Original Article

Exploring the impact of sleep quality on intrahepatic cholestasis of pregnancy

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Objective: To explore the association of poor sleep quality with the development of intrahepatic cholestasis of pregnancy (ICP).

Methodology: This prospective cohort study was conducted at Islamic International Medical college in collaboration with Rawalpindi Medical University. We enrolled 182 pregnant women between the ages of 20-40 years, from Railway Hospital and Holy Family Hospital, in their second trimester. Sleep quality was determined using Pittsburgh Sleep Quality Index (PSQI). The participants were divided into two groups: Group I, n = 113 (good sleep quality), and Group II, n=69 (poor sleep quality). Blood samples were withdrawn for Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), bilirubin and fasting Total bile acids (TBA) to establish their baseline values. During their third trimester (between 28th to 36th week), same tests were repeated. History of pruritus, a main symptom of ICP was also explored. Differences between continuous and categorical variables among two groups were evaluated using the Mann-Whitney U test and Chi-square test, respectively. Regression analysis was also employed.

Results: Significant differences in liver enzymes and TBA were found between the two groups ($p<0.001$). A significant correlation of sleep score with ALT, AST, ALP, TBA and age ($p<0.05$) was found. Significantly higher proportion of participants who developed disease in the third trimester were in group II as compared to group I ($p=0.000$). Logistic regression analysis showed that poor sleep quality was an independent risk factor for the development of ICP (OR:1.410, $p=0.01$).

Conclusion: The study concluded that poor sleep quality is an independent risk factor for the development of ICP in pregnancy.

Keywords: Alanine transaminase, alkaline phosphatase, intrahepatic cholestasis of pregnancy, sleep quality, total bile acids.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver dysfunction during pregnancy, affecting about 0.3-1.5% of pregnancies worldwide. In Pakistan, the prevalence has been reported to be around 1.5%.[1,2] Multiple pregnancies, increasing maternal age and obesity serve as risk factors. The condition typically manifests in the second or third trimester and is characterized by intense itching, which is more pronounced on palms and soles, especially at night, along with raised liver enzymes and total bile acid levels (TBA>10 µmol/l).[2] Around 80% of the cases present after the 30th week of gestation.

ICP poses significant risks for both maternal and fetal health, including postpartum haemorrhage, preeclampsia, gestational diabetes, fetal distress and stillbirth. While the exact aetiology remains unclear, genetic, hormonal, immunological and environmental factors are believed to contribute to its development.[1]

Circadian rhythms are biological cycles that regulate a wide array of physiological processes, including liver function and sleep patterns. Proper alignment of sleep with circadian rhythms supports health by promoting biological restoration and preventing disease.[3] Disruption of circadian rhythm as with poor sleep quality, disturbs the bile acid homeostasis. Recent studies indicate that transcription of liver genes is regulated by circadian rhythm, as cholesterol 7a-hydroxylase (cyp7a1) is involved in the conversion of cholesterol to bile acids.[4] Lack of sleep produces oxidative stress that dysregulates bile acid metabolism and, in return, elevates liver enzymes.[5]

While the effect of poor sleep on liver enzymes has been recognized, this relationship remains unexplored in pregnancy. Although several studies have linked poor sleep quality to negative pregnancy outcomes; however, most are cross-sectional and tend to focus on a wide range of outcomes such as diabetes mellitus, prematurity, premature rupture of membranes, hypertension and an increased incidence of caesarean section. Therefore, the current study aimed to explore the relationship between poor sleep quality and cholestatic liver dysfunction during pregnancy.

METHODOLOGY

This prospective cohort study was carried out in the department of Physiology, Islamic International Medical

College (IIMC), Rawalpindi, in collaboration with Rawalpindi Medical University. Data was collected from all the pregnant women presenting to Railway hospital and Holy Family Hospital, Rawalpindi from April 2024 to April 2025, after taking written informed consent. The formal ethical approval was obtained from IIMC (Ref No: Riphah/IIMC/IRC/2 4/1050).

We enrolled 182 women, with the exclusion of 5 who lost follow-up. Healthy pregnant women, 20-40 years of age, in the second trimester of pregnancy, both primigravida and multigravida were included in the study. Pregnant women with preexisting liver diseases, any congenital malformation, those on hormonal therapy, women diagnosed with anxiety, depression, or sleep disorders, and twin pregnancies were excluded from the study.

A structured proforma was used to gather basic participant information, including age, body mass index (BMI) and gravidity from 18th to 26th week. The participants' sleep quality was assessed using Pittsburgh Sleep Quality Index (PSQI). The PSQI is a validated questionnaire that assesses the sleep quality over the past four weeks. It comprises of 19 self-reported questions with seven components: subjective sleep quality, sleep latency, sleep length, sleep efficiency, sleep disruption, and daytime dysfunction. Each component is scored from 0 to 3, generating PSQI ranging from 0 to 21.[6] A total score of 0 to 5 was considered as good sleep. Accordingly, participants were categorized into Group I (good sleep quality) with score 5 or less and Group II (poor sleep quality) with score >5.

