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Original Research Article

A multifactorial prospective study investigating temperature and sex steroids as seasonal and hormonal triggers of intrahepatic cholestasis of pregnancy

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Abstract

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a liver disorder that is unique to pregnancy. The important characteristic features of this disease are pruritus and elevated bile acid levels that result in adverse consequences. Despite the complexity of its etiology, recent research suggested that environmental, seasonal, and hormonal factors play a vital role in the onset and severity of the disease.

Materials and Methods: Cardinal symptoms (Pruritus and elevated bile acid levels) and biochemical tests were used to screen pregnant women with IHCP. The prevalence of IHCP in summer, spring, autumn, and winter seasons was assessed. Biochemical analyses were carried out at the time of enrolment and end of the study to gain insights into possible contributing factors in the etiology of the disease.

Results: During the study, a total of 101 pregnant women were diagnosed with IHCP, yielding a 9.7% prevalence. A significant seasonal difference was observed, with the winter months having the highest prevalence (86%) and the summer months having the lowest (14%). Progesterone and estradiol levels were considerably higher in IHCP than in non-IHCP subjects. A statistical analysis revealed a relationship between the occurrence of IHCP and both hormonal imbalance and seasonal variability.

Conclusion: This study revealed that low temperature and elevated estradiol and progesterone levels increased the prevalence of IHCP, pointing to a potential involvement of environmental, hormonal, and climatic factors in the disease's onset.

Keywords: Environmental factors, Estradiol, Intrahepatic cholestasis of pregnancy, Progesterone, Seasonal variability, Ursodeoxycholic acid.

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1. Introduction

Intrahepatic cholestasis of pregnancy (IHCP) is a liver disease that is unique to pregnancy. The characteristic features of this disease are pruritus and increased serum bile acids. It usually manifests in the third trimester.[1] Although its precise etiology is still complex and not fully understood, it is well established that seasonal and hormonal factors might influence the onset and severity of the disease.[2]

Numerous epidemiological studies reported that variation in the incidence of IHCP has been linked with seasonal variation, indicating that the disease's pathogenesis may be influenced by variables like daylight duration, humidity, and ambient temperature.[3] Additionally, increased incidence of IHCP occurred during the winter season in some geographical areas, suggesting potential connections to decreased sunshine exposure, changed melatonin metabolism, and altered hormonal levels. Furthermore, environmental stress and diet associated with varied seasons might play an important role in altering liver functions during pregnancy.[4,5]

Sex-steroid hormones such as estrogen and progesterone play a pivotal role in the onset of disease among the various contributing factors. Though these hormones are essential for sustaining pregnancy but their elevated level, especially during the last trimester, may impair hepatic function and the

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bile acid transport mechanism in genetically or environmentally susceptible subjects.[6] Estrogen has been demonstrated to decrease bile acid excretion by downregulating hepatobiliary transport proteins; yet, progesterone metabolites may worsen cholestasis by compromising bile acid clearance.[7] The interplay between these hormones and genetic predisposition is thought to initiate the cardinal symptoms of disease.[8]

It is essential to comprehend the seasonal and hormonal fluctuations in IHCP in order to clarify the mechanisms behind its development and to pinpoint possible treatment targets. Therefore, this study is designed in order to better understand how pregnancy-related seasonal variability and hormonal variations affect the onset and severity of IHCP.

2. Materials and Methods

2.1. Study design and setting

This prospective observational study was carried out at the Department of Obstetrics and Gynaecology, SGT Hospital, for 1 year from 5 July 2023 to 31 July 2024 on all pregnant women. The study was done after obtaining prior approval from the Institutional Ethical Committee, FMHS, SGT University, Gurugram (IEC/FMHS/S/05//07/23-59). This study was registered in CTRI with registration number CTRI/2024/03/063580.

2.2. Sample size calculation

The sample size was determined via the G-Power statistical analysis software using necessary factors such as α-value, the power of the study, and the type of statistical test. Using these factors, the sample size (n) was determined to be 98. The adjusted sample size was found to be 101, considering the percentage of dropouts as 10%. But in our study, there was no dropout. A total of 101 IHCP subjects completed this study successfully.

2.3. Study population

Pregnant ladies between 28 to 36 weeks of gestation diagnosed with intrahepatic cholestasis of pregnancy (IHCP) were enrolled in the study. Data collection was also done for non-IHCP subjects reported in the study period. IHCP was diagnosed based on the presence of pruritus with or without papules, elevated serum bile acid levels (>10 μmol/L), and/or deranged liver function tests (SGPT, SGOT, ALP, Bilirubin).

