefore, it was concluded that RLS was related to BMI and hemoglobin level differences. During pregnancy, the recommended dietary allowance (RDA) for folate is 600 μg/day of dietary folate equivalent. Natural folate with foods and folate supplementation since pregnancy may help to prevent fetal morbidity. The major sources of dietary folate are citrus fruits and juices, legumes, whole-wheat bread, and green leafy vegetables. To prevent fetal morbidities, women planning childbirth or pregnant should consume 400 μg per day of synthetic folic acid from natural foods (cereals and other grains), or supplement drugs. Pregnant women may need advice from a physician or a qualified dietetics professional to follow nutritional guidelines, especially for folate and iron. Pregnant women; must be provided a wide range of nutrition quality and evaluation. We suggest that more studies are needed to assess the relationship

between low quality of sleep, iron and folate supports in nutrition, RLS symptoms, and/or preeclampsia. *Conclusion:* Our study demonstrates the need to establish quality care and interventions for the protection of both maternal and fetal health due to poor sleep quality and RLS symptoms during pregnancy. Pregnant women should be presented with a variety of evidence-based patient care interventions. In the presence of RLS, signs of systemic arterial hypertension and iron supplementation in pregnant women should be examined carefully and if necessary, pregnancy interventions should be added.

Key words: nutritional knowledge, pregnant women, fetal well-being, dietary recommendation

Introduction

Restless leg syndrome (RLS) is a disorder characterized by an irresistible impulse to move the legs. In the literature, the prevalence of RLS in the population was found as 2-10%. RLS is twice as common in women as men. The risk of occurrence increases in pregnant women compared with the normal female population, increasing 2 to 3 times in pregnant women, affecting 15-25% of pregnant women (1, 2). The prevalence varied from 11% to 30% in studies performed in pregnant women from different societies (3-6). Early detection of severe RLS is very important to prevent maternal discomfort, poor sleep, and possible health risks.

The reason for the increased incidence of RLS during pregnancy is still not fully understood. RLS in pregnant women at the beginning of the condition increases the risk of reduced sleep quality, systemic arterial pressure increase, anxiety level increase, and iron deficiency anemia (2). In addition, symptoms develop with movement and lead to increased symptoms in the evening. Additional diagnostic criteria of RLS include symptoms presenting when people are not moving, and a progressive urge to move the legs.

Pregnancy is reported as a risk factor in the initiation and progression of RLS symptoms. The majority of affected pregnant women have not previously experienced RLS and almost all patients with pre-existing RLS had worsened symptoms during pregnancy (2, 7). Causes of RLS in pregnancy are various. According to the literature, the most common causes are thought to be hormonal factors (estrogen, progesterone), psychomotor factors, physical changes, decreased sleep quality, anxiety or organic factors (decreasing folate and iron level) (8-10). In most pregnant women, RLS often occurs in the last trimester. The presence of RLS in pregnancy is often a risk factor for chronic RLS that will develop later. Symptoms often disappear in the 6 to 18 weeks after birth. Early detection of severe RLS is important in pregnant women. Early intervention is very important to prevent discomfort, poor sleep quality, and possible health risks in pregnant women. RLS can significantly affect maternal health; it is a common disorder that can lead to negative consequences in the short and long term. RLS in pregnancy causes negative fetal and maternal effects (8, 11).

Many studies in the literature evaluated sleep quality using the Pittsburgh Sleep Quality Index (PSQI) in pregnant women (10, 12). 14-27% of pregnant women have low sleep quality. The decrease in sleep quality as measured using the PSQI during pregnancy is associated with a number of negative outcomes related to maternal health and fetal well-being. A reduction of sleep quality in pregnant women may increase the likelihood of premature birth. Low sleep quality leads to increased levels of systemic inflammation and is associated with shorter pregnancy duration. Pregnant women who have low sleep quality are more likely to have a caeserean section. Poor sleep quality is a potential risk factor for depression both before and after the birth (13-16).

Hypertension in pregnancy and preeclampsia are the leading causes of maternal and fetal mortality and morbidity worldwide. With preeclampsia there is an increased incidence of placental abruption, fetal growth restriction, and preterm births. Due to its potential severity and frequent occurrence, early diagnosis, knowledge of related parameters, and appropriate management are essential (11, 17).

