Original Article

Cholestasis of Pregnancy : A Prospective Study

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Abstract

Background: Intrahepatic cholestasis of pregnancy (ICP) typically occurs during the last trimester of gestation. The most accurate marker for diagnosis and follow-up of ICP is increased total bile acid levels (above 11.0 micro mol/L) [1]. ICP is a benign disease with no consequences to the mother but it is associated with an increased rate of fetal morbidity and mortality.
Method: A prospective study was carried out in 1500 deliveries which included 27 cases of ICP. The mode of delivery, complications and fetal outcome of intrahepatic cholestasis group were compared with rest of the deliveries. Cases having pruritic lesions of skin, viral hepatitis, gall stones, autoimmune liver diseases were excluded. Random selection of 300 pregnancies in the control group was done and their liver function tests were carried out for comparison. All the patients with cholestasis of pregnancy were treated with ursodeoxycholic acid.
Result: The levels of the aminotransferases and alkaline phosphatase levels rose significantly ($p < 0.05$) in the study group. Cholestatic group did not have any significant difference in mode of delivery or fetal outcome from the control group. The patients in the study group were treated with ursodeoxycholic acid with significant relief in symptoms ($p < 0.01$), while improvement in serum bilirubin levels, alkaline phosphatase levels and aminotransferases levels were not statistically significant.
Conclusion: In absence of serum bile acids levels, alkaline phosphatase and aminotransferases levels may help in diagnosis and management of cholestasis of pregnancy. Ursodeoxycholic acid treatment is effective in reducing the pruritus.

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Key Words : Serum bilirubin; Alkaline phosphatase; Aminotransferases; Ursodeoxycholic acid; Cholestasis

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus, elevated serum aminotransferases and bile acid levels with onset in the second or third trimester of pregnancy. There is spontaneous relief of signs and symptoms within two to three weeks after delivery. There is a wide demographic variation, with highest incidence from South America e.g. Chile, Bolivia (6-27%) and lowest in Europe (0.2%). Both genetic and hormonal factors appear to play important roles in its development [2]. A strong family history of cholestasis of pregnancy may be typically described by the patient [3]. The most predictive and accurate markers for diagnosis and follow-up of ICP are increased total bile acid levels (> 11.0 micromol/L), enhanced cholic acid percentage (> 42%) and decreased glycine/taurine bile acid ratio (below 1.0). Cholestasis is evaluated by measuring alkaline phosphatase, bilirubin, 5'-nucleotidase or gamma glutamyl transpeptidase levels [4].

Maternal prognosis is good and symptoms resolve rapidly after delivery, accompanied by normalization of serum liver tests. Persistent abnormalities should prompt reconsideration of other underlying chronic liver diseases like primary biliary cirrhosis, primary sclerosing cholangitis or chronic hepatitis C. ICP recurs during subsequent pregnancies in 45-70% cases with varying severity of recurrent episodes. ICP increases the risk of preterm delivery (up to 19–60%), meconium staining of amniotic fluid (up to 27%), fetal bradycardia (up to 14%), fetal distress (22–41%) and fetal loss (0.4-4.1%), particularly when associated with fasting serum bile acid levels > 40 µmol/L [5]. The pathogenesis of fetal complications is still poorly understood, although a role for bile acids or toxic metabolites of bile acids has been suggested.

Ursodeoxycholic acid (UDCA) treatment has shown to reduce the bile acid content in the fetal compartment, while restoring the ability of the placenta to carry out vectorial transfer of these compounds towards the mother, decreasing bile acid levels in maternal serum and its passage to the foetus. In addition, UDCA administered to the mother also lowers the amount of bile acids present in colostrum without either increasing the UDCA concentration or causing major changes in lithocholic acid levels [1]. The measurement of bile acid levels in the blood is diagnostic, but it is not commonly available. Hence we used alternate markers and clinical presentation for the management of this disease.

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Table 1

Liver function test in ICP and Control group

	Control group n=300	ICP group n=27	t value of difference	p value #
Age				
Mean (SD)	25.078 (±3.24)	25.815 (±3.64)	-1.016	0.158
Serum bilirubin				
Mean (SD)	0.709 (±0.15)	0.893 (±0.57)	-1.664	0.055
AST				
Mean (SD)	36.404 (±25.77)	70.333 (±88.54)	-1.984	0.029 (S)
ALT				
Mean (SD)	32.538 (±18.24)	88.296 (±119.5)	-2.422	0.011 (S)
Alkaline phosphatase				
Mean (SD)	183.208 (±62.27)	631.407 (±393.2)	-5.917	< 0.001(S)

SD - Standard deviation; AST - aspartate transaminase; ALT- alanine transaminase; # - p values are all one - tailed probabilities

Methods

A prospective study was carried out in 1500 deliveries including 27 cases of intrahepatic cholestasis of pregnancy from May 2004 to Apr 2007. Their mode of delivery, complications and fetal outcome of intrahepatic cholestasis was compared with rest of the deliveries. Cases having pruritic lesions of skin, viral hepatitis, gall stones, autoimmune liver diseases were excluded. Systematic random selection of 300 pregnancies (taking every 5th woman) in the control group was done and their liver function tests including serum bilirubin, aminotransferases and alkaline phosphatase were carried out for comparison. Criteria of raised serum aminotransferases (>30 IU/L) and alkaline phosphatase (>300 IU/L) in patients with pruritus of pregnancy in absence of any dermatosis, viral hepatitis, cholelithiasis and autoimmune liver disorders was used for diagnosis of ICP. All patients with ICP were treated with ursodeoxycholic acid. Statistical analysis was done with t tests of difference and Fisher exact test. All ICP group patients were given vitamin K from 32 weeks onwards and delivered by 38 weeks to avoid intrauterine death. In cases of jaundice not responding to UDCA treatment, delivery was done after 34 weeks.