2.4. Inclusion criteria

1. Singleton pregnancy
2. Age 18-40 years
3. Confirmed diagnosis of IHCP
4. Gestational age between 28 to 36 weeks
5. Informed written consent.

2.5. Exclusion criteria

1. Pre-existing liver diseases such as hepatitis, cirrhosis
2. Multiple pregnancy
3. History of gallstones or biliary obstruction
4. Severe comorbidities such as diabetes, hypertension
5. Known allergy to UDCA

2.6. Data collection

1. Demographic data: Maternal age, gestational age at diagnosis, parity, BMI, and obstetric history of each subject were recorded.
2. Hormonal data: Serum levels of estrogen (estradiol) and progesterone were assessed at the time of enrolment and end of the study. These values were then compared with trimester-specific hormonal reference ranges in IHCP and non-IHCP subjects.
3. Seasonal data: The date of diagnosis of IHCP was used to determine season variability based on **Table 1**.

Table 1: Seasonal classification by months

Season	Months
Summer	June to August
Autumn	September to November
Winter	December to February
Spring	March to May

2.7. Statistical analysis

Descriptive statistics were used to summarize patient characteristics. The incidence rates of IHCP were compared across seasons using a pie diagram. The monthly distribution of IHCP cases was represented by a line chart, and the seasonal distribution of IHCP and non-IHCP subjects was compared by the chi-square test. Hormonal levels were analyzed using ANOVA tests to compare IHCP and non-IHCP subjects during enrolment and end of study. Pearson Correlation analysis was done to explore the relationship between estradiol, progesterone, and serum bile acid concentrations.

3. Results

A total of 101 singleton pregnant women were enrolled in this study. Out of 101 subjects, 42 (42.8%) had mild IHCP (<40 micromol/L), and 59 (58.4%) had severe IHCP (≥ 40 micromol/L) according to their serum bile acid levels **(Figure 1).** The highest prevalence of IHCP cases was recorded during the winter months, suggesting potential seasonal influence**.** The seasonal distribution of IHCP and non-IHCP cases was analyzed using the Chi-square test. A significant difference was observed between these groups, which is depicted in **Table 2**. The monthly distribution of IHCP cases is shown using a line chart **(Figure 2).**

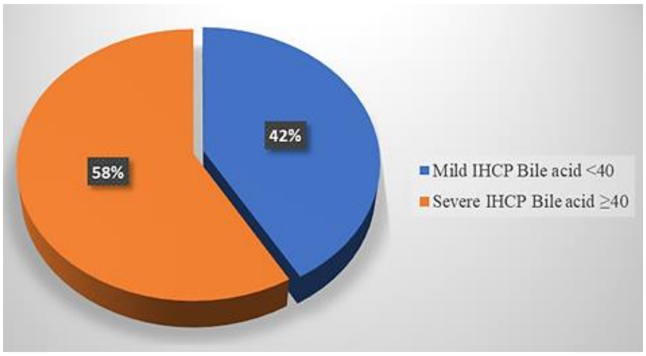

Figure 1: % of Mild versus severe IHCP subjects

The baseline characteristics of enrolled subjects were taken and analyzed statistically using the Chi-square test, which is depicted in **Table 3**. Age groups showed a significant difference, while other variables such as BMI, POG at diagnosis, parity, and onset of pruritus showed an extremely significant difference.

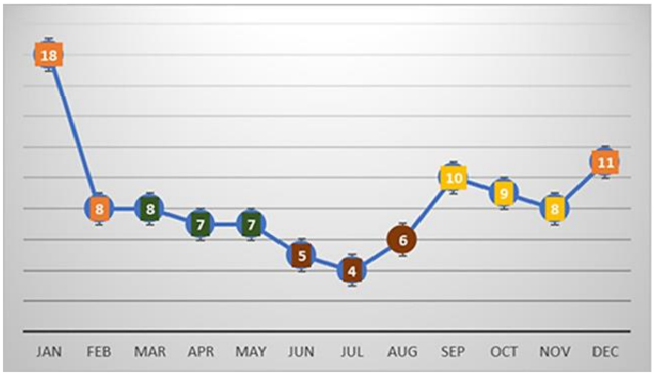

Figure 2: Line chart showing monthly trends to highlight peaks during colder months

The frequency of all the cardinal symptoms of IHCP was determined. A chi-square model was used for the statistical analysis, which is depicted in **Table 4.** A significant difference was observed between mild and severe cases of IHCP in sleep disturbance, however, no significant difference was observed in other symptoms.