The aim of this study was to evaluate the role of

RLS and its interaction with preeclampsia, anemia, folate deficiency, and low sleep quality.

Methods

Our study was conducted between July 2018 and February 2019 in Trakya University Medical Faculty Hospital, Obstetrics and Gynecology Department. Pregnant women with symptoms related to RLS were investigated in terms of sleep quality and preeclampsia. The recommendations of the International Restless Legs Study Group (IRLSSG) were considered in the performance of our study (11, 17).

The participants were informed about the study, after which each provided written informed consent. An interview form was completed with the pregnant women during face-to-face interviews. Sociodemographic characteristics (age, height, body weight, education, number of previous pregnancies) were questioned in this form. The IRLSGG criteria were used for RLS evaluations (11). Pregnancy hypertension was defined according to the American College of Obstetricians and Gynecologists (ACOG) criteria (15, 16). The sleep quality of the participants was assessed using the PSQI. The validity and reliability of the PSQI as a sleep assessment tool has been proven in the literature (13, 14).

The International Restless Legs Syndrome (IRLS) scale was evaluated using the four main criteria developed by the IRLSSG. The IRLS provides a good indication of the current situation in individuals, and is useful for clinical practice. The IRLS is a reliable, 10-question rating tool that has been adopted in the international literature (11, 18). The IRLS scale comprises questions about the typical symptoms of RLS; the scale is graded 0-4 on each of the typical symptoms of RLS and consists of 10 questions. In the evaluation, 0-10 points are mild, 11-20 points are in the middle, 21-30 points are serious, and 31-40 points indicate severe RLS. The literature on RLS in pregnancy supports the use of the IRLS scale in pregnant women (19-21). The IRLSGG criteria can be used during pregnancy. The most important factor suggesting the appropriateness of the of IRLSGG criteria in pregnancy is that the symptoms of RLS associated with pregnancy and idiopathic RLS are similar. A familial predisposition and the similarity of symptoms are common features of both. In addition, pregnancy is considered as an aggravating factor in families predisposed to RLS (22).

Patients with symptoms of leg cramps, venous stasis, leg edema, and stress were excluded from the study due to the risk of being confused with symptoms of RLS. Women with pre-pregnancy RLS symptoms or those with chronic hypertension were not included in the study.

To evaluate sleep quality, the PSQI was used, which is a commonly used instrument to evaluate sleep. It includes 19 questions and 7 clinical themes. It includes subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime sleepiness (12, 23). A PSQI total score equal to or greater than 5 shows poor sleep quality with 90% sensitivity and 67% specificity. The PSQI can be used safely in the examination of sleep quality in pregnant women and mothers in the first six months after birth (14, 24).

The iron status of pregnant women was questioned. Pregnant women were asked whether they received prophylactic iron medication (at least one dose per day at least 5 times in a week).

After evaluation the pregnant women in our study, if we detected a risk for RLS we reported this to the clinic's physicians and nurses. Pregnant women with symptoms of RLS were contacted during the postpartum period to determine whether there was regression in RLS findings.

The study was approved by the Ethics Committee of Scientific Research of Trakya University Faculty of Medicine (Decision No: 2018-343-21). Official permission was obtained from the management of Trakya University Medical Faculty. Written informed consents were obtained from the participants of this study.

All statistical analyses were performed using the SPSS 21.0 package program. Normal distribution of the data was tested using the Shapiro-Wilk test. Bivariate group comparisons were performed using Student's t-test and the Mann-Whitney U test. The data are summarized with appropriate descriptive statistics. Mean and standard deviation were evaluated for numerical variables, and frequency and percentage were evaluated for categorical variables. One-way analysis of variance

(ANOVA) was used for the comparison of multiple groups. The Chi-square test was used for the associations between categorical variables. Level of significance for all statistical analyses was accepted as 5%.

Results

Three hundred twenty-four volunteer pregnant women who presented to the obstetrics clinic of Trakya University Medical Faculty Hospital were included in the study.

