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PREGNANCY OUTCOMES IN OBSTETRIC CHOLESTASIS ASSOCIATED WITH COAGULOPATHY; A HOSPITAL BASED MIXED COHORT STUDY

Obstetrics & Gynaecology

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ABSTRACT

Introduction- Intrahepatic cholestasis of pregnancy/ obstetric cholestasis usually occurs in second and third trimester of pregnancy. Clinically characterized by pruritus, icterus, or both. More commonly seen in multifetal pregnancy, and there is a significant genetic influence (1). Coagulopathy is a condition in which the blood's ability to coagulate is impaired. This condition causes a tendency towards prolonged or excessive bleeding (7). Intrahepatic cholestasis of pregnancy is seldom associated with significant vitamin K deficiency and severe coagulopathy (8). **Aims & Objectives-**To assess the incidence of IHCP, incidence of coagulopathy in IHCP, Comparison of maternal outcomes in patients of IHCP with coagulopathy to those without coagulopathy and Comparison of foetal outcomes in IHCP mothers with coagulopathy to those without coagulopathy. **Materials And Methods** The study was a hospital based mixed cohort study and retrospectively data collected from departmental register and medical record department of the hospital. **Summary & Conclusion** The study was aimed to find out the incidence of IHCP & coagulopathy in IHCP patients along with maternal and foetal outcome in IHCP patients. In our study the Prevalence of IHCP was 5.1% & coagulopathy affected 2% of IHCP patients.11.11% had adverse maternal outcome & 15.03% had adverse foetal outcome. 123 IHCP patients had pruritis. There was 1 maternal death while 4 intrauterine deaths In conclusion IHCP is common pathology and condition can be more dangerous to foetus as compared to mother and should be diagnosed early with continuous foetal surveillance.

KEYWORDS

INTRODUCTION

IHCP (Intrahepatic cholestasis of pregnancy)/ obstetric cholestasis is defined as recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum which usually occurs in second and third trimester of pregnancy. Clinically characterized by pruritus, icterus, or both. It is more commonly seen in multifetal pregnancy, and there is a significant genetic influence [(1)].

Exact cause of obstetrical cholestasis is not known. High and low sex steroid levels have been pointed out as a cause, but recent research implicates on various mutations that have been seen in many of the genes that control hepatocellular transport system. Eg. mutation of the ABCB4 gene encoding multidrug resistance protein 3 4 (MDR3) associated with progressive familial intrahepatic cholestasis, as well as a bile salt export pump encoded by ABCB11 [(2)]. Another potential gene products associated with this are Farnesoid X receptor and transporting ATPase encoded by ATP8B1 [(3)].

In IHCP, bile acids are not cleared completely and accumulate in plasma. Hyperbilirubinemia results due to retention of conjugated bile pigment, but total plasma concentrations rarely exceed 4 to 5 mg/dL. Serum aminotransferase levels are normal to moderately elevated but seldom exceed 250 U/L . Alkaline phosphatase is usually elevated even more so than in normal pregnancy . Liver biopsy shows mild cholestasis with bile plugs in the hepatocytes and canaliculi of the centrilobular regions, but without inflammation or necrosis. These changes disappear after delivery but often said to recur in subsequent pregnancies or with estrogen-containing contraceptives.

Pruritus appears in late pregnancy, although it occasionally manifests earlier. There are no constitutional symptoms, and generalized pruritus shows predilection for the soles. Skin changes are limited to excoriations from scratching. Other symptoms can be steatorrhea, malabsorption and fat soluble vitamins and weight loss. [(4)]Biochemical tests may show elevated serum bile acids and abnormal liver function test, but pruritus may precede laboratory findings by several weeks.

Obstetrics cholestasis is more common among women of Indian-Asian or Pakistani-Asian origin, with 15 in 1000 women affected, around 1.5 % [(6)].

