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RESEARCH ARTICLE

PROSPECTIVE OBSERVATIONAL COMPARATIVE STUDY OF ASSOCIATION OF INTRAHEPATIC CHOLESTASIS IN PREGNANCY WITH GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Introduction: Intrahepatic cholestasis of pregnancy (ICP) is a most common pregnancy-related liver disorder. It frequently develops in late pregnancy. It is associated with increased rates of maternal and foetal adverse outcomes including spontaneous preterm labour, foetal hypoxia, meconium-stained liquor and stillbirth. It is therefore essential to increase interest in knowledge of the disease and to find a safe medical treatment that improve foetal outcomes. **Aims and Objectives**: This study aims to determine the association between ICP with gestational diabetes mellitus (GDM). **Material & Methods:** It was a prospective observational comparative study conducted in the Department of OBG S.M.S. Medical college Jaipur from June 2018 to July 2019. Two groups with 30 patients in each group were included in this study. Cases were diagnosed by h/o pruritus at 24 weeks and above and controls were without h/o ICP. Both groups were subjected to DIPSI testing. Results were tabulated and statically analysed by using SPSS software. **Results:** ICP women were belonging to mean age group of 22.2 ± 1.85 years. Serum bile acid was found to be significantly higher in ICP group (35.97 ± 26.47) compared to control subjects (4.19 ± 0.84 μmol /L) with p <0.001. Mean DIPSI was higher in intra hepatic cholestasis cases (153.4 ± 44.6 mg/dl) as compared to controls (118.2 ± 40.9 mg/dl) and statistically significant (p=0.002). **Conclusion:** ICP is characterized by glucose intolerance and dyslipidaemia, consistent with the changes seen in the metabolic syndrome. GDM also occurs more commonly in pregnancies complicated by ICP. Given the growing evidence in support of an association between ICP and GDM, Further work is required to help clarify which metabolic pathways are altered in ICP in order to better promote both maternal and fetal well-being.

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INTRODUCTION

ICP was originally described in 1883 by Ahlfeld as recurrent Jaundice in pregnancy that resolved following delivery. Pruritus was not mentioned in this report, but in subsequent case reports published in the 1950's, severe pruritus with or without jaundice was reported in conjunction with this condition, in addition to complete resolution following delivery and high recurrence rates in subsequent pregnancies (Svanborg, 1954; Thorling, 1955). Over the years, ICP has also been described as jaundice in pregnancy, recurrent jaundice in pregnancy, idiopathic jaundice of pregnancy, obstetric-hepatosis, gestational hepatosis or obstetric cholestasis.ICP is a common liver disease during pregnancy (Joshi, 2010), with reported incidence rates of between 0.4 and 15% in different countries and populations (Lammert *et al*., 2000; Geenes, 2009).

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ICP is characterised by otherwise unexplained pruritus, with elevated bile acids and/or serum transaminases in the late second and third trimester of pregnancy. Pruritus spontaneously resolves and deranged liver function tests typically normalize within 4 weeks of delivery (Williamson, 2014). Liver is a central organ in major metabolic pathways in body namely lipogenesis, gluconeogenesis and cholesterol metabolism. Cholestasis associated changes glucose and lipid metabolism may potentially be explained by bile acid receptors such as farnesoid X receptor and TGR5 (G-protein coupled bile acid receptor) which are also involved in glucose and lipid metabolism (Ma, 2006; Lambert *et al*., 2003; Pineda Torra, 2003; Cariou, 2007). Hence pathological conditions with diseased liver can manifest with deranged metabolic profile including glucose intolerance and dyslipidemia (Fiorucci, 2009; Sharma, 2011). In the pathogenesis of ICP, progesterone metabolites seem to play an even more important role than estrogen (Jovall, 2000). In liver progesterone is reduced to pregnenolone and pregnanediol.Sulfated metabolites of progesterone have been shown to antagonize farnesoid-X receptor (FXR) and hence affects metabolism of bile, glucose

and lipids (Glantz, 2008; Abu-Hayyeh, 2013). The mechanism of changes in glucose metabolism may potentially be related to reduced activity of FXR which influences glucose, lipid and bile acid homeostasis. As mentioned above ICP patients have downregulated FXR function due to antagonism by sulfated progesterone metabolites. Physiologically, primary bile acids-cholic acid and chenodeoxycholic acid, suppress the expression of key enzymes involved in gluconeogenesis by interaction with FXR (Ma, 2006). Additionally bile acids have recently been reported to act synergistically with glucose to promote β-cell insulin secretion (Seyer, 2013; Shen *et al*., 2008), as well as induce expression of insulin-regulated glucose transporter GLUT-4 through FXR mediated pathways (Roberts, 211). Disruption in these homeostatic pathways may promote impaired glucose tolerance observed in ICP.

