FETAL OUTCOME OF ACTIVE MANAGEMENT OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY AMONG PREGNANT WOMEN PRESENTING AT TERTIARY CARE CENTRE

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Abstract:
Introduction: Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by maternal pruritis in the third trimester, raised serum bile acids and increased rates of adverse fetal outcomes. So far, the outcome of active management of ICP has not been routinely practiced. So we conducted this study to find the beneficial role of active management of ICP.

Objective: To determine the fetal outcome of ‘active management’ of intrahepatic cholestasis of pregnancy among pregnant women presenting at a tertiary care center.

Material & Methods:
Study Design: Descriptive case series
Setting: Gynecological units of Lady Willingdon Hospital, Lahore. Duration: 6 months from 1st June 2014 till 30th November 2014.
Data collection: Total 300 patients were included and given active management. It consists of chlorpheniramine and topical emollients. Ursodeoxycholic acid was added if itching/pruritis persists. Vitamin K supplementation was commenced by 34 weeks. All women had undergone alternate day cardiotocograph monitoring, weekly ultrasonographic assessment of liquor volume and two weekly ultrasound assessment of growth. Elective delivery was offered at 37–38 weeks of gestation. The patients were followed up the birth of neonate for the outcome parameters i.e. fetal bradycardia, meconium passage and fetal loss.

Results: Mean age of all these females was 28.72±3.84 years. Fetal bradycardia was observed in 18(6%) fetuses while the remaining 282(94%) fetuses were normal. Meconium passage in 22(7.3%) fetuses and fetal loss was seen in 5(1.7%) cases.

Conclusion: It was concluded that active management of ICP can produce good outcome results while minimizing the fetal complications.

Key Words: Fetal outcome, Active management, Intrahepatic Cholestasis

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INTRODUCTION:
Intrahepatic cholestasis of pregnancy (ICP) is a reversible type of hormonally influenced cholestasis. It frequently develops in late pregnancy in individuals who are genetically predisposed [1]. It is the most common pregnancy-related liver disorder [2,3]. The incidence varies according to geographical location and ethnic background with rates of up to 15% in Chile and Bolivia and less than 1% in Europe [4,5]. It affects 1.2–1.5% women of Indian Asian or Pakistani-Asian origin [6].

It is characterized by generalized itching, often commencing with pruritis of the palms of the hands and soles of the feet, with no other skin manifestations. It most often presents in the late second or early third trimester of pregnancy. The condition rarely presents before 25 weeks gestation, with 80% of women presenting after 30 weeks gestation [5]. The condition typically resolves within 48 hours of women giving birth, with biochemical markers predominantly becoming normal within 2-4 weeks postnatally [8].

From a maternal viewpoint, the main consideration is intense pruritis, which may become so intolerable that delivery is considered as early as 35-37 weeks [9]. The fetal viewpoint is more concerning, as even with modern treatment the risk for fetal demise can range from 2-11 %. Thus, many would advocate induction at 37 weeks gestation [10,11]. Since fetal death rarely occurs before 36 weeks’ gestation, many authors, as noted above, favor delivery when 37 weeks gestation is reached [12].

Active management of the patients with ICP consists of palliation of their pruritis initially with chlorpheniramine and topical emollients. Ursodeoxycholic acid (starting dose 900mg/day), vitamin K supplementation (10mg orally daily), alternate day cardiotocograph monitoring, weekly ultrasonographic assessment of liquor volume and two weekly ultrasound assessment of growth and offering the elective delivery was offered at 37–38 weeks of gestation [13]. In another study by Jain R, et al, there were 69 patients who received active management of obstetric cholestasis consisting of chlorpheniramine, Ursodeoxycholic acid (starting dose 900mg/day), vitamin K supplementation (10mg orally daily), alternate day cardiotocograph monitoring, weekly ultrasonographic assessment of liquor volume and two weekly ultrasound assessment of growth and offering the elective delivery was offered at 37–38 weeks of gestation. There were no stillbirths (0%) in the study. No episode of fetal asphyxia (0%) or bradycardia (0%) was observed. The overall rate of meconium passage was 7.46%. However, there was no case of meconium aspiration syndrome (0%) [14].

