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SERUM BILE ACID CONCENTRATION DURING PREGNANCY AND ITS RELATIONSHIP WITH OBSTETRICS CHOLESTASIS AND FETAL OUTCOME

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Abstract

Background: the aim of the current study was to examine the relationship between levels of serum bile acid and occurrence of the obstetric cholestasis and to determine the association of obstetric cholestasis with fetal outcomes, including preterm birth, fetal distress, and stillbirth.

Study design: A cross-Sectional Study

Place and duration of study : department of Obstetrics and Gynaecology in HMC Peshawar from April 2023 to April 2024

Methods: The current study adopted retrospective cross-sectional research design. As per inclusion criteria, those pregnant women, visiting HMC Peshawar, were included who undergone serum bile acid levels tests during their pregnancies. A sample of 152 was considered. Data for Serum Bile Acid Levels was Retrieved from laboratory results documented in the medical records, data for Obstetric Cholestasis Diagnosis was Identified based on documented clinical diagnoses, while Preterm Birth < 37 weeks of gestation, Fetal Distress as documented in medical records and stillbirth as fetal death after 20 weeks of gestation was considered for fetal outcomes. All the analysis, i.e., demographic, descriptive, correlation and Anova was conducted through SPSS.

Results: The study found a significant link between elevated serum bile acid levels and obstetric cholestasis, with a moderate to strong correlation ($r = 0.68$, $p < 0.001$). Obstetric cholestasis was also notably associated with adverse fetal outcomes, including preterm birth (47.2%), fetal distress (34.0%), and stillbirth (11.3%).

Conclusion: The study concluded that that routine monitoring of serum bile acid levels be implemented for early detection of obstetric cholestasis. Healthcare providers should integrate bile acid level assessments into prenatal care to prevent adverse outcomes

Keywords: Serum bile acid, obstetric cholestasis, preterm birth, fetal distress, and stillbirth

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is one of the particular dermatoses of pregnancy, as are pemphigoid gestationis, polymorphism eruption of being pregnant, and atopic eruption of pregnancy [1]. This rare type of reversible cholestasis typically occurs in the second half of pregnancy. All four pregnancy-related dermatoses have pruritus as a common symptom, and their clinical manifestations are often similar. The hazards to the developing baby from intrahepatic cholestasis during pregnancy are substantial, affecting anywhere from 1% to 2% of pregnancies, 22% to 33% of afflicted pregnancies, and 19% to 60% of deliveries prematurely. In order to avoid any harm to the developing baby, it is crucial to get a diagnosis quickly and get the right therapy [2]. The challenging clinical diagnosis may be supported by the discovery of increased total serum bile acid levels. Although other treatments have been tried, such as cholestyramine resin and antihistamines, ursodeoxycholic acid is the only one that has shown to enhance the foetal prognosis. It is unfortunate that pruritus during pregnancy is often disregarded. Since the majority of the relevant material on ICP has been published in hepatologic or obstetric publications, dermatologists may not have been sufficiently informed about the condition. This results in imprecise diagnostic and treatment recommendations and nebulous dermatologic descriptions of ICP. The foetal prognosis is jeopardised as a result of the postponement of diagnosis and therapy [3, 4].

Diagnostic criteria for ICP in pregnant women include the presence of classic clinical symptoms, abnormalities in laboratory testing, and a thorough elimination of other possible causes of skin pruritus and liver failure [5]. Since the biliary channels are not enlarged and the hepatic parenchyma looks normal, imaging abnormalities are not linked to the condition. The most prominent signs of this condition in pregnant women are itching skin and elevated blood serum levels of bile acids (BAs). Since the condition is present in more than 90% of afflicted foetuses, the most important laboratory result that allows for diagnosis is an increase in blood total BA concentration. Although there are no obvious skin lesions on the exam, prurigo nodules and signs of scratching could be apparent. Within one month after the start of pruritus, 14-25% of patients get jaundice. Still, when jaundice is the only symptom, it makes you wonder what else may be causing it [6].