Intrahepatic cholestasis of pregnancy is seldom associated with significant vitamin K deficiency and severe coagulopathy [(8)]. The fetus and the newborn are dependent on maternally derived vitamin K facilitated diffusion transport across the placenta for coagulation stability. Cholestasis in pregnancy causes decreased enterohepatic circulation of bile acids and a subsequent reduction in the absorption of fat soluble vitamins (D, E, A, K) from the terminal ileum. Fetal vitamin K is derived from the mother through transplacental passage. At birth, activities of the vitamin K dependent factors II, VII, IX, and X and the concentrations of the contact factors XI and XII are reduced to about 50% of normal adult levels. [(9)]Till date, there are minimal evidence of vitamin K deficiency and coagulopathy associated with cholestasis of pregnancy in the literature. Few research only identified anecdotal and reports of increased postpartum hemorrhage and fetal intraventricular bleeding with suspected cholestasis of pregnancy. These relatively old case studies lack confirmatory laboratory analyses for bile acids and vitamin K levels. [(10)(11).]

Considering few literatures giving evidence of IHCP associated with coagulopathy and due to my personal interest in pregnancy outcomes in IHCP in pregnant women , we are planning to assess pregnancy outcomes in IHCP associated with or without coagulopathy.

AIMS & OBJECTIVES

1. To assess the incidence of IHCP
2. To assess incidence of coagulopathy in IHCP
3. Comparison of maternal outcomes in patients of IHCP with coagulopathy to those without coagulopathy.
4. Comparison of foetal outcomes in IHCP mothers with coagulopathy to those without coagulopathy.

MATERIALS AND METHODS

The study was a hospital based mixed cohort study carried out in the Obstetrics & Gynaecology department of Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, over a period of 19 months from January 2020 to July 2021.

The study population comprised of all pregnant women with liver dysfunction attended antenatal OPD of Mahatma Gandhi hospital, from Jan 2020 to Dec 2020 with the defined inclusion & exclusion criteria. Retrospectively, the data of all pregnant women with liver dysfunction who attended antenatal OPD and delivered at MG Hospital from Jan2019 – Dec 2019 were also collected from departmental register and medical record department of the hospital.

Inclusion Criteria

- Pregnant patients with Serum bilirubin- >1 mg/dl and Aspartate Transaminase (AST)- >200 U/L.
- Patients who gave consent to participate in the study.

Exclusion Criteria

- Patients with liver disease before pregnancy
- Immunocompromised patients
- Patients with viral hepatitis
- Patients not willing to participate
- Other causes of cholestasis (gall stones, etc)

Data Entry And Statistical Analysis
The collected data were transformed into variables, coded and entered in Microsoft Excel sheet.

1. OBSERVATIONS & RESULTS

The data was entered in Microsoft Office Excel worksheet. Qualitative data is presented in numbers and percentage while quantitative data is presented in mean and standard deviation.

Table 1: Distribution according to Intrahepatic Cholestasis of Pregnancy (IHCP) with and without coagulopathy

Variable	Number	Percentage
Intrahepatic Cholestasis of Pregnancy without coagulopathy	150	5.09
Intrahepatic Cholestasis of Pregnancy with coagulopathy	3	0.101
Normal pregnancy	2793	94.80
Total	2946	100

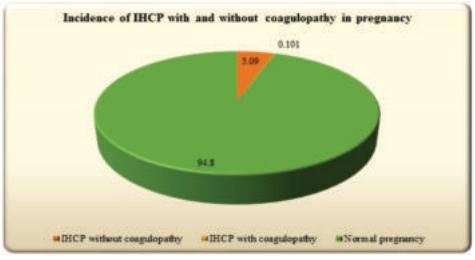

Figure 1: Bar diagram showing the incidence of IHCP with and without coagulopathy

Table 2: Distribution according to adverse feto-maternal outcome

Adverse outcome		Number	Percentage
Adverse maternal outcome	Yes	17	11.11
	No	136	88.88
Adverse foetal outcome	Yes	30	19.60
	No	123	80.39
Adverse pregnancy outcome	Yes	34	22.22
	No	119	77.77
Total		153	100

Post-partum haemorrhage, requirement of blood transfusion, requirement of ICU admission and mortality were considered as adverse maternal outcome while Still birth/ Intra-uterine death, poor APGAR score, requirement of NICU admission, meconium-stained liquor and intraventricular haemorrhage were considered as adverse foetal outcome.