Aims and objectives: To determine association between intrahepatic cholestasis of pregnancy (ICP) with gestational diabetes mellitus (GDM).

MATERIAL AND METHOD

This is prospective observational comparative study, conducted in department of Obstetrics and Gynaecology, S.M.S. Medical College and attached group of hospitals, Jaipur from June 2018 to June 2019. Cases included in the study were the women diagnosed with intra-hepatic cholestasis of pregnancy. Similar Age, BMI and gestation matched pregnant females without intra-hepatic cholestasis of pregnancy were included in control group. Sample size is calculated at 80% study power and alpha error of 0.05%, assuming 30% GDM in pregnancy with ICP and 0.01% GDM in pregnancy without ICP as per results of the seed article (Marcus G Martineau, 2015). Following above assumption 22 pregnant females with ICP and 22 pregnant females without ICP are required for this study. It is further enhanced and rounded off to 30 patients in each group as the final sample size for present study expecting 30% drop outs / lost to follow up.

Inclusion Criteria

- Women admitted in hospital with singleton pregnancy.
- Age group: 20-25 years.
- Gestational age:24 weeks to term
- BMI: 18.5 -24.9kg/m²

Exclusion Criteria

- Other causes of hepatic dysfunction
- Preeclampsia
- HELLP syndrome
- Acute fatty liver of pregnancy
- Primary biliary cirrhosis
- Active viral hepatitis
- USG abnormality suggesting any biliaryobstruction
- History of previous gestational or pre-conceptional diabetes.
- Use of oral/intramuscular steroids, calcineurin inhibitors, beta blockers.
- Multiple gestation.

Pregnant women with history of pruritus at 24 weeks and above, and fulfilling the inclusion criteria, were included in case group and subjected to testing of serum bile acids and liver transaminases. ICP was diagnosed if the serum bile acid level is > 10µmol/L and SGOT /SGPT (more than twice the normal) are elevated[34]. Control subjects were matched for BMI (±3.0kg/m²),maternal age (±2 years),gestational age (±2 weeks).Both groups were subjected to DIPSI testing with 75 gm oral glucose and results obtained after 2hours. Results were collected and statistical analysis was done, as mentioned in flow chart.

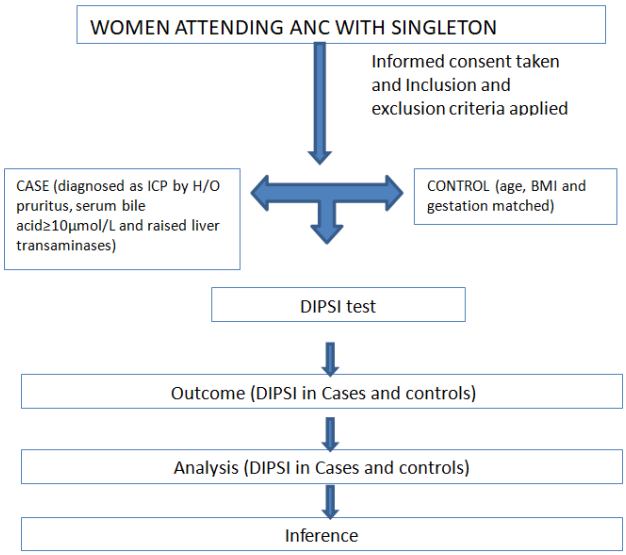

Figure 1. Flowchart showing Method Algorithm

Statistical Analysis

Data collected was entered in MS Excel sheet. Continuous variables were summarized as Mean and Standard Deviation, whereas nominal / categorical variables as percentage and proportions. Unpaired t test was used for analysis of continuous variables whereas chi square test / Fischer exact test was be used for categorical or nominal variables. P value < 0.05 was taken as significant. MEDCALC 16.4 version statistical software was used for all statistical calculations.