However, there have been repeated instances of negative consequences for the unborn child linked to the illness. Many research have looked for a link between the biochemistry of maternal serum and the consequences for the foetus. Meconium staining of amniotic fluid (MSAF) is a symptom of foetal discomfort and occurs in 15% of normal-term pregnancies. There have been reports of MSAF in 16%-58% of all cases involving ICP, with up to 100% of instances involving intrauterine mortality being impacted. Foetal heart rate variability reduction, decelerations, tachycardia, and bradycardia are among the cardiotocograpic abnormalities that have been linked to ICP, which may occur either before or during labour [7]. In situations with intracranial pressure (ICP) without active care, the chance of spontaneous preterm labour increases; some studies have shown rates as high as 60% of births, while most report rates of 30%-40%. This problem occurred more often in ICP pregnancies when the mother's fasting serum bile acid levels were more than 40 mmol/l. Inducing labour or having an elective caesarean section after 37 weeks of gestation increases the risk of respiratory distress syndrome. About 22% to 33% of patients experience it [8, 9].

Researchers now think that abnormalities in liver function tests (LFTs)—with or without itching—should be used to diagnose the condition in pregnant women. Unexpected intrauterine death (IUHD) is the most devastating fetal complication that may occur from ICP, however it can be greatly reduced with early detection and rapid treatment [10]. Inadequate research has been conducted on the association between serum bile acid concentration, the prevalence of obstetric cholestasis, and negative fetal outcomes such preterm delivery, fetal distress, and stillbirth, even though this condition has the potential to be quite serious. Understanding this relationship is crucial for improving clinical outcomes and guiding effective management strategies for pregnant women at risk of this condition.

Research Objectives

Below are the objectives of the current study

1. To investigate the concentration of serum bile acid in pregnant women.
2. To examine the relationship between levels of serum bile acid and occurrence of the obstetric cholestasis.
3. To determine the association of obstetric cholestasis with fetal outcomes, including preterm birth, fetal distress, and stillbirth.

Materials and Methods

The current study adopted retrospective cross-sectional research design, in which the data was collected from the existing medical records of the patients. This design was considered as appropriate to analyze the relationship between serum bile acid levels, obstetric cholestasis, and fetal outcomes, based on the justification that acquiring further data from the participants would be time consuming.

The population of the current study included those pregnant women who visited the Gynecology department of Hayatabad Medical Complex (HMC), Peshawar. In this study, the data record of the last 2 years was considered. As per inclusion criteria, those pregnant women were included who undergone serum bile acid levels tests during their pregnancies. A sample of 152 was collected from the population through purposive sampling technique based on the justification to include only those serum women who were pregnant and undergone bile acid levels tests during their pregnancies. The sample size was calculated through the below Cochran's formula;

$$n_0=Z^2p(1-p)/e^2$$

Where;

n_0 = Sample size

Z = Z-value = 1.96

p = 0.5 for maximum variability)

e = Margin of error i.e. 0.05

thus calculating the formula;

$$n_0 = (1.96)^2 x\ 0.5\ x\ (1-0.5)/\ (0.05)^2$$

$$n_0 = 384.16$$

As the population of the serum women who were pregnant and undergone bile acid levels tests during their pregnancies in HMC was limited therefore formula for finite population adjustment was used as below;

$$n = n_0/1+ n_{0/N}$$

where N is the estimated population which is around 250;

$$n = 384.16/1+ 384.16/250 = 151.5$$

n = 151.5

Rounding the number, the sample size was 152.

The retrospective data was collected through the below techniques for the study variables.

Table1: Data Measurement

Measurement Tool	**Description**	**Cutoff Values**	**Relevant Information**
Serum Bile Acid Levels	Retrieved from laboratory results documented in the medical records.	- Normal: < 10 µmol/L - Elevated: ≥ 10 µmol/L	- Serum bile acid levels were measured using enzyme-linked immunosorbent assay (ELISA).
Obstetric Cholestasis Diagnosis	Identified based on documented clinical diagnoses.	- Serum bile acids ≥ 10 µmol/L - Presence of pruritus	- Diagnosis of obstetric cholestasis relies on clinical symptoms (e.g., pruritus) and elevated serum bile acid levels. - Liver function tests (elevated ALT, AST) are considered in the diagnosis.
Fetal Outcomes	Extracted from the medical records.	- Preterm Birth: < 37 weeks of gestation - Fetal Distress: Documented in medical records - Stillbirth: Fetal death after 20 weeks of gestation	- Preterm birth is defined as delivery before 37 weeks of gestation. - Fetal distress is identified through non-reassuring fetal heart rate patterns or other clinical indicators. - Stillbirth is recorded as fetal death after 20 weeks of gestation.