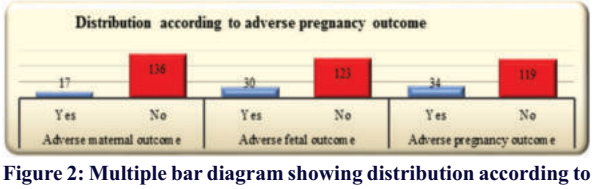

Figure 2: Multiple bar diagram showing distribution according to adverse pregnancy outcome

Table 3: Distribution of patients of IHCP with adverse pregnancy outcome according to their symptoms

Variables		Adverse pregnancy outcome	
		Yes N (%)	No N (%)
Pruritis	Yes	33 (97.05)	90 (75.63)
	No	1 (2.94)	29 (24.36)
Icterus	Yes	20 (58.82)	13 (10.92)
	No	14 (41.17)	106 (89.07)
Total		34 (100)	119 (100)

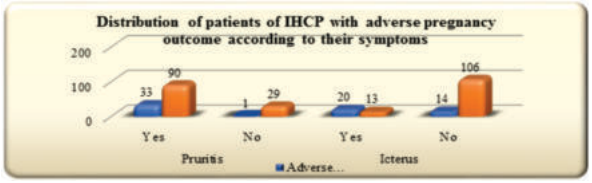

Figure 3: Distribution of patients of IHCP with adverse pregnancy outcome according to their symptoms

Table 4: Distribution of patients of IHCP with adverse pregnancy outcome according to the investigations

Variables		Adverse pregnancy outcome	
		Yes	No
SGOT/AST	Mean	466.88	195.31
	Standard Deviation	269.55	98.09
SGPT/ALT	Mean	486.38	224.38
	Standard Deviation	256.87	99.40
Prothrombin Time	Mean	20.41	12.79
	Standard Deviation	11.35	2.03
INR	Mean	2.04	1.13
	Standard Deviation	1.25	0.24
Total		34	119

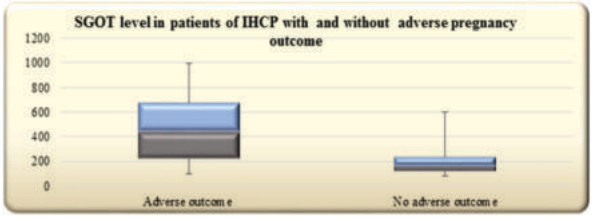

Figure 4: Box and Whiskers plot showing SGOT/AST level in patients of IHCP with and without adverse pregnancy outcome

Figure 4 shows box and whiskers plot showing SGOT/AST level in patients with and without adverse pregnancy outcome. The entire range of SGOT/AST in patients with adverse pregnancy outcome was from 97 to 995 with median level of 443.5 while the entire range of SGOT/AST level in patients without any adverse pregnancy outcome was from 78 to 600 with median level of 166.

Table 5: Distribution of patients of IHCP with adverse pregnancy outcome according to presence of coagulopathy

Variables		Adverse pregnancy outcome	
		Yes N (%)	No N (%)
Coagulopathy	Yes	3 (8.82)	0 (0.00)
	No	31 (91.17)	119 (100)
Total		34 (100)	119 (100)

Out of 34 patients of IHCP with adverse pregnancy outcome, 3 patients (8.82%) had coagulopathy while 31 patients (91.17%) didn't have coagulopathy. In 119 patients of IHCP without any adverse pregnancy outcome, none of the patients had coagulopathy. (Table 5, Figure 5)

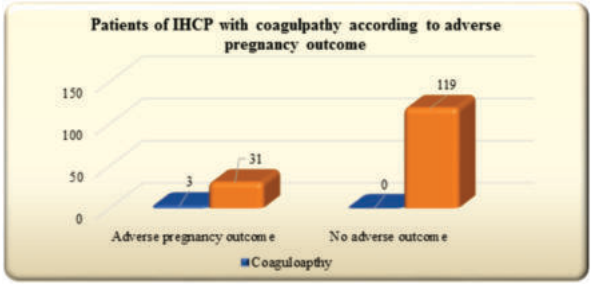

Figure 5: Distribution of patients of IHCP with coagulopathy according to adverse pregnancy outcome