The sociodemographic and clinical characteristics in pregnant women and presence of preeclampsia of mothers with and without RLS symptoms were compared.

The mean age of the pregnant women in the study was 29.18±6.19 (range, 18-45) years. The mean age of patients with no RLS symptoms was 28±6.27 years. The mean age of patients with RLS symptoms was 30.04±5.90 years (Table 1). The body mass index (BMI) of pregnant women with RLS was 33.6 kg/m^2. The mean BMI of pregnant women with no RLS symptoms was 30.90 kg/m^2 *(p= 0.011)*. There was no statistically significant difference between the two groups in terms of BMIs in pregnant women with and without RLS. The mean Hgb (hemoglobin) of the pregnant women with RLS was 11.21 g/dL (±1.75), and the average use of iron medication was 3 days or less per week. The mean values of those without RLS symptoms were as follows: Hgb 11.71 g/dL (±1.55); the use of iron prophylaxis was 4 days or more per week. There was a significant difference between women with and without RLS regarding hemoglobin levels, but it was not clinically important. Low hemoglobin was more frequent in patients with RLS findings and iron prophylaxis was less frequent (Table 2).

Among the patients with RLS and without RLS symptoms, there was a significant difference in the level of alanine aminotransferase (ALT) *(p= 0.002)* (Table 3). Women with RLS (n=90) were compared with pregnant women without RLS (n=234) and there was no difference between the groups in terms of PSQI, aspartate transaminase (AST), and number of child births. However, pregnant women with RLS generally scored higher on the PSQI than women without RLS.

The evaluation of the relationship between RLS, sleep quality, and preeclampsia in the pregnant women showed that RLS and PSQI levels had statistically significant differences according to trimesters *(p=0.019 and p<0.001)* (Table 4). As the trimesters of pregnancy progressed, the incidence of RLS symptoms increased and sleep quality decreased. There were statistical differences between women with preeclampsia and those with RLS. Symptoms of preeclampsia and RLS increased as the trimesters of the participants advanced. Patients with RLS symptoms had more frequent preeclampsia findings (Table 5).

It was observed that 27.77% of the pregnant women met the RLS diagnostic criteria. The mean IRLSSG score of the pregnant women in our study was 15.59. RLS symptoms in previous pregnancies were examined and 31% of all the pregnant women reported having RLS previously.

Discussion

Our study evaluated the frequency of RLS, the relationship between RLS, preeclampsia and sleep quality in pregnant women. In this respect, it is among the first of its kind in the literature. RLS is a frequently encountered disorder in pregnant women but it remains unrecognized and undiagnosed.

Our rate of RLS in pregnancy was 27.7%, which is consistent with data in the literature, citing 11-30%. In recent studies, the frequency of RLS in the last trimester of pregnancy has been shown to increase to 36% (4, 12, 25). It was determined that the severity and frequency of RLS increased in the last months of pregnancy. Among the pregnant women in our study, the difference between the second and third trimesters was significant in terms of RLS *(p= 0.019)*.

RLS is more common in pregnant women who do not receive iron support. Low iron levels contribute to the development of RLS. However, there may be some differences. RLS may occur in patients with preeclampsia without low iron levels. The mean serum ferritin concentration and hemoglobin levels may be higher in patients with preeclampsia than in healthy pregnant women (26, 27). Clinical and laboratory (hemoglobin) analysis revealed some differences between the groups.

Table 1. RLS and some differences in pregnant women

Mean (SD)	Parameters	Restless Legs Syndrome (-)	Restless Legs Syndrome (+)	*p*
	Age	28.00 (6.27)	30.04 (5.90)	*0.123**
	BMI[1]	30.90 (7.12)	33.06 (5.51)	0.011*
	Hgb[2]	11.21 (1.75)	11.71 (1.55)	0.013*

