ORIGINAL RESEARCH

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Examining the Effect of Chronotype Differences on Sleep Quality and Pregnancy Symptoms in Pregnant Women: A Parallel Clinical Trial

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ABSTRACT Objective: The study aimed to examine the effect of chronotype differences on sleep quality and pregnancy symptoms in pregnant women. **Material and Methods:** Eighty-five pregnant women in the second trimester were included in the study. The chronotypes of pregnant women were determined using the Morningness-Eveningness Questionnaire (MEQ). Then, Oral Glucose Tolerance tests (OGTT) were performed on the participants between 24-28 weeks. Also, pregnant women's nausea and vomiting conditions were evaluated with the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) and sleep quality with the Pittsburgh Sleep Quality Index (PSQI). **Results:** A significant difference was found when OGTT-fasting glucose and 2-hour glucose values were compared between groups ($p<0.05$). When the differences between the morningness chronotype (MC) and intermediate chronotype (IC) groups were compared, there was no significant difference between the two groups ($p>0.017$). When the MC group was compared with the eveningness chronotype (EC) group, OGTT fasting glucose values were statistically lower ($p<0.017$). Also, the differences in PUQE scores of the MC group were significantly lower than the IC and EC groups ($p<0.017$). When PSQI values were compared between the groups, a statistically significant difference was found ($p<0.05$). In the PSQI post-hoc comparison, the MC group was statistically significantly lower in both the IC and EC groups ($p<0.017$). It was also seen that the IC group was statistically significantly lower than the EC group ($p<0.017$). **Conclusion:** The present results showed that pregnant women with evening chronotypes had significantly worse sleep quality. Also, chronotype differences are a potential connection affecting sleep quality and pregnancy symptoms.

Keywords: Circadian rhythm; sleep quality; pregnancy; pregnancy outcome

The circadian rhythm affects reproduction in humans. Daily cycles in sleep/wake, metabolism, hormone production, locomotor activity, and many other activities are produced by circadian clocks in the brain and tissues.[1] The circadian rhythm also determines the chronotype. The portion of the day that is physically and mentally active is influenced by chronotype. Based on the circadian rhythm, there are three primary chronotypes: morning, intermediate, and evening.[2] A person with an early chronotype rises early and has an early sleep midpoint. A person with a late chronotype rises late and has a late sleep midpoint.[3] Morning-evening preference influences mood, eating habits, body temperature, and other biological functions. The light-dark cycle and other regular environmental cues cause these clocks to synchronize, or entrain. For instance, a healthy circadian rhythm is necessary for a typical pregnancy and changes in the circadian system may potentially raise the chance of unfavorable pregnancy outcomes in people.[4] One circadian behavioral expression that can significantly impact pregnancy outcomes is the sleep-wake cycle.[5] However, not much research has been conducted into the role it plays during pregnancy.

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Pregnancy is cyclical and is associated with a fluctuating expression of the circadian rhythm.[6] Therefore, during gestation, a functioning circadian system is required.[7] Pregnancy success in mice is significantly decreased when endogenous circadian timekeeping is disrupted.[8] Changes in the circadian system may also raise the chance of unfavorable pregnancy outcomes in people.[9] One circadian behavioral expression that can have a significant impact on pregnancy outcomes is the sleep-wake cycle.[10]

There are not many studies on the relationship between chronotype differences and pregnancy. A study investigated the relationship between chronotype and weight gain during early pregnancy. It was found that pregnancies with the evening type of chronotype were more likely to gain weight during pregnancy.[11] It is also thought that pregnancies with the evening type have an increased risk of adverse pregnancy outcomes, including pre-eclampsia, premature birth, gestational diabetes, cesarean delivery, and fetal growth restriction. A disturbance of the circadian rhythm is linked to a metabolic imbalance.[12] An ongoing problem affecting 7.5% to 27.0% of pregnancies worldwide is a glucose metabolism disorder. Pregnancy-related hyperglycemia increases the likelihood of several negative consequences, including macrosomia (infant size abnormal for gestational age) and pre-eclampsia/hypertensive disorders in the mother. Preterm birth is also associated with disturbances in glucose metabolism.[13]