Table 6: Distribution of patients of IHCP with adverse pregnancy outcome according to presence of coagulopathy

Variables		Coagulopathy	
		Yes N (%)	No N (%)
Post-partum hemorrhage	Yes	3 (100)	14 (9.33)
	No	0 (0.00)	136 (90.66)
Blood transfusion	Yes	3 (100)	13 (8.66)
	No	0 (0.00)	137 (91.33)
ICU admission	Yes	3 (100)	3 (2.00)
	No	0 (0.00)	147 (98.00)
Maternal mortality	Yes	1 (33.33)	0 (0.00)
	No	2 (66.66)	150 (100)

Meconium-stained liquor	Yes	3 (100)	23 (15.33)
	No	0 (0.00)	127 (84.66)
Intraventricular hemorrhage	Yes	3 (100)	5 (3.33)
	No	0 (0.00)	145 (96.66)
Neonatal Jaundice	Yes	3 (100)	20 (13.33)
	No	0 (0.00)	130 (86.66)
Still birth/IUD	Yes	0 (0.00)	4 (2.66)
	No	3 (100)	146 (97.33)
Total		3 (100)	150 (100)

Study	Adverse Maternal Outcome	Adverse Foetal Outcome
Senocak GNC et al	11%	40%
Ovadia C et al	-	29%
Marathe JA et al	10.3%	23.1%
Present Study	11.1%	15%

DISCUSSION

Out of all the pregnant patients admitted and delivered in our hospital during above mentioned time period, 153 had IHCP and amongst these 153 women only 3 had coagulopathy and majority of the women had no coagulopathy. The prevalence of IHCP in our study was found to be 5.1% but the reported prevalence in other studies is in the range of 1% to 3% depending upon the geographical location of the patients. Coagulopathy in pregnancy increases the probability of maternal and foetal adverse events manifold.. 34 out of 153 patients(22%) with IHCP had adverse pregnancy outcome, these outcomes were in the form of low APGAR score, still birth/ Intra-uterine death, requirement of NICU admission, meconium-stained liquor and intraventricular haemorrhage and maternal or foetal deaths..Corroborated by past studies, the risk to foetus is more as compared to the mother with increased risk in cases with more abnormally pronounced liver function test[12]. The studies done in the past have put the risk in the similar range as our present study and the table below summarises these findings compared to the present study.

Pruritis[12,16] which is usually new onset and found the second or third trimester is in most IHCP patients and is due to increased bile acids and found statistically significant. The second most common symptom was icterus also a marker for increasing bile acids and more statistically significant. Both these symptoms with increased bile salts in the blood, correlates with adverse pregnancy outcome[12]. In Study by Hafeez et al, pruritis was seen in 83% of patients while icterus was seen in only 6.5%. This pruritis is often present in the extremity and precedes the elevation of bile acids as seen in certain studies[16]. However IHCP is a diagnosis of exclusion and other conditions like pruritis gravidarum, pemphigoid gestations, atopic dermatitis etc should be excluded before branding the patients with pruritis in IHCP.[17]

The underlying pathology is manifested in lab investigations as deranged Liver Function Tests with increased SGOT/AST and SGPT/ALT along with Bilirubin[17]. The markers of patients with adverse outcome were significantly higher In our present study, unlike previous studies, we measured SGOT/AST and SGPT/ALT and did not explore the relation of bile acids. Juusela AL et al[17] found that high bile acid levels of mother is a strong predictor of the adverse foetal outcome. While in the study by Juusela AL et al, the cut-off level of AST was 62 IU/L and Bile Acids was 42µmol/L for predicting adverse foetal reaction, in the study by Pusl T et al[12] the bile acid level cut-off was 40µmol/L while the outcome was similar in both the studies. Rook M et al[15] in their study also had similar findings with adverse foetal outcome in IHCP, the mean ALT was 62 IU/L and increased level of all Bile acid levels specially Cholic acid. Çetinkaya Demir B et al[18] noted the AST and ALT levels as high as 1000 and 881 IU/L respectively and serum bile acid levels of 178.1. These high levels were linked to adverse foetal outcome similar to our present research. Gao XX et al[19] in their study found a significant difference between the control and patients with IHCP, the median values of SGOT/AST, SGPT/ALT and Serum Bilirubin being 66, 58 and 10 as compared to 29 U/L, 18 U/L and 7.45µmol/L respectively. The increase in bile acids is not only an underlying pathology in the occurrence but also is an essential marker for the diagnosis and in a similar manner previous studies have linked the increasing values to the adverse outcome. The present study also finds a significant relation between the high values and outcome.