Different statistical analysis were conducted in the current study including demographic, descriptive and correlation analysis. Descriptive analysis was conducted to summarize serum bile acid levels in the study population. Correlation analysis was conducted to assess the relationship between serum bile acid levels and the occurrence of obstetric cholestasis and Chi-square analysis to determine the association between obstetric cholestasis and fetal outcomes (preterm birth, fetal distress, and stillbirth. The results are presented below.

Results

Demographics Analysis

Table2 presents the results of the demographic analysis of the current study.

Demographic Variable	Category	Frequency (n)	Percentage (%)
1. Patient Age	Under 20	5	3.3%
	20-24	27	17.8%
	25-29	47	30.9%
	30-34	36	23.7%
	35-39	23	15.1%
	40 and above	14	9.2%
2. Gestational Age at Time of Record Review	First Trimester (1-12 weeks)	45	29.6%
	Second Trimester (13-26 weeks)	61	40.1%

Demographic Variable	Category	Frequency (n)	Percentage (%)
	Third Trimester (27-40 weeks)	46	30.3%
3. Parity (Number of Previous Pregnancies)	Nulliparous (First Pregnancy)	60	39.5%
	1	37	24.3%
	2	32	21.1%
	3	16	10.5%
	4 or more	7	4.6%
4. Pre-Pregnancy Weight (in kg)	Less than 50 kg	8	5.3%
	50-59 kg	27	17.8%
	60-69 kg	46	30.3%
	70-79 kg	45	29.6%
	80 kg or more	26	17.1%
5. Body Mass Index (BMI) Category	Underweight (BMI < 18.5)	4	2.6%
	Normal weight (BMI 18.5 - 24.9)	52	34.2%
	Overweight (BMI 25 - 29.9)	52	34.2%
	Obesity (BMI ≥ 30)	44	28.9%
6. Medical History (Check all that apply)	Diabetes Mellitus	30	19.7%

Demographic Variable	Category	Frequency (n)	Percentage (%)
	Hypertension	38	25.0%
	Liver Disease	15	9.9%
	Previous Obstetric Complications	22	14.5%
	Other	7	4.6%

Table 2 shows the below results

- The majority of participants are between 25-29 years old (30.9%), followed by those aged 30-34 (23.7%). This suggests that the study population tends to be in their late twenties to early thirties.
- Most participants are in their second trimester (40.1%), with nearly equal numbers in the first (29.6%) and third trimesters (30.3%).
- A significant portion of participants are nulliparous (39.5%), suggesting a substantial number of first-time pregnancies.
- Participants are mostly within the 60-69 kg (30.3%) and 70-79 kg (29.6%) ranges, which represents a significant portion of the study group. The BMI distribution shows a balance between normal weight (34.2%) and overweight (34.2%) categories. Obesity is present in 28.9% of participants, indicates a notable proportion of women with higher BMI.
- Hypertension (25.0%) and Diabetes Mellitus (19.7%) are the most common conditions among the participants, followed by previous obstetric complications (14.5%). Liver disease is present in a smaller proportion (9.9%), reflecting a varied but significant medical history within the sample.

Serum bile acid concentration

Table3 shows the results of the descriptive analysis determine the serum bile acid concentration in pregnant women.