Maternal adaption in pregnancy induces changes in circadian rhythms with marked alterations in the expression of circadian clock genes and this is crucial since irregular sleep patterns and low sleep quality during pregnancy have been connected to several unfavorable obstetrical outcomes, such as gestational diabetes.[14,15] The first and second trimester of pregnancy is characterized by an earlier sleep period start time, longer sleep duration, and poorer sleep quality than pre-pregnancy.[16] Also, pregnancy is deeply influenced by the circadian rhythm and the misalignment of the maternal rhythm can lead to disturbances in the temporal organization of physiological and metabolic functions. Sleep-related variables, e.g., chronotype, may be associated with maternal and fetal outcomes in gestational diabetes mellitus (GDM) patients.[17] There is established evidence that pregnant night-shift workers are at risk of miscarriage, prematurity, low birth weight, and hypertensive disorders.[18] Another complication of pregnancy is nausea and vomiting. Referred to as morning sickness, emesis gravidarum, or pregnancy sickness, this condition, varying in severity, is a complaint seen in 50-70% of pregnant women.[19] We consider that changes in the sleep-wake cycle may increase the risk of gestational diabetes, sleep quality and pregnancy adverse symptoms. This study aimed to examine the effect of chronotype differences on sleep quality and pregnancy symptoms in pregnant women.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This study is a single-blind (participants), parallel clinical trial. It was performed in line with the principles of the Declaration of Helsinki. The Non-interventional Ethics Committee granted approval at Medipol University (date: October 13, 2022, no: 859). The study protocol was registered at ClinicalTrials.gov (NCT06413784). Informed consent was obtained from all individual participants included in the study. Participants were women who consulted an obstetrics and gynecology specialist at Çamlıca Medipol Hospital. The following were the study's inclusion requirements: being between the ages of 18-40, having a singleton pregnancy, being between 24-28 weeks of gestation, and not having any known chronic disease such as cardiovascular diseases, diabetes, thyroid disorders, and sleep disorders that could affect pregnancy and sleep quality. Exclusion criteria are working night shifts or rotating shifts, having a high-risk pregnancy, and having a neurological or orthopedic disease.

The study included 85 individuals who met the inclusion criteria out of 89 participants who were screened. Two participants were excluded due to high-risk pregnancy, and two declined to participate in the program. Therefore, the study was conducted with a total of 80 women.

The chronotypes of pregnant women who presented in the second trimester were determined using the Morningness-Eveningness Questionnaire (MEQ).

Then, Oral Glucose Tolerance tests were performed on the participants between 24 and 28 weeks.

DATA COLLECTION

The physical therapist conducted personal interviews to collect data. Information on clinical, obstetric, and sociodemographic factors was gathered through a structured questionnaire. Patient interviews yielded information about maternal age, weight gain, and number of pregnancies. Additionally, they were questioned about their smoking status, alcohol consumption, caffeine consumption, current/history of diabetes/gestational diabetes, and current/history of hypertension/hypertensive disorder of pregnancy. Also, pregnant women's chronotypes, nausea and vomiting conditions, fasting glucose and HbA1c values, and sleep quality were evaluated. Participants were assessed once during the second trimester between weeks 24 and 28, and no further follow-up was conducted.

ASSESSMENT OF CHRONOTYPE

The MEQ was used to measure the preference for a certain chronotype. This validated questionnaire evaluates individual differences in the degree to which respondents are aware and active at different times of the day. It has 19 items on sleep patterns and exhaustion. The responses to the scale items indicate preferences for waking and sleeping hours as well as the subjective "peak" times when respondents feel most refreshed. People were categorized as morningness chronotype (MC) (>65), intermediate chronotype (IC) (53-64), or eveningness chronotype (EC) (score of <52). The reliability of MEQ was 0.77 and the test alpha was equal to 0.78.[20]

THE PREGNANCY-UNIQUE QUANTIFICATION OF EMESIS AND NAUSEA

The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) is a scoring system for nausea and vomiting during pregnancy, which consists of three items. The PUQE was developed for pregnant women and focuses on three symptoms: nausea, vomiting, and retching. The original PUQE entailed rating the daily number of vomiting episodes, the length of nausea in hours per day, and the number of retching episodes per 12 hours. Its validation was confirmed by Koren et al. A total score of 3-6 is considered mild nausea and vomiting, a total score of 7-12 is considered moderate nausea and vomiting, and a total score of 13-15 is considered severe nausea and vomiting.[21] The PUQE questionnaire was administered during the study visit, which took place between 24 and 28 weeks of gestation.