Table 2: Seasonal variability in IHCP and non-IHCP cases

Season	No. of IHCP Cases	No. of Non-IHCP Cases	$\chi^2_{calculated}$	$\chi^2_{critical}$	p-value	Significance level
Winter	37	240	5752.78	7.81	0	*
Spring	22	247				
Summer	15	238				
Autumn	27	243				

*Data were analyzed using the Chi-square test, and a p< 0.05 was considered significant (*), p< 0.01 was considered very significant (**), p< 0.001 was considered highly significant, and p< 0.0001 was considered extremely significant.

Table 3: Baseline characteristics of enrolled subjects

Variables	Ranges	Frequency (n)	p-value	Significance
Age	18-25 years	47	0.0090	*
	26-30 years	32		
	Above 30 years	22		
BMI	18-25	23	$6.1058X10^{-12}$	****
	26-30	67		
	Above 30	11		
POG at diagnosis	<20 weeks	0	$1.3685X10^{-44}$	****
	20-32 weeks	0		
	> 32 weeks	101		
Parity	0	18	$9.9977X10^{-17}$	****
	1-2	74		
	<2	9		
Onset of Pruritus	I trimester	0	$7.5008X10^{-33}$	****
	II trimester	10		
	III trimester	91		

Table 4: Cardinal symptoms of IHCP according to the severity of IHCP

S. No.	Cardinal symptoms	Mild IHCP (n=42)	Severe IHCP (n=59)	p-value	Significance
1	Papules on skin	8	15	0.1444	ns
2	Sleep disturbance	29	47	0.0389	*
3	Itching	42	47	0.5961	ns
4	Pruritus	33	46	0.1435	ns

Table 5: Comparison of Hormonal Levels at diagnosis and delivery in IHCP and Non-IHCP subjects

Time point	Hormonal level	Sidak's Multiple comparison test		Statistical results	
		IHCP	Non-IHCP	p-value	Significance
Time of diagnosis	Estradiol (pg/ml)	11699.19±438.03	5648.51±213.23	<0.0001	****
	Progesterone (ng/ml)	143.21±3.21	82.27±4.367	<0.0001	****
Time of termination of pregnancy	Estradiol (pg/ml)	14983.17±62.64	8952.72±188.98	<0.0001	****
	Progesterone (ng/ml)	272.51±16.99	182.37±30.89	0.0095	**

Table 6: Correlative analysis between bile acid levels and Estradiol or progesterone levels in IHCP subjects

S. No.	Hormone level	Bile acid level	p-value	Significance
1	Progesterone	r^2= 0.85	0.023884	*
2	Estradiol	r^2= 0.98	0.000525	****

Table 7: Correlative analysis between bile acid levels and Estradiol or progesterone levels in non-IHCP subjects

S. No.	Hormone level	Bile acid level	p-value	Significance
1	Estradiol	r^2= 0.44	0.22	ns
2	Progesterone	r^2= 0.10	0.6	ns

Biochemical investigations (Estradiol and progesterone levels, and liver function test) were done during enrolment and end of the study. All data were represented as mean ± standard deviation. Two-way ANOVA (Sidak's multiple comparisons test) was used to analyze the data and is depicted in **Table 5.**

A correlational analysis was done to assess the correlation between serum bile acid levels and estradiol and progesterone concentrations in pregnant individuals. This analysis included both IHCP and non-IHCP subjects. In IHCP subjects, a strong positive relationship between bile acid levels and estradiol concentrations was observed, suggesting that increased estradiol levels may be associated with increased bile acid levels. However, bile acids and progesterone levels showed a moderate relationship, suggesting a less pronounced relationship than estradiol, as depicted in **Table 6.** On the other hand, in non-IHCP subjects, no correlation was observed between bile acid levels and estradiol or progesterone, as depicted in **Table 7**.