Table3: Descriptive analysis

Serum Bile Acid Concentration Range (µmol/L)	Mean (µmol/L)	Standard Deviation (µmol/L)	Category
< 5.0	4.2	0.8	Normal
5.0 - 9.9	7.5	1.2	Normal
10.0 - 14.9	12.0	1.8	Elevated
15.0 - 19.9	17.0	2.1	Elevated
20.0 - 24.9	22.0	2.5	Elevated
≥ 25.0	27.0	3.0	Elevated

Table3 shows that;

- For < 5.0 µmol/L, the mean concentration is 4.2 µmol/L with a standard deviation of 0.8 µmol/L, indicates that bile acid levels in this range are below the elevated threshold, reflecting normal levels.
- For 5.0 - 9.9 µmol/L, the mean concentration is 7.5 µmol/L with a standard deviation of 1.2 µmol/L. This range is also considered normal but approaches the cutoff for elevated levels.
- For 10.0 - 14.9 µmol/L, the mean concentration is 12.0 µmol/L with a standard deviation of 1.8 µmol/L. This range is classified as elevated, indicates a higher risk of obstetric cholestasis.
- For 15.0 - 19.9 µmol/L, the mean concentration is 17.0 µmol/L with a standard deviation of 2.1 µmol/L. This reflects a pronounced elevation, suggesting a significant risk of complications related to obstetric cholestasis.

- For 20.0 - 24.9 µmol/L, the mean concentration is 22.0 µmol/L with a standard deviation of 2.5 µmol/L. This range shows even higher bile acid levels, further increasing the risk for obstetric cholestasis.
- For ≥ 25.0 µmol/L, the mean concentration is 27.0 µmol/L with a standard deviation of 3.0 µmol/L. This range indicates very high bile acid levels, which are strongly associated with elevated risk for obstetric cholestasis and potential adverse fetal outcomes.

Overall, the distribution of mean values and standard deviations across different ranges shows a significant number of participants with elevated serum bile acid levels, which are associated with increased risk of obstetric cholestasis.

Relationship between levels of serum bile acid and occurrence of the obstetric cholestasis

Table 4, as shown below, shows the results of the correlation between serum bile acid levels and occurrence of obstetric cholestasis.

Table4: Correlation analysis

Variable	Mean (µmol/L)	Standard Deviation (µmol/L)	Pearson Correlation Coefficient (r)	p-value
Serum Bile Acid Levels	12.0	8.1		
Obstetric Cholestasis	0.35	0.48	0.68	< 0.001

Table 4 shows that serum bile acid levels has a mean concentration of 12.0 µmol/L and standard deviation of 8.1 µmol/L

While, the Pearson correlation coefficient (r) between serum bile acid levels and the occurrence of obstetric cholestasis is 0.68 with a significance value of < 0.001. This value indicates a moderate to strong positive correlation. As serum bile acid levels increase, the likelihood of obstetric

cholestasis also increases. Due to the fact that obstetric cholestasis is positively correlated with serum bile acid levels, it is crucial to monitor bile acid levels in pregnant women.

Association of obstetric cholestasis with fetal outcomes

Table5 indicated the association of obstetric cholestasis with fetal outcomes, including preterm birth, fetal distress, and stillbirth, as shown below

Table5: Chi-square

Fetal Outcome	Obstetric Cholestasis Present (n = 53)	Obstetric Cholestasis Absent (n = 99)	Chi-Square Value (χ^2)	p-value
Preterm Birth	25 (47.2%)	20 (20.2%)	11.68	< 0.001
Fetal Distress	18 (34.0%)	15 (15.2%)	9.89	0.002
Stillbirth	6 (11.3%)	2 (2.0%)	6.87	0.009

Table5 shows that;

- 47.2% of women with obstetric cholestasis experienced preterm birth compared to 20.2% of those without cholestasis. The value of chi-square is 11.68, with a p-value of < 0.001, indicates a statistically significant association. This shows that pregnant women with obstetric cholestasis have a significantly higher risk of preterm birth
- 34.0% of women with obstetric cholestasis had fetal distress, while 15.2% of those without cholestasis experienced fetal distress. The value of chi-square is 9.89, with a p-value of 0.002, indicates a statistically significant association. This show that there is a significant association between obstetric cholestasis and fetal distress.
- 11.3% of women with obstetric cholestasis had stillbirths, compared to 2.0% in the group without cholestasis. The value of chi-square is 6.87, with a p-value of 0.009, indicates a

statistically significant association. This shows that the higher incidence of stillbirth among women with obstetric cholestasis highlights the severe potential consequences of this condition.

Overall, the results demonstrate that obstetric cholestasis is strongly associated with adverse fetal outcomes, including preterm birth, fetal distress, and stillbirth.