ORAL GLUCOSE TOLERANCE TESTING

Pregnant women undergo a 75 g Oral Glucose Tolerance Testing (OGTT) test between 24 and 28 weeks of gestation as part of a universal screening American Diabetes Association protocol.[22] A plasma fasting blood glucose >126 mg/dL in a pregnant woman is considered an overt value >92 mg/dL a one-hour plasma glucose value>180 mg/dL or a two-hour plasma glucose value >153 mg/dL.

PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index (PSQI) was developed in 1989 by Buysse et al. to evaluate patients' sleep quality over the past month in clinical trials.[23] Ağargün et al. established the scale's validity and reliability in Türkiye in 1996.[24] There are 24 questions in all, 18 of which are used to determine the score. Subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disruptions, usage of sleeping pills, and dysfunction throughout the day are its seven constituent parts. The PSQI score is determined by assigning a point value between 0 and 3. A cumulative score of more than five indicates that the sleep quality was inadequate. The score goes from 0 to 21. The PSQI was administered during the same assessment period as the PUQE, between weeks 24-28 of pregnancy.

STATISTICAL ANALYSES

A sample size and power calculation determined that 42 patients had sufficient power (power of 0.80, α of 0.05, and β=0.20) using G*Power software (latest ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The power calculation was based on changes in the PSQI.[25] SPSS 25.0 for Windows (IBM, USA) was used for statistical analysis. The normal distribution of the variables was tested by the Kolmogorov-Smirnov test. Descriptive data are shown with number (n) and percentage (%) tables. One-way analysis of variance analysis was used

for normally distributed data, and statistical differences were evaluated with Bonferroni post hoc comparisons to identify differences between chronotype groups. Kruskal-Wallis analysis was performed if the values were not normally distributed.

RESULTS

A total of 80 pregnant women who met the inclusion criteria were enrolled for the study, of which 38 women were MC, 14 women were IC, and 28 women were EC.

The sociodemographic and clinical characteristics of the participants divided according to chronotypes were given in Table 1. The mean maternal ages of women in MC, IC, and EC groups were 32.94±3.17, 30.28±4.57, and 34.78±6.54 years, respectively. The mean PUQE scores of women in the MC, IC, and EC groups were 6.84±2.11, 11.71±3.09, and 12.14±2.71, respectively. There was a significant difference in the mean PUQE scores of the women between groups ($p<0.05$). The differences in PUQE scores of the MC group were significantly lower than the IC and EC groups ($p<0.017$). There was no statistically significant difference in the PUQE results of the IC and EC groups ($p>0.017$).

A significant difference was found when OGTT-fasting glucose values were compared between groups ($p<0.05$). When the differences between the MC and IC groups were compared, there was no significant difference between the two groups ($p>0.017$). However, when the MC group was compared with the EC group, OGTT fasting glucose values were found to be statistically lower ($p<0.017$). Also, there was a significant difference in the mean OGTT- 2 hrs glucose level between groups ($p<0.001$). The differences in OGTT- 2 hrs glucose level of the MC group were significantly lower than the IC and EC groups ($p<0.017$). There was no statistically significant difference in the OGTT- 2 hrs glucose level of the IC and EC groups ($p>0.017$) (Table 2).

When PSQI values were compared between the groups, a statistically significant difference was found

TABLE 1: Sociodemographic and clinical characteristics of the participants.