BMI[1]: Body Mass Index; Hgb[2]: Hemoglobin; *statistical significance

Table 2. Comparison of pregnant women with and without restless leg symptoms

Paramaters	Range	Restless Legs Syndrome (-)	Restless Legs Syndrome (+)	p
Folate intake	≥ 400 mcg/ day	193 (82.5%)	65 (72.2%)	*0.040**
	< 400 mcg/ day	41 (17.5%)	25 (27.8%)	
Leukocyte	high	192 (82.1%)	83 (92.2%)	*0.022**
	normal	42 (17.9%)	7 (7.8%)	
Preeclampsia	Available	220 (94%)	83 (92.2%)	*<0.001**
	No	14 (6%)	7 (7.8%)	
Taking iron prophylaxis	insufficient	77 (32.9%)	45 (50%)	*0.004**
	Sufficient	157 (67.1%)	45 (50%)	

*statistical significance

Table 3. Some differences according to the RLS symptoms in terms of PSQI, AST, and number of child births.

RLS symptoms	Percentiles	ALT	AST	Number of child births	PSQI
RLS (-) (n= 234)					
	25	8.75	16.00	1.00	3.00
	50	12.00	20.00	2.00	5.00
	75	15.00	24.00	3.00	10.00
RLS (+) (n= 90)					
	25	9.00	15.00	1.00	3.00
	50	14.00	20.00	2.00	8.00
	75	36.25	30.00	3.00	13.00
P		*0.002**	*0.513*	*0.404*	*0.174*

*statistical significance; ALT: Alanine aminotransferase, AST: Aspartate transaminase, RLS: Restless legs syndrome, PSQI: Pittsburgh Sleep Quality Index

Table 4. Evaluation of the relationship between restless leg syndrome, sleep quality and preeclampsia in pregnant women in our study, according to gestational weeks

Parameters	1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)	Total N (%)	*P*
Restless legs syndrome (RLS)					*0.019**
Present	2 (2.2%)	7 (8.8%)	81 (90%)	90 (100%)	
Absent	23 (9.8%)	31 (13.2%)	180 (76.9%)	234 (100%)	
Sleep quality disorder (PUKI)					*<0.001**
>6 (unwell)	2 (8%)	23 (60.5%)	148 (56.7%)	173 (53.3%)	
≤5 (good)	23 (92%)	15 (39.5%)	113 (43.3%)	151 (46.6%)	
Total	25 (100%)	38 (100%)	261 (100%)	324 (100%)	

*statistical significance; RLS: Restless legs syndrome, PSQI: Pittsburgh Sleep Quality Index

Table 5. Preeclampsia and restless leg syndrome evaluation in the participants

Parameters		1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)	Total N (%)	*P*
Pre-eclampsia (-)	Restless leg syndrome (-)	23 (92%)	30 (78.9%)	167 (64%)	220	*0.067*
	Restless leg syndrome (+)	2 (8%)	6 (15.8%)	70 (26.8%)	78	
Pre-eclampsia (+)	Restless leg syndrome (-)	0	1	13	14	
	Restless leg syndrome (+)	0	2 (53.%)	24 (20.9%)	26	
	Total	25 (100%)	38 (100%)	261 (100%)	324 (100%)	

As the hemoglobin levels and iron supplementation decreased, the incidence of RLS symptoms was found to increase *(p=0.013; p= 0.004)*. Iron deficiency in pregnant women should be eliminated and re-evaluated. For the treatment of RLS, non-pharmacologic treatments in pregnant women should be considered first; however, the use of iron medication is usually recommended. After the iron requirement is met, additional treatment planning should be made by investigating whether the RLS symptoms have regressed. Therefore, it was concluded that RLS was related to BMI and hemoglobin level differences. Anemia and iron deficiency increase the tendency to sleep in pregnant women. However, more extensive studies are needed.

During pregnancy, the recommended dietary allowance (RDA) for folate is 600 μg/day of dietary folate equivalents (28, 29). Natural folate with foods and folate supplementation since pregnancy may help to prevent fetal morbidity. The major sources of dietary folate are citrus fruits and juices, legumes, whole-wheat bread, and green leafy vegetables. To prevent fetal morbidities, women planning childbirth or pregnant women should consume 400 μg per day of synthetic folic acid from natural foods (cereals and other grains), or supplement drugs. Research indicates that abnormal folate metabolism and malnutrition may also play a role in birth defects (30).