RESULTS

The mean age of intra hepatic cholestasis cases was 22.2 ± 1.85 years, while that of control group was 22.83 ± 1.76 years with no significant difference was seen (p=0.179).Most of the cases(66.7%) and controls(63.3%) were of Muslim religion (p=1.000).70% of pregnant women with intrahepatic cholestas is were from urban area whereas 53.3% of pregnant women without intrahepatic cholestasis belonged to urban area.Majority of pregnant women with intrahepatic cholestasis and pregnant women without cholestasis (43.3% both) were literate with secondary education, while 10% of subjects in both groups were illiterate. Majority of cases (50%) were primigravida followed by second gravida (30%). Majority of controls (43.3%) were second gravida (p value =0.177). Mean BMI of intra hepatic cholestasis cases was 22.98 ± 1.36 Kg/m^2 (19.6 – 24.8 Kg/m$^{2)}$, while among controls the mean BMI was 23.25 ± 0.96 Kg/m^2 (20.7 – 24.6 Kg/m^2) (p=0.371). Pruritus was found in all cases with intrahepatic cholestasis while icterus was found only in 16.7% these cases. The liver enzymes were slightly higher in intra hepatic cholestasis cases as compared to controls, but this difference was not found to be statistically significant (p>0.05), as seen in Table 1.

Table 1. Demographic features, Clinical features and Lab Investigations

	CASE	CONTROL	P- Value
AGE (Mean +/- SD)	22.2 ± 1.85	22.83 ± 1.76	p = 0.179
BMI (Mean +/- SD)	22.98 ± 1.36	23.25 ± 0.96	p = 0.371
RELIGION (%)			p= 1.000
Muslims	66.7	63.3	
Non Muslims	33.3	36.7	
RESIDENCE (%)			p = 0.288
Rural	30	38.3	
Urban	70	61.7	
Education(%)			p = 0.391
Illiterate	10	10	
primary	20	36.7	
Secondary	43.3	43.3	
Graduate / PG	26.7	10.0	
Gravida(%)			p = 0.177
Primigravida	50	26.7	
Second Gravida	30	43.3	
>2 Gravida	20	30	
Gestational age (%)			p = 0.684
<34 weeks	16.7	13.3	
34 – 37 weeks	60	53.3	
>37 weeks	23.3	33.3	
Clinical features			
Pruritus (%)	100		
Icterus (%)	16.7		
Lab Investigations			
TotalBilirubin	0.8 ± 0.4	0.8 ± 0.5	0.645
DirectBilirubin	0.3 ± 0.2	0.3 ± 0.2	0.248
IndirectBilirubin	0.5 ± 0.2	0.5 ± 0.3	0.964
SGOT (U/L)	77.2 ± 70.1	70 ± 81.5	0.718
SGPT (U/L)	113 ± 128.5	85.8 ± 100.3	0.366
Bile Acid Level (µmol/L) (Mean +/- SD)	35.97 ± 26.47	4.19 ± 0.84	P < 0.001
DIPSI values (mg/dL) (Mean +/- SD)	153.4 ± 44.6	118.2 ± 40.9	p = 0.002
DIPSI (%)			P < 0.001
≥140 mg/dL	73.3	26.7	
<140 mg/dL	26.7	73.3	

The liver transaminases were raised in cases (SGOT was twice the normal in 70% cases & SGPT was twice the normal in 73.3% cases), while among controls none of the subjects had SGOT or SGPT raised to twice the normal value. This difference in SGOT and SGPT level between the two groups was found to be statistically significant (p value <0.001). However, no significant difference with respect to serum bilirubin level was found between case and control groups. The serum bile acids was found to be significantly higher in ICP group (35.97 ± 26.47) compared to control subjects (4.19 ± 0.84 µmol /L) with p <0.001. The mean DIPSI values were higher in intra hepatic cholestasis cases (153.4 ± 44.6 mg/dL) as compared to controls (118.2 ± 40.9 mg/dL), this difference was found to be statistically significant (p=0.002).