Variables	MC (n=38)	IC (n=14)	EC (n=28)	p value
Maternal age (years)	32.94±3.17	30.28±4.57	34.78±6.54	NS
Gestational age (years)	18.78±3.15	20.00±3.69	19.92±3.17	NS
Number of pregnancy n (%)				
First	20 (52.6)	6 (42.9)	14 (50)	
Second	16 (42.1)	6 (42.99	14 (50)	NS
Third	2 (5.3)	2 (14.3)	-	
Education level n (%)				
High school	14 (36.8)	8 (57.1)	14 (50)	
University	12 (31.6)	2 (14.3)	10 (35.7)	NS
Master degree	10 (26.3)	4 (28.6)	4 (14.3)	
Employment status n (%)				
Full time	18 (47.4)	8 (57.1)	18 (64.3)	
Part time	-	6 (42.9)	-	NS
Unemployment	20 (52.6)	-	10 (35.7)	
Weight gain (kg) n (%)				
7-10 kg	6 (15.8)	4 (28.6)	4 (14.3)	
10-15 kg	26 (68.4)	2 (14.3)	10 (35.7)	NS
15-18 kg	6 (15.8)	8 (57.1)	14 (50.0)	
Smoking n (%)				
Yes	10 (26.3)	6 (42.9)	-	
No	28 (73.7)	8 (57.1)	28 (100)	NS

MC: Morning chronotype; IC: Intermediate chronotype; EC: Evening chronotype; NS: $p>0.05$ is statistically not significant.

TABLE 2: Comparison of the outcomes measures according to chronotypes.

Outcome measures	MC (n=38)	IC (n=14))	EC (n=28)	p value	post-hoc
PUQE	6.84±2.11	11.71±3.09	12.14±2.71	p<0.001	MC<IC*, MC<EC*, IC-EC (NS)
OGTT Fasting glucose (mg/dL)	91.31±3.33	97.42±3.55	108.07±6.97	p<0.001	MC-IC (NS), MC<EC*, IC<EC
OGTT 2 hrs glucose (mg/dL)	143.05±6.74	156.42±2.43	160.35±6.51	p<0.001	MC<IC*, MC<EC*, IC-EC (NS)
PSQI	5.94±1.47	9.14±2.91	13.42±1.82	p<0.001	MC<IC*, MC<EC*, IC<EC*

*Statistically significant (p<0.017); MC: Morningness chronotype; IC: Intermediate chronotype; EC: Eveningness chronotype; PUQE: Pregnancy-Unique Quantification of Emesis and Nausea; OGTT: Oral Glucose Tolerance Testing; PSQI: Pittsburgh Sleep Quality Index; NS: Not significant (p>0.017).

(p<0.05). In the PSQI post-hoc comparison, the MC group was statistically significantly lower in both the IC and EC groups (p<0.017). It was also seen that the IC group was statistically significantly lower than the EC group (p<0.017) (Table 2).

DISCUSSION

Our study investigated the effects of chronotype differences on pregnancy complications. Regarding the PUQE scores, OGTT results, and sleep quality, the scores were significantly different between the groups. Pregnant women in the evening chronotype group reported significantly worse sleep quality. Women with morning chronotype had significantly lower PUQE scores. The differences in OGTT-fasting and 2-hour glucose levels of the MC group were significantly lower than the IC and EC groups.

A recent systematic review and meta-analysis of research applying the MEQ to determine chronotypes revealed gender differences in the distribution of chronotypes, with males being more likely to be evening-oriented and women more likely to be morning-types.[26] However, research results are frequently inconsistent. For instance, evening types have been estimated to comprise 11-13% of adult persons in a major population-based study conducted in Finland, with eveningness being slightly more common in females than in males. Also, one study demonstrated that pregnant women have earlier sleep period start times in the first and second trimesters. Similarly, women's sleep onset developed earlier in the first and second trimesters (gestational weeks 4-13 and 14-27) than in pregnancy, and the third trimester (weeks 28 till delivery).[27] In our study, 47.5% of the pregnant women were in the morning chronotype, consistent with the literature.

Fluctuations in reproductive hormones, specifically in estrogen and/or progesterone levels, also appear to have an impact on changes in chronotype and activity levels during pregnancy in both women and female mice as determined by wrist actigraphy and running wheel activity, respectively.[28] But chronotype may not be the only reproductive function influenced by hormones; on the other hand, chronotype also seems to influence women's reproductive functions, including the duration of their menstrual cycle and their potential of becoming pregnant. The circadian tendency for evening hours is linked to numerous health issues and unhealthful lifestyle choices.[29] Compared to morning types, evening types during pregnancy experience more sleep problems. Additionally, compared to other chronotypes, evening types may be more vulnerable to adverse pregnancy outcomes, particularly decreased sleep quality.[25] It was observed that the sleep quality of evening-type pregnant women was worse in this study. We consider that it may be because pregnant women with evening chronotypes have difficulty falling asleep due to going to bed late.