The pregnancy outcome was different for IHCP patients with or without coagulopathy, table 7 of the result clearly demonstrates that the foetal outcome like MSL, neonatal jaundice, IVH, NICU admission and IUD was more pronounced in the females who had coagulopathy along with IHCP. Similarly maternal morbidity with coagulopathy was more. Out of 3 who had coagulopathy, there was one death while ICU admission and PPH was seen in each one of them. Suresh I et al[13] also found that while coagulopathy was significantly linked to the adverse foetal outcome, the relation with adverse maternal outcome was not present. Review by Pusl T et al[12] also reveals a similar picture but did not differentiate between coagulopathy in IHCP and its relation with adverse outcome.

Coagulopathy is a rare phenomenon in pregnancy, while IHCP can be one of its causes during pregnancy, the major causes of coagulopathy in pregnancies can be placental abruption, amniotic fluid embolism, and retained products of conception in utero, however irrespective of the causes, the results are generally catastrophic, and the chances of maternal morbidity and mortality increases manifold. As evident from our study too, all the patients with coagulopathy had post-partum hemorrhage, required ICU admission and blood transfusion.

Apart from early diagnosis, IHCP should be managed properly during the pregnancy, the management is mostly symptomatic however coagulopathy requires aggressive management[20] as the risk of post-partum haemorrhage is more in such females and Vitamin-K is given as soon as the diagnosis is made. The guidelines suggest a step-wise approach in dealing with the symptom of pruritis. The direction of treatment should include elimination of pruritis causing agents like bile acid sequestrants, rifampicin, etc. which target the metabolism,[12] Ursodeoxycholic acid as a treatment is proved to be beneficial in not only the symptomatic relief in cholestatic pruritis but has shown good results in mitigating the adverse outcome in IHCP. Dexamethhasone was also studied as a treatment option as it decreases the total bile levels and provide symptomatic relief however there is a risk of fatal exposure to antenatal corticosteroids[16].

Our study not only studied the adverse events in the pregnancies who had IHCP but also tried to explore the ignored topic of coagulopathy in such patients and from the results it is clear that the pregnant female with IHCP are at increased risk of pre-term birth, this risk becomes tremendously pronounced in the females who had coagulopathy in IHCP, though a very small number of IHCP patients suffer from the coagulopathy, the watchfulness should be commenced during the diagnosis with an anticipation of adverse outcome

SUMMARY & CONCLUSION

The study was aimed to find out the incidence of IHCP & coagulopathy in IHCP patients along with maternal and foetal outcome in IHCP patients.

In our study the Prevalence of IHCP was 5.1% and coagulopathy affected 2% of the total patients with IHCP. 22.2% of the patients had adverse pregnancy outcome and among them 17 patients (11.11%) had adverse maternal outcome while 23 patients (15.03%) had adverse foetal outcome. There was 1 maternal death while 4 intrauterine deaths. Pruritis was present in 123 out of all 153 patients with IHCP. Patients with adverse outcome had significantly high AST (SGOT), ALT (SGPT), PT-INR as compared to other patients. There was increased risk of meconium stained liquor, pre-term birth, NICU admission, blood transfusion, IUD as well as Maternal Deaths in patients with coagulopathy.

In conclusion it can be said that, Intra-hepatic cholestasis of pregnancy is a not an uncommon pathology during pregnancy that usually presents in third trimester with pruritus. The condition can be more dangerous to foetus as compared to mother and should be diagnosed early by keeping a watch on the symptoms of pruritis along with an increase in the biomarkers like bile acids and AST/ALT. The treatment should be started immediately using standard guidelines and the pregnancy should be monitored with continuous foetal surveillance and preferably should not be carried beyond 37 weeks if disease is not stabilised.

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