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MATERNAL AND PERINATAL OUTCOME IN CASES OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Gynaecology

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ABSTRACT

Objective: The objective of our study was to compare the maternal and perinatal outcome in pregnancies affected by intrahepatic cholestasis of pregnancy (ICP) when compared to normal pregnancies delivering at the same gestational age.

Material and methods: This s a case control study conducted in a tertiary hospital over a period of 2years from December 2018 to December 2020. Our study included 100 patients who were divided into 2 groups. Group A included 50 patients who were affected by ICP and group B included 50 patients with normal or low risk pregnancies.

Result: The mean age of women suffering from ICP was 30 years. The mean gestational age at the onset of pruritus was 32weeks.The mean age of diagnosis of ICP was at the gestational age of 33weeks. There were 29 cases of mild cholestasis (bile acid [BA] ≤10 µmol /L) and 15 cases of moderate cholestasis (BA≥40 but≤ 99 µmol/L) and 6 cases of severe cholestasis. There were 4 still birth and 2 intrauterine deaths in the ICP group and no cases of intrauterine fetal deaths in the control group. The rate of respiratory distress syndrome was higher in neonates of women with ICP 62% versus 06%. The 78% neonates of ICP group required NICU admission of which 44% were ventilated. Among the control group there were 3 cases of respiratory distress and 4 of the neonates required NICU admission of which 1 required mechanical ventilation. The rate of cesarean section in ICP group was 64% as compared to control group where it was 16 %. The postpartum hemorrhage rate was twice as high among the case mothers as compared to the control group,22% versus 3%.

Conclusion: ICP increases maternal morbidity and is also associated with adverse perinatal outcome like increased risk of preterm birth, respiratory distress, increased admission to neonatal intensive care unit, still birth and sudden intrauterine deaths at term.

KEYWORDS

INTRODUCTION

Intrahepatic cholestasis of pregnancy also known as pruritus gravidarum or idiopathic jaundice of pregnancy is characterized by pruritus in the absence of skin rash with elevated bile acids and aminotransferases level, occurring in the second or third trimester of pregnancy and with spontaneous relief of signs and symptoms within two or three weeks of delivery [1,2]. The ICP is most common liver disease during pregnancy. The incidence of obstetric cholestasis of pregnancy is 1.2-1.5% in the Indian-Asian women [3]. The clinical importance of obstetric cholestasis lies in the potential fetal risk which may include spontaneous preterm birth, iatrogenic preterm birth, still birth, intra utero death, meconium-stained amniotic fluid, respiratory distress syndrome, neonatal intensive care unit admission. The prevalence of in utero and perinatal mortality is estimated at 0.5%. Severe cholestasis with higher bile acid levels is associated with a higher risk of fetal complications [4,5].

Also increased maternal CS rate has been subsequent to early intervention that is early induction in case of ICP and thereby increasing maternal morbidity and prolonged hospitalization. There can also be maternal morbidity in association with the intense pruritus and consequent sleep deprivation [6]. Apart from distressing pruritus prolonged and severe ICP can cause coagulopathies due to vitamin K deficiency leading to increased incidences of postpartum hemorrhage noted amongst cholestasis women group as compared to the control group. ICP recurs during subsequent pregnancies in 40-60% cases with varying severity of recurrent episodes [7]. Overall maternal prognosis is good and symptoms resolve rapidly within 48hours of delivery.

The mechanism relating cholestasis to stillbirth remains uncertain. Several studies have shown that high BA levels have a harmful effect on cardiomyocytes which might induce fetal arrhythmias leading to stillbirth [8].

The prenatal management and optimal delivery time remain unclear in cases of ICP. The recommendations of various national professional societies for time to delivery in ICP complicated pregnancies are also divergent. The Royal College of obstetrics and Gynecology does not endorse routine early delivery of these pregnancies [9] while the American College of Obstetrician and Gynecologists supports active management, induction of labour protocols for ICP [10]. However, the aim of active attitude is to avoid stillbirth.

Our study is aimed to evaluate the neonatal and maternal outcome in cases of ICP with routine induction when compared to low-risk normal pregnancy control group.

MATERIALAND METHOD:

This is a case control study conducted at a tertiary hospital, Patna medical college and hospital, Patna, over a period of 2 years from December 2018 to December 2020.The study included 100 women who were divided into 2 groups of 50 women in each group. Group A included 50 women who were diagnosed as cases of ICP. Group B included 50 women with normal pregnancy or low risk pregnancy.