Table 1: Descriptive characteristics of population under study (n=182).

Characteristics	Group I Good Sleep Quality PSQI score ≤ 5 (n=113)	Group II Poor Sleep Quality PSQI score >5 (n=69)	p value
Age (years)			
< than 30 years	82(89.62%)	37(53.13%)	.03*
≥30 years	31(27.4%)	32(46.37)	
BMI (Kg/m²)			
Normal weight	82(66.7%)	41 33.3%)	.07
Overweight	31(53.4%)	28 (46.7%)	
Gravidity			
Primigravida	55 (48.67%)	18(26%)	.003**
Multigravida	58 (51.32%)	51(73.9%)	
Outcome			
Diseased	29(25.66%)	54(58.3%)	.000**
Non diseased	84(84.8%)	15(21.7%)	
PSQI score#	4 ±1.07	7.43±1.59	<.001**

$Comparison done via Chi-square and # independent sample t-test. **p<0.001 is taken as highly significant, *p<0.05 is taken as significant

Table 2: Comparison of liver function parameters between Groups.

Parameters	Group I Good Sleep Quality (PSQI score ≤ 5) (n=113)	Group II poor Sleep Quality (PSQI score >5) (n=69)	p value
ALT (U/L)	19(16-33.5)	64 (28-92)	<0.001**
AST (U/L)	23 (21-27.5)	34 (23 -45)	<0.001**
ALP (U/L)	174 (117.0-212.50)	232(202-305.5)	<0.001**
Bilirubin (mg/dL)	0.5(0.4-0.9)	0.5 (0.3-0.7)	<0.94
TBA(μmol/L)	3(2.9-7.7)	12 (9.3-21.6)	<0.001**

Data is represented as Median (interquartile range). The Mann-Whitney U test was used for comparison between the two groups. **p<.05 is significant

Liver enzymes, ALT, AST and ALP were determined by the enzymatic method. Whereas bilirubin levels were determined by Diazo method. TBAs sample was taken after 12 hours fasting for analysis by the calorimetric method. Outcome was defined by the presence of pruritus, raised TBA with or without increased ALT levels. If a participant experiences itching, with or without an elevated ALT level above 34 U/L and has a fasting total bile acid concentration exceeding 10 μmol/L, she is diagnosed with ICP.[2]

Statistical Analysis: The data were analyzed using SPSS 27. The Shapiro-Wilk test was used to assess the normality of the data, which was then presented as mean ± standard deviation or median and interquartile range

(IQR). Independent sample t-test and Mann-Whitney U test were applied to assess differences between continuous variables. Differences between categorical variables were evaluated using the Chi-square test. Spearman's correlation was utilized to determine the relationship among the sleep quality, liver enzymes and total bile acids. Regression analysis was applied to see the association of sleep quality along with BMI and age, with the outcome. $p<0.05$ was considered significant.

Table 3: Correlation of PSQI score with liver function parameters, total bile acids, BMI and age.

Parameters	r_s	p value
ALT (U/L)	.436	.000**
AST(U/L)	.374	.000**
ALP(U/L)	.405	.000**
TBA (µmol/L)	.410	.000**
Bilirubin(mg/dL)	-.124	.09
BMI(Kg/m^2)	.094	.20
Age(Years)	.262	<.001**

r_s is the Spearman correlation coefficient. **p<0.000 is taken as highly significant

Table 4: Logistic regression analysis of risk factors in predicting cholestasis.

Variable	OR	CI	p value
Model 1			
PSQI score	1.811	(1.11-2.512)	.001**
Model 2			
PSQI score	1.410	(1.25-2.57)	.01*
BMI(Kg/m^2)	.256	(.792-.281)	.34
Age (Years)	1.531	(1.708-4.769)	.35

**p<0.000 is highly significant

RESULTS

Table 1 represents a comparison of demographic characteristics, clinical outcomes and PSQI score between the two groups. Clinical outcomes differed significantly between the groups (p=0.000), with a greater number of participants in Group II being diagnosed with the disease (54, 58.3%) compared to Group I (29, 25.66%). BMI did not differ significantly between groups (p=0.07). There was a significant difference in ALT, AST, ALP and TBA among the two groups (p<0.001) (Table 2). No significant difference was found regarding bilirubin level among the two groups (p<0.94).