4. Discussion

An analysis of seasonal variability revealed significant differences in the incidence of IHCP across different months of the year. The occurrence of IHCP was found to be highest during the winter months (December to February), followed by a gradual decline in the spring, autumn, and summer seasons. The least incidence of IHCP was reported in the summer months (June to August), indicating a possible impact of environmental factors such as sunlight exposure, temperature, and vitamin D levels on the pathogenesis of IHCP. Autumn (September to November) showed a moderate number of cases, with a slight rise compared to the summer period. These results indicated that increased incidence of IHCP cases in the winter season might be linked to less sunshine exposure, which could have an impact on immunological modulation, melatonin levels, or metabolism of vitamin D, all of which have been proposed to be involved in the regulation of bile acids. These results align with those of Geenes V et al.[5] Both low selenium levels and poor glutathione peroxidase activity have an impact on the antioxidant system, which is crucial for preventing oxidative stress and is a major factor in the pathophysiology of IHCP. This provides the best explanation for why wintertime selenium levels are lower, leading to a higher prevalence of IHCP.[8,9] In patients with IHCP, low selenium levels impair the microsomal cytochrome P-450 system and reduce glutathione peroxidase activity, which leads to the generation of free radicals that might damage hepatocytes and reduce bile output.[10,11] These explanations lead to the conclusion that there is a positive correlation between the deficiency of selenium and the occurrence of IHCP in pregnant women.

The baseline characteristics of enrolled subjects were also taken. It was observed that the highest percentage of women (46.53%) in the age group of 18-25 years were affected by the IHCP, whereas the highest percentage of overweight women (66.33%) with having BMI in the range of 26-30 were mostly affected by the IHCP. Furthermore, it was also observed that POG at diagnosis of IHCP was more than 32 weeks in all enrolled subjects, suggesting that IHCP occurred in the early third trimester of pregnancy in our study population.[12,13]

The cardinal symptoms of IHCP were evaluated according to their severity, revealing a significant difference in sleep disturbance related to the severity of the IHCP. In contrast, no significant results were observed in the remaining symptoms, such as pruritus, itching, and papules on the skin.

Furthermore, this study also explored the potential relationship between hormonal shifts and the development of

IHCP. Our findings revealed that serum levels of estradiol and progesterone were significantly increased in IHCP subjects as compared to non-IHCP subjects, especially during the third trimester. This period coincides with the peak in endogenous hormone production, supporting the hypothesis that increased hormone levels may contribute to impaired bile acid transport and disrupted hepatic function. These results align with those of Mutlu MF et al.[14] Progesterone metabolites may worsen cholestasis by disrupting bile flow, while estrogen is known to hinder bile acid transfer by downregulating hepatic transporter proteins, including BSEP (bile salt export pump).

A strong association between increased hormone levels and bile acid accumulation was observed in IHCP cases, indicating a hormone-driven mechanism behind the etiology of the disease. This supports the hypothesis that compromised bile flow and the pathophysiology of IHCP may be caused by increased levels of pregnancy hormones like progesterone and oestradiol, especially in the third trimester.[15] These findings highlight the importance of hormonal surveillance in high-risk patients and the potential role of progesterone and estradiol in the development or exacerbation of cholestasis during pregnancy.

5. Conclusion

The pathophysiology of pregnancy-related intrahepatic cholestasis may be significantly influenced by seasonal and hormonal factors, particularly changes in ambient temperature and sex hormone levels, as demonstrated by this study. The idea that environmental and physiological factors combine to affect disease onset and severity is supported by the connection that has been found between higher temperatures, heightened oestrogen levels, and an increased incidence of IHCP.

This study demonstrated that low temperature and increased sex steroid hormones may increase the incidence of IHCP, supporting the hypothesis that environmental and hormonal factors interact to influence the onset and severity of the disease.

Enhanced surveillance throughout the winter season, individualized risk evaluation, and increased public awareness are key steps that should be taken to reduce the impact of IHCP. Pregnant individuals at higher risk should undergo early detection and be advised to take a selenium-rich diet. Additionally, further research into hormonal interventions may offer future preventive strategies. In summary, obstetric treatment pathways that incorporate environmental monitoring, hormonal profiling, and patient education may enhance maternal and foetal outcomes by lowering the frequency and severity of IHCP.

6. Future Prospects

Further research is needed to explore seasonal associations and to understand whether seasonal monitoring and preventive strategies could help in the early identification and management of IHCP in susceptible populations. Further investigation is also warranted to determine whether hormonal modulation could offer therapeutic benefits in managing or preventing IHCP, especially in high-risk populations.

7. Authors' Contribution

Nidhi Sharma: Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. Rashmi Ray: Methodology, Investigation. Rubina Bhutani: Writing – review & editing, Visualization, Validation, Supervision.

8. Source of Funding

None.

9. Conflict of Interest

None.

10. Ethical Approval

Ethical No.: IEC/FMHS/S/05/07/23-59.

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