A recent study revealed that evening chronotypes are more at risk of gestational diabetes, unstable marital status, depression, and insomnia both before and during pregnancy, and are more prone to adverse pregnancy outcomes such as pre-eclampsia.[30] Studies have demonstrated a correlation between short sleep duration and/or poor quality sleep and an exaggerated inflammatory response in pregnancy. This response is thought to be responsible for the pathogenesis of unfavorable pregnancy outcomes, including intrauterine growth retardation, preterm birth, and pre-eclampsia, by inhibiting trophoblast invasion, and gestational diabetes.[30,31] Thus, poor sleep quality may be considered a physiological contributor to pre-

eclampsia. Pre-eclampsia is a common complication of GDM pregnancy. One study's results show that pregnant women with evening preference are more likely to develop GDM and pre-eclampsia. Furthermore, the evening chronotype has also been related to sleep problems and unhealthy life habits during pregnancy.[30] Another study showed that late-chronotype pregnant women are about 2.5 times more likely to develop gestational diabetes in their second trimester than those who have an earlier chronotype.[31] Importantly, in our analysis, when OGTT tests were performed in the second trimester of the pregnant women we included in the study in the first trimester, it was concluded that pregnant women with the morning chronotype were less likely to have GDM compared to women with IC and EC. We believe that circadian rhythm disorders in pregnant women increase the risk of gestational diabetes. That's because the body's circadian clock is essential for controlling hormone release, metabolism, sleep/wake cycles, and a host of other functions.[29]

Pregnant women have been reported to have nausea in the morning, which makes them eat more at night and less throughout the day.[32] This was corroborated by a Brazilian study that followed pregnant women from 4 to 37 weeks of gestation and found that night eaters were more likely than day eaters to neglect breakfast during pregnancy.[33] Another study with pregnant Norwegian women at 17-22 weeks gestation found a positive correlation between nausea and a predisposition toward an evening meal schedule.[34] In our study, it was observed that nausea-vomiting scores in morning-type pregnant women were less than in evening-type and intermediate-type pregnant women. We consider that this is because pregnant women with evening type have more night snacking. After all, they sleep later. Indeed, chronotypes and night eating habits have been related; evening-type individuals are more prone to eating at night. High-calorie intake before bedtime and frequent nighttime meals have been linked to evening preferences.[35]

STRENGTH AND LIMITATIONS

To the authors' knowledge, it is one of the few studies investigating chronotype differences in pregnancy symptoms and sleep quality. However, the present study has several limitations. Women who worked night shifts were not included in our study. Another limitation of this study pertains to the evaluation of sleep, which was conducted by questionnaires rather than objective sleep metrics like actigraphy or polysomnography.

CONCLUSION

The present results showed that pregnant women with evening chronotypes had significantly worse sleep quality. PUQE scores of women with morning chronotype were significantly lower. Differences in OGTT-fasting and 2-hour glucose levels of the MC group were significantly lower than those of the IC and EC groups. The results revealed a potential connection between sleep quality, pregnancy outcomes, and chronotype. To validate these findings, more investigation is needed to determine if the onset of the sleep issue happened before or during pregnancy, and whether the risk varies according to the disorder's chronicity.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Merve Yılmaz Menek;* ***Design:*** *Merve Yılmaz Menek, Ayşe Kavasoğlu Kaya;* ***Control/Supervision:*** *Merve Yılmaz Menek;* ***Data Collection and/or Processing:*** *Ayşe Kavasoğlu Kaya, Merve Yılmaz Menek;* ***Analysis and/or Interpretation:*** *Merve Yılmaz Menek;* ***Literature Review:*** *Ayşe Kavasoğlu Kaya, Merve Yılmaz Menek;* ***Writing the Article:*** *Merve Yılmaz Menek;* ***Critical Review:*** *Ayşe Kavasoğlu Kaya;* ***References and Fundings:*** *Ayşe Kavasoğlu Kaya;* ***Materials:*** *Ayşe Kavasoğlu Kaya, Merve Yılmaz Menek.*

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