The diagnosis of cholestasis was made when there was association of pruritus along with bile acid levels ≥10µmol/l (all other causes of itching and liver dysfunction were ruled out), and also post-delivery there were normalization of biochemical parameters and symptoms as well.

Inclusion criteria for the case group were

A) singleton pregnancy
b) cephalic presentation
c) no fetal congenital malformation
d) no maternal medical illness requiring preterm induction
e) no obstetric disorder requiring preterm induction

Exclusion criteria for the study group were

a) recurrence of cholestasis over the study period (each woman was included only one time)
b) multiple pregnancy
c) congenital malformation in the fetus
d) chromosomal abnormalities in the fetus

The control group was matched for maternal age (± one year), date of delivery (same calendar year), same parity but did not having ICP.

In our study we collected demographic characteristics, pregnancy related history, obstetric outcomes, including term at delivery, spontaneous or induced labour, mode of delivery, meconium-stained liquor during labour, birth weight, postpartum hemorrhage (defined as blood loss ≥500ml) and indicated transfusion in both case and control group.

For neonatal status adverse neonatal outcome was defined as pHa<7.10. Apgar score <7 at 5 minutes intubation, NICU admission or perinatal deaths. Cholestasis severity was defined by bile acid levels. If BA ≥10 but ≤ 39 µmol/L it was mild cholestasis, if BA ≥40 but ≤ 99 micromol/L it was moderate cholestasis and severe if BA≥ 100micromol/L.

The ethical committee approval was taken and recruitment of patients were done after taking written informed consent.

STATISTICALANALYSIS

The neonatal and maternal outcomes of cases and control were compared as mean, median, standard deviation and percentage. The differences were defined as significant when p<0.05.

RESULT

Our study was conducted between December 2018 to December 2020 at a tertiary hospital in Patna medical college and hospital, Patna. A total of 100 100 women of the study group delivered at this tertiary centre.

Table1: Maternal characteristics of the ICP women and control group women

Sl. no.	Maternal characteristics	ICP group (n=50)	Control group(n=50)
1.	Maternal age in years	30(25-35)	30(23-35)
2.	Parity a) nullipara b) multipara	 44 06	 41 09
3.	BMI (kg /m2)	21.9(20-25)	22.8(21-26.2)
4.	Severity of cholestasis a) mild b) moderate c) sever	 29 15 06	 NA NA NA

Table 1 summarizes the maternal characteristics of the ICP group and the control group. There was no significant difference in the baseline characteristics of the two group as seen from the table 1. The average maternal age was 30 years in both the groups. The average BMI was also similar in both the groups. The study included 29 women with mild cholestasis,15 with moderate cholestasis and 6 cases of sever cholestasis.

Table 2: Maternal Symptoms In Icp Group

Sl. no.	Characteristics	ICP group n (%)
1.	Excessive pruritus	12(24%)
2.	Sleep deprivation	7(14%)
3	Anxiety secondary to pruritus and sleep deprivation	5(10%)
4	More than one symptom	14(28%)

Table 2 shows the various maternal symptoms in the ICP group of women. The most common symptom was pruritus in 24% of the women, which even lead to anxiety and sleep deprivation in 10% of the women of the ICP group.

Table3: Maternal outcome of the ICP and control group

Sl.no.	characteristics	ICP group	Control group
1.	Induction of labour	40(80%)	8(16%)
2.	Mode of delivery a) vaginal delivery b) caesarean section	18(36%) 32(64%)	42(84%) 08(16%)
3.	Postpartum haemorrhage	11(22%)	3(06%)
4.	Maternal transfusion	11(22%)	2(04%)

Table 3 shows the maternal obstetric outcome in both the groups. Active obstetric management resulted in induction of labour in 40 out of 50 women of ICP group compared to 8 out of50 women of the control group(p<0.001). The induction rate was significantly higher in the ICP group 80% as compared to control group which was only 16%. In the ICP group rate of caesarean section was higher which was 64% as compared to control group where it was only 16%.The vaginal delivery rate was more in the control group which was 84% and only 36% in the ICP group. The table shows that the rate of postpartum haemorrhage was higher in the ICP group which was 22% and it was only 6% in the control group.