Results

During the study period, 27 (1.8%) pregnancies were diagnosed as ICP out of total 1500 pregnancies. There were no significant differences in the maternal age, race or parity between the two groups. The mean age of the mothers in both groups was slightly over 25 years and majority were nulliparous (48% in control vs 52% in ICP group) .

There was no significant rise in the serum bilirubin (p = 0.0551), but the aminotransferase levels were significantly raised (p = 0.029 for AST and 0.011 for ALT). The level of alkaline phosphatase rise was highly significant (p= 0.000002). On an average, serums aminotransferases were raised two to three times and alkaline phosphatase levels by three to four times above the control in most of the pregnancies (Table 1).

There was lower mean birth weight (2.792 kg vs 2.869 kg), higher incidence of fetal distress (18.52% vs 8.67 %), higher incidence of caesarean section (29.63 % vs 22.67 %), higher incidence of meconium staining (18.52% vs 15 %) and preterm birth (14.81% vs. 6.33%) but these differences were statistically not significant (Table 2). There was no increase in perinatal mortality or morbidity. Out of 27 patients treated with ursodeoxycholic acid (UDCA), only three (11.11%) had residual pruritus after treatment (Table 3).

Table 2

Comparison of fetal outcome in ICP and Control group

	Control group n=300	ICP group n=27	t value	p value
Birth weight				
Mean	2.869	2.792	0.69	0.7499
SD	0.416	0.566		
Fetal distress##	26 (8.67%)	5 (18.52 %)		0.158#
LSCS	68 (22.67%)	8 (29.63%)		0.475#
Vacuum/forceps	21 (7%)	2 (7.41%)		1#
PIH	16 (5.33%)	2 (7.41%)		0.652#
Meconium stained liquor	45 (15%)	5 (18.52%)		0.582
Preterm delivery	19 (6.33%)	4 (14.81%)		0.109
Still birth	1 (0.33%)	0		1#

Fisher Exact Test; ##- manifested by fetal bradycardia, variable or late decelerations;

Discussion

The frequency of ICP in our study was 1.8 % (95% confidence interval 1.12%-2.48%), while the average incidence varies from 0.1-1% and it is higher amongst Asian women [6]. The pathogenesis is multifactorial, with higher estrogen levels being the main implicating factor [7]. Genetic factors are also likely as many women have a family history and recurrence is common. In this study no family history could be elicited in the ICP group, only two women experienced similar complaints in previous pregnancies. Low incidence of recurrence may be due to fact that majority (52%) were primipara. There were no twins in the ICP group.

The liver function tests may be suggestive of cholestasis although there is no uniform agreement on the criteria for diagnosis. Serum transaminases may be

Table 3

Effect of ursodeoxycholic acid treatment on liver function tests in ICP group (n=27)

	Before treatment	After treatment	Fall (%)
Pruritus	27	3	89.9
Serum Bilirubin (mean)	0.893	0.875	2.97
AST (mean)	70.333	29	58.77
ALT (mean)	88.296	32.375	63.33
Alkaline phosphatase (mean)	631.407	489.125	22.54

AST - aspartate transaminase; ALT - alanine transaminase

elevated 2-10 fold or greater, bilirubin may be 6 mg/dl and alkaline phosphatase may be elevated four fold. In our study, aminotransferases were increased by two to three times and alkaline phosphatase three to four times above normal, which was statistically significant.

The incidence of intrapartum meconium staining of amniotic fluid varies from 12-22% in a normal pregnancy and 25% in ICP. It is considered as a warning signal of possible fetal distress. However, animal studies show that high maternal bile acid levels stimulate fetal colonic motility, causing the fetus to void meconium. We had an incidence of 18.42% in the study group.

The mechanisms of preterm delivery in ICP is not clear, but studies show an increased response of myometrial strips from healthy women to oxytocin and an increased oxytocin-receptor expression after being incubated with cholic acid [8]. 14.81% deliveries in ICP group resulted in preterm deliveries as compared to 6.33% in control group. In some studies, upto 44 % preterm deliveries have been observed in ICP [7].

The policy of early delivery has decreased the perinatal mortality rates to 2-4% from earlier rates of 11% [7]. Studies show an alteration to electrical signaling in myocytes following exposure to bile acids [8].

No single test is diagnostic. An increase in serum bile acids maybe the only biochemical marker of obstetric cholestasis. The sensitivity of bile acids as a predictive marker of outcome is also debated [9].

Fetal outcome may be improved with increased antenatal surveillance, although obstetric cholestasis has not been shown to produce changes either on doppler or on cardiotocograph and has no increased rates of small for gestational age infants [9].

The role of drug therapy has not been established by a large randomized control trial but certain treatments including ursodeoxycholic acid [10] and dexamethasone appear effective in small series. These measures do not improve fetal outcome but can be helpful for symptom control and are well tolerated. In this study, UDCA treatment alleviated pruritus and reduced levels of aminotransferases and alkaline phosphatase. Delivery should be planned around 37-38 weeks to prevent the increased risk of stillbirth and earlier if there is suspicion of compromised fetal and maternal status [7]. Parenteral vitamin K helps in correcting prothrombin deficiency. Symptoms usually abate within two weeks of delivery. There is a significant risk of recurrence with subsequent pregnancies and with the use of oral contraceptives or other estrogens.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Lt Col G Singh
Drafting & Manuscript Revision : Lt Col G Singh
Statistical Analysis : Lt Col G Singh
Study Supervision : Lt Col G Singh, Maj K Sidhu

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