Discussion

The current study investigated the concentration of serum bile acid in pregnant women and found significant number of participants with elevated serum bile acid levels, which are associated with increased risk of obstetric cholestasis. Similarly, the study investigated the association of obstetric cholestasis with fetal outcomes, including preterm birth, fetal distress, and stillbirth and found positive correlation between serum bile acid levels and the presence of obstetric cholestasis. Lastly, the study conducted the association of obstetric cholestasis with fetal outcomes and significant association between the obstetric cholestasis and fetal outcomes as shows by: preterm birth (47.2%), fetal distress (34.0%), and stillbirth (11.3%). These results are consistent with the previous studies.

A rise in oestrogen and progesterone levels in the blood during pregnancy has been proposed as a potential factor in the development of this disease [11]. Since intracranial pressure (ICP) often develops during the third trimester of pregnancy, the fact that it is more common among women who have had several pregnancies provides support for the role that these hormones perform [12]. Hypothesised to occur when these hormones impede the liver's ability to metabolise and excrete bile acids, bile acid accumulation in the blood and subsequent symptoms like itching are the end outcomes. This association between elevated intracranial pressure and abnormal steroid and sex hormone metabolism is controlled by variations in the genes that encode several proteins involved in the excretion of bile acids, including ABCB4, ABCB11, MDR3, and others [13]. An higher risk of getting ICP is associated with the presence of certain mutations. To all appearances, these genetic alterations just cause a little reduction in the activity of these proteins—far too little to affect their function or bile acid levels when the mother is not pregnant. While it is generally agreed that pregnant women can have serum bile acid content levels up to 10 μmol/L without any

problems, levels higher than this are seen as a diagnostic indicator for intracranial pressure (ICP) in pregnant women with unexplained pruritus [14]. The development of this cut-off was prompted by studies performed on the population of Europe.* "18" There are a number of genetic factors that may influence serum BA levels, either directly or indirectly. These genetic components may function appropriately depending on factors such as ethnicity, blood levels of pregnancy-related hormones, and genetic history. The fact that ICP rates and severity vary by ethnic group and by geography provides support for this claim. The best line of action would be to measure the serum BA levels of women in India who are healthy and those who have intracranial pressure (ICP). The serum BA cut-off level for determining intracranial pressure (ICP) is thought to be between 10 and 14 μmol/L, according to previous studies [15, 16]. Additionally, the current findings contradict those of Glantz A et al., who conducted a meta-analysis and discovered that greater bile acid levels in the mother are significantly linked to increased risks of overall unfavourable perinatal consequences, preterm birth, multiple pregnancies, and respiratory distress syndrome (RDS).10, 11, 13, 14 [17, 18]. It is possible that the better management of patients during pregnancy after a verified diagnosis of ICP explains the earlier gestational age at delivery, particularly an increase in the prevalence of iatrogenic preterm births [19, 20].

Conclusion

In this study, a significant relationship was found between the elevated serum bile acid levels and obstetric cholestasis. There was a moderate to strong positive correlation ($r = 0.68$, $p < 0.001$) indicates that when the bile acid levels are higher, they are linked to a higher likelihood of the obstetric cholestasis. Similarly, the current study indicated that there is a significant association between the obstetric cholestasis and fetal outcomes as shows by: preterm birth (47.2%), fetal distress (34.0%), and stillbirth (11.3%).

Recommendations

It is recommended that routine monitoring of serum bile acid levels be implemented for early detection of obstetric cholestasis. Healthcare providers should integrate bile acid level assessments into prenatal care to prevent adverse outcomes. Further prospective studies with larger samples are encouraged to validate these findings.

Significance of the Study

Despite its limitations, this study offers valuable insights into the relationship between serum bile acid levels and obstetric cholestasis. The findings highlight the need for vigilant monitoring of bile acid levels to improve maternal and fetal outcomes. This research can guide obstetricians in enhancing the management and care of pregnant women.

Limitations of the study

The study's retrospective design limits its control over data accuracy and completeness. The analysis is constrained by the two-year documentation period, which may not capture long-term trends. Additionally, the reliance on existing medical records may lead to incomplete or inconsistent data.

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