Spearman correlation analysis (Table 3) revealed a positive correlation of PQSI scores with age, ALT, AST, ALP, and TBA levels (r=.262, p=0.001, r=.436, p=0.000, r=.374, p=0.000; r= .405, p=0.000; r=.410, p=0.000, respectively). Correlation of PSQI score with bilirubin and BMI was not found to be significant (r=-.124, p=0.09; r=.094, p=0.20). Logistic regression analysis (Table 4) demonstrated that the PSQI score was a significant predictor of adverse outcomes. Model 1 revealed that PSQI score significantly predicted the outcome (OR: 1.811; 95% CI: 1.11–2.512; p=0.001). In Model 2, PSQI score remained a significant independent predictor (OR: 1.410; 95% CI:1.25-2.57; p=0.01), whereas age and BMI did not show significant predictive value.

DISCUSSION

Intrahepatic cholestasis of pregnancy is a reversible condition of unknown aetiology that appears in the late second and third trimester of pregnancy. Our study showed that poor sleep quality significantly impaired liver function and increased the risk of developing ICP, compared to individuals with good sleep quality. PSQI score showed significant correlation with ALT, AST, ALP, and total bile acids, showing that sleep quality significantly affects the liver health. Moreover, regression analysis showed that sleep quality was an independent predictor of cholestatic liver dysfunction. According to a recent study, poor sleep quality is associated with elevation in liver enzymes, indicating liver damage and is risk factor for liver cancer.[7] A similar study reported elevated liver enzymes in individuals with untreated sleep apnea.[8]

In the present study, BMI showed no significant correlation with the PSQI score. This finding is in contrast with a prospective cohort study by Tang et al, that reported a strong association between increasing BMI and sleep quality.[9] The adverse effect of poor sleep quality on liver function parameters could be partially mediated by increasing BMI.[10] In the current study, the difference in BMI among the two groups was insignificant, which can account for the insignificant correlation of BMI with PSQI score.

Various studies have discussed the association of sleep with liver function parameters but to date no study has discussed the role of sleep quality in the development of ICP. A study by Um et al, reported that poor sleep quality was significantly associated with development of non-alcoholic fatty liver disease and even after adjustment for BMI, the relationship remained significant.[11] In a review, it was discussed that poor sleep quality disrupts the circadian rhythm, which can lead to alterations in liver enzymes and development of non-alcoholic fatty liver disease.[12] Bile acids show an increasing trend in pregnancy but poor sleep quality leads to alteration in bile acid homeostasis, leading to cholestasis.[13] Another cross-sectional study reported that sleep disturbance was associated with higher odds of adverse pregnancy outcomes in terms of abortion, increased incidence of C-section, and abnormal fasting blood sugar.[14]

A study on mice reported that sleep disruption leads to altered liver function in mice and increased liver enzymes indicating liver injury along with disruption of the circadian rhythm of lipid and carbohydrate metabolism.[3] Another research reported that poor sleep quality has been associated with increased incidence of liver cancer and raised liver function markers.[15] Poor sleep quality has also been linked to a decrease in mitochondrial DNA copy number, which can affect liver health by posing oxidative stress in the liver.[16] Recent research reported that maternal sleep deprivation can alter the gut microbial composition, leading to dysbiosis and systemic inflammation ending up in pregnancy complications[17] and alteration in gut microbiome leads to disturbed homeostasis in bile salts metabolism, potentially leading to cholestasis.[18]

A study examined the effect of sleep on inflammatory parameters in pregnancy and concluded that sleep leads to an increase in the inflammatory markers in pregnancy.[19] Increase in inflammation and oxidative stress has been linked to the development of cholestatic liver dysfunction in pregnancy.[20] Heightened inflammation in pregnant women with poor sleep quality has also been associated with the development of ICP.[21] It has been proven that the Hypothalamic pituitary adrenal axis (HPA) activation occurs in cholestatic liver diseases.[22] Linking it with sleep studies has reported that poor sleep quality can lead to dysregulation of HPA axis. In the current study, age was found to be correlated with sleep quality; however, no association between age and the outcome was observed. A study reported that maternal age is a significant determinant of sleep quality.[23] Another study found that sleep quality to be same across various maternal age groups.[24] The disparity in findings can most likely be attributed to varying study methodology and different geographical location of study population.

A larger sample size that includes oxidative stress markers would have strengthened the investigation into the impact of sleep quality on outcomes. Additionally, supplementing subjective sleep quality assessments with objective measures, such as actigraphy, would have enhanced the reliability of the findings.

CONCLUSION

Poor sleep quality has emerged as an independent predictor of ICP. This association remains significant even after adjusting for potential confounders such as age and BMI. The findings highlight the critical role of sleep in liver health during pregnancy. Addressing sleep disturbances may offer a novel approach to managing or mitigating ICP risk.

Author Contributions
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