Table 4: Neonatal outcome of the ICP and control group.

Sl. no.	characteristics	ICP(n=50)	Control(n=50)
1.	Mean gestational age at birth in weeks	37(34-38)	38(39-40)
2.	Preterm delivery at <37 weeks	38(76%)	4(08%)
3.	5 minutes Apgar score<7	37(74%)	3(06%)
4.	Admission to neonatal intensive care unit	39(78%)	4(08%)
5.	Respiratory distress syndrome	31(62%)	3(06%)
6.	Mechanical ventilation or intubation	22(44%)	1(02%)
7.	Meconium-stained fluid	6(12%)	4(08%)
8.	still birth	4(08%)	0
9.	intrauterine death	2(04%)	0
10.	birth weight in grams	2.2(2-2.6gm)	2.9(2.7-3.2gm)

The mean birth weight was 2.2grams in the case group whereas it was 2.9grams in the control group(p<0.001). The neonates who were exposed to cholestasis had a greater risk of having respiratory distress in comparison to the control group. The incidence of RDS in the ICP group was 62% as against 6% in the control group(p<0.001). The rate of admission to neonatal intensive care unit was very high in the ICP group (78%) as compared to control group (8%). There were 4 still birth and 2 intrauterine deaths in the ICP group and no fetal demise in the control group. The rate of meconium stained liquor was almost same in both the groups, 12% in ICP group and 8% in the control group.

DISCUSSION

Intrahepatic cholestasis of pregnancy is associated with adverse perinatal outcome and also increased maternal morbidity. In this study we aimed to quantify the adverse perinatal effects of ICP. Iatrogenic preterm birth is a major contribution to the high prevalence of preterm birth in intrahepatic cholestasis of pregnancy than in control pregnancies. In our study we found a higher rate of RDS and neonatal morbidity among neonates of the cholestasis group. The RDS rate was significantly higher in the among the neonates of the cholestasis group which was consistent with the findings from other studies. Zeeca et al, in a case control study showed a risk of RDS in ICP new-borns 2.5 times higher than in control infants (28.6% vs 14%) regardless of bile acid levels [5].In our study the rate of respiratory distress syndrome amongst the ICP group was 62% as compared to only 6% in the control group which was statistically significant. Also, mothers with ICP had more postpartum haemorrhages than control group and also required more blood transfusion. Maternal morbidity was more in the ICP group than in the control group who delivered in the same late preterm period [11]. Hypothesis to explain increased neonatal morbidity among case infants include a direct effect of BA on neonatal lung, which could include a "bile acid pneumonia"[5,12]. BA have been found detectable in the bronchoalveolar lavage fluid of case neonates affected by RDS, some authors have speculated that BA inhibits surfactant activity [12]. The PITCHES trial outcome was to evaluate perinatal outcome in ICP affected pregnancies of ursodeoxycholic acid versus placebo [13]. Authors founded that treatment with ursodeoxycholic acid does not reduce adverse perinatal outcome.

With ICP reported still birth rates vary between 0.4% and 7% [14,15]. The risk of stillbirth also increased after 37 weeks and with increased bile acid levels>100µmol/L or more [16]. In ICP, stillbirth prevention must be weighed against the long-term consequences of "late preterm" birth. American College of Obstetrician and Gynaecologist recommends active management in ICP cases however it does not define an ideal term for childbirth [10]. There are two studies that advocate 36 weeks of gestation is the best compromise between the risk of preterm birth and risk of stillbirth or neonatal death [17,18]. Consistent with our study Royal College of obstetrics and Gynaecology does not recommend systematic active management [9]. In our study planned caesarean rate was significantly higher in ICP cases than the control group. Also induction of labour for women with ICP increased the caesarean section rate. The postpartum haemorrhage rate was also higher in the ICP cases properly due to liver dysfunction and vitamin K deficiency. There was also increased transfusion rates and maternal haemostasis problem in the ICP group. This result was unlike study done by Brouwers et al [19].

CONCLUSION

Intrahepatic cholestasis of pregnancy increases maternal morbidity

and is, associated with adverse perinatal outcome including respiratory distress syndrome, preterm birth, still birth, fetal distress, meconium-stained liquor, sudden intrauterine death at term, increased NICU admission as evidenced from this study. A timely intervention will help in reducing these adverse outcomes.

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