DISCUSSION

In our study, we investigated association of intrahepatic cholestasis of pregnancy with gestational diabetes mellitus. Both the groups were matched in the socio- demographic profile. The mean age of intra hepatic cholestasis cases was 22.2 ± 1.85 years, while that of control group was 22.83 ± 1.76 years. In a similar study done by Martineau *et al* (2014), mean age of ICP was more than 28.4 years. This could be because of early age at first child birth in Indian population. In our study,70% of pregnant women with intrahepatic cholestasis were from urban area whereas 53.3% of pregnant women without intrahepatic cholestasis belonged to the urban area with no significant difference. This finding was consistent with results of study done by Antony T. Dann *et al* (2006)[22] and Martineau *et al* (2014) in a study done by Antony T. Dann *et al* (2006)[22],in the intrahepatic cholestasis of pregnancy group, the mean maternal age (± standard deviation) was 31 ± 5 years, with the median gestation at diagnosis being 33 + 4 weeks (range 12 + 0 to 40 + 5) weeks and the onset of pruritus occurred at 30 (range 4–39) weeks, as recalled by women at the time of recruitment. These findings were consistent with our study. Pruritus was found in all cases with intrahepatic cholestasis while icterus was found only in 16.7% of these cases. This was in accordance to the study done by Martineau *et al* (2014). In our study, the levels of liver enzymes were slightly higher in the intra hepatic cholestasis cases as compared to the controls but not statistically significant (p>0.05). This result was consistent with the study done by Martineau *et al* (2014)[21], in which abnormal liver enzymes were present in the cases as compared to the controls {in cases ALT (mean -129U/l), (median range 83[11-886])}. In another study done by Agata Majewska *et al* (2019), the mean transaminases levels (ALT and AST) showed no significant difference between non-GDM and GDM group (ALT: 194.35 vs 147.77, p = 0.27; AST: 110.2 vs 78.07, p = 0.12). Martineau *et al* (2014) studied that the serum bile acids were in the range of (4-249 mmol/L) with mean value of 40 mmol/L). These findings were consistent with the observations in our study as serum bile acids were found to be significantly higher in the ICP group (35.97 ± 26.47) as compared to the control subjects (4.19 ± 0.84 µmol /L) with p <0.001. We observed that the mean DIPSI values (single step with 75 gm glucose) were higher in the intra hepatic cholestasis cases (153.4 ± 44.6 mg/dl) as compared to the controls (118.2 ± 40.9 mg/dl) (p=0.002), which is similar to the observations obtained by Marcus *et al* (2015) (metabolic profile in ICP)as maternal

blood glucose concentrations were significantly increased in ICP using ambulatory CGM (P < 0.005) and following a GTT (P < 0.005) in their study. Similarly, a study conducted by Gulenay Gencosmanoglu Turkmen *et al*. (2019) was also consistent with our study. They observed that the mean 50-gm GCT values were significantly higher in the pregnant women with ICP compared to the healthy controls (128.7±28.2, 106.6±27.0; p <0.0001) and it was slightly higher in women with severe disease than women with mild disease (132.7±30.1, 125.5±26.5; p=0.26). In our study, we observed that the DIPSI values (single step with 75 gm glucose using >/=140 mg/dL as cut-off) was positive in 73.3 % of the cases whereas, only 26.7% of the controls were found to have positive DIPSI values. Similar study done by Martineau, Christina Raker *et al*. (2014) showed that compared to the control group the incidence of GDM in pregnancies complicated by ICP was 13.6% (OR 1.68 CI1.04–2.72, p = 0.03). When the ICP group was divided into women in whom GDM screening was performed before and after adiagnosis of ICP, the incidence of GDM was found to be 13.4% in the cases screened before they developed ICP (OR 1.66 CI 0.89–3.10, p = 0.11), rising to30% (OR 4.69 CI 1.98–11.1, p = 0.0002) following the onset of cholestasis . The statistically significant associationbetween ICP and GDM in the group as a whole remained afteradjustment for racial group, a variable known to influence the riskof both ICP and GDM, (unadjusted OR 1.68 95% CI 1.04–2.72,p = 0.03 vs. adjusted OR 1.69 95% CI 1.04–2.75, p = 0.03).

Conclusion

ICP is a pregnancy specific disorder which typically commences in the late second or third trimester and resolve after delivery. It is characterized by mild to severe pruritus, without any specific dermatologic features, elevated liver enzymes and increased serum bile acids. The etiology of ICP is still not completely explicit. Pathogenesis includes a combination of hormonal and environmental factors superimposing on a genetic predisposition. During recent years ICP is recognized to be associated with an abnormal metabolic profile, including glucose intolerance and dyslipidemia although it is considered to be secondary to aberrant bile acid homeostasis. Total serum bile acids typically peak 30–90 minutes after meals. The criteria for diagnosing ICP are subjective & there are no current uniform criteria for the diagnosis of ICP. Most studies use elevated serum bile acids or serum transaminase levels combined with pruritus during pregnancy; however, the serum bile acids may not necessarily be elevated at the time of a blood drawn due to fasting versus non fasting state and there may be a greater rise towards the later weeks of pregnancy. The turnaround time for receiving the laboratory results may be 1–2 weeks, making it an impractical tool for immediate risk stratification. In present study, gestational diabetes mellitus was found to be associated with ICP. Hence, DIPSI values and should be estimated in ICP women. Large scale clinical trials are required to discover which metabolic pathways are altered in ICP. Due to limitation of time, the study sample size was small. For more conclusive evidence, larger number of cases need to be studied. The study was done at Tertiary Care Hospital; thus, it is not representative of the whole population .More multi-centric trials need to be done.

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