RLS is usually associated with insomnia and sometimes excessive daytime sleepiness (31). It was determined that the frequency of RLS increased in pregnant women with poor sleep quality. In some (53.3%) patients with RLS, sleep quality was low, as measured using the PSQI. Also, according to the trimesters, pregnant women with RLS expect more sleep problems. We found worse sleep quality in the third trimester than in the second trimester. The mean PSQI score worsened as the gestational week progressed *(P<0.001)*.

However, RLS symptoms and PSQI levels, independent from trimester, was not found statically significant. The median PSQI score was 8 (3-13) in RLS (+) pregnant women. The median PSQI score was 5 (range, 3-10) in RLS (-) pregnant women *(p=0.174)*.

The discussion regarding the PSQI cut-off value in pregnant women continues in the literature. In a recent meta-analysis, the PSQI score in pregnancy was 6.07, and 45.7% of pregnant women were reported to have a PSQI score of 5 or more, expressing poor sleep quality. The results of this study show that the average PSQI score of the pregnant women increased by 1.68 points from the second trimester to the third trimester (12, 32). In our study, the findings showed that low sleep quality was common in pregnant women. In order to preserve maternal and fetal health, it is recommended to give importance to sleep quality and to add to health services.

The findings of our study show that future research should determine whether higher global cut-off scores are more appropriate in pregnancy. Our study of the PSQI in pregnant women shows the necessity of providing different cut-off values for variables such as gestational age, the sociocultural characteristics of pregnant women, and the presence of comorbid RLS symptoms.

Although the data were limited in our study, there was no specific sociodemographic differences between the number of child births and patients with and without RLS symptoms *(p= 0.404)*.

When the literature is examined, it is shown that preeclampsia has increased in the same direction with RLS in various countries (30, 33, 34). There are different hypotheses that the incidence of preeclampsia development tends to increase with RLS. One of the most commonly held is that hypertension and increased sympathetic activation causes disturbances in blood pressure regulation, which converge in RLS and preeclampsia. Increased systemic arterial pressure is

seen in both RLS and preeclampsia (16). Our study shows that there is a positive relationship between RLS and preeclampsia during pregnancy. Although not statistically significant, it presents evidence that there is an increasing trend in preeclampsia and RLS with increased trimesters *(p= 0.067)*. More pregnant women with RLS had more preeclampsia than non-RLS pregnant women.

Factors that contribute to the reduction of sleep quality during pregnancy should be evaluated in pregnant women, especially when they attend healthcare facilities for routine checks.

Pregnant women may need advice from a physician or a qualified dietetics professional to follow nutritional guidelines, especially for folate and iron. Pregnant women; must be provided a wide range of nutrition quality and evaluation.

We suggest that more studies are needed to assess the relationship between low quality of sleep, iron and folate supports in nutrition, RLS symptoms, and/or preeclampsia. Care should be taken with regard to the development of preeclampsia in pregnant women with RLS symptoms.

We recommend further research on how to distinguish pregnant women in need of care in order to preserve maternal and fetal health during pregnancy.

Limitations

Our study had some limitations. Pregnant women who had RLS symptoms were referred to the clinical responsible health care providers. However, their treatment process could not be followed because it was not initiated by the responsible clinicians; without different consultations for women's symptoms.

Additional imaging and laboratory evaluations for sleep disturbances could not be performed because the clinician was not authorized.

Iron prophylaxis was evaluated, but serum iron, folate, ferritin laboratory values were not because the women could not be evaluated for them in the clinic by their physicians. The diagnosis of preeclampsia was made according to diagnostic criteria; however, no detailed data were available regarding the medical treatments used for preeclampsia.

Conclusion

Our study demonstrates the need to establish quality care and interventions for the protection of both maternal and fetal health due to poor sleep quality and RLS symptoms during pregnancy. RLS findings and assessment of sleep quality should be included in the follow-up evaluations of pregnant women. Pregnant women should be presented with a variety of evidence-based patient care interventions.

In the presence of RLS, signs of systemic arterial hypertension and iron supplementation in pregnant women should be examined carefully and if necessary, pregnancy interventions should be added. Care should be taken in terms of preeclampsia in the presence of RLS symptoms.

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