The rational of my study is 1). The protocols of the management of intrahepatic cholestasis are not completely defined in literature. The current management consists of ICP is early induction of labor regardless of the condition of term. 2). However, the study by Jain R, et al have shown promising fetal outcome (in terms of still birth, fetal asphyxia, bradycardia and meconium passage) with the active management of the patients with obstetric cholestasis. 3). So far, the outcome of active management of obstetric cholestasis has not been routinely practiced and is not taken as gold standard. 4). Previously, no such local study is available for the at least last 10 years. (I have searched google, pubmed, and pakmedinet). 5) The results of this study will help us to know whether active management should be adopted among our patients or not. The active management of the patients with intrahepatic cholestasis of pregnancy will be done if it showed good outcome.

OBJECTIVE
To determine the Fetal Outcome of ‘active management’ of Intrahepatic Cholestasis of pregnancy among pregnant women presenting at a tertiary care center

MATERIALS AND METHODS:
STUDY DESIGN: It was a case series study
SETTINGS: This study was conducted all three gynaecological units of Lady Willingdon Hospital, Lahore.
STUDY DURATION: Six months after approval of synopsis.
SAMPLE SIZE: The calculated sample size was approximately 300 patients with 3% margin of error, 95 % confidence level taking expected percentage of meconium passage i.e. 7.46%.
SAMPLING TECHNIQUE: Non probability consecutive sampling.

SAMPLE SELECTION:
INCLUSION CRITERIA:
• Age: 20 – 40 years
• Singleton pregnancy at >25 weeks of gestation with complaints of itching/pruritis in palms soles, jaundice and diagnosis of intrahepatic cholestasis (the complaint of itching without a skin rash. Laboratory investigations show
bilirubin level (>1–5 mg/dl) and serum transaminases ranging from 50 - 250 IU/ml)

EXCLUSION CRITERIA:
- Women with positive serology for Hepatitis A, B or C,
- Patients with cholecystitis (assessed on USG of abdomen, positive Murphy’s sign on examination and deranged liver function tests)
- The patients in whom liver function did not normalize within two weeks of delivery will be excluded from this study

DATA COLLECTION PROCEDURE:
Informed verbal consent was taken from the patient and then all the information was collected on pre-designed performa. General data including age and parity was collected. All the patients were offered with active management. It consists of chlorpheniramine (maximum 4mg tds) and topical emollients. Ursodeoxycholic acid (900mg/day) was added if itching/pruritis persists. Vitamin K supplementation (10mg orally daily) was commenced by 34 weeks. All women had undergone alternate day cardiotocograph monitoring, weekly ultrasonographic assessment of liquor volume and two weekly ultrasound assessment of growth. Elective delivery was offered at 37–38 weeks of gestation. The patients were followed up the birth of neonate for the outcome parameters i.e. fetal bradycardia, fetal distress and fetal loss. **FETAL BRADYCARDIA:** It was assessed intrapartum and was assigned to fetal heart rate of < 100 beets / min. This was confirmed by continuous electronic FHR monitoring by CTG.

**FETAL LOSS:** It was assigned to the intrauterine death of the fetus expected to be born among pregnant women with diagnosis of obstetric cholestasis. This was confirmed by absent fetal heart sound and loss of movements.

**MECONIUM PASSAGE:** Meconium-stained amniotic fluid appearing before and during labour

**DATA ANALYSIS:**
All the collected data was entered into SPSS version 10 and analyzed. The quantitative data like age (20-40 years) that was described as mean and SD. The qualitative data i.e. the outcome parameters [fetal bradycardia, fetal loss and meconium passage] that was described as frequency and percentage.

**RESULTS:**
The mean age of all these females was 28.72±3.84 years. There were 63(21%) female in the age group 20-25 years, 121(40.3%) female were in the age group 26-30 years, 105 (35%) females were in the age group 31-35 years and 11(3.7%) female were in the age group 36-40 years. **(Table-1)**

Fetal bradycardia was observed in 18(6%) fetus while the remaining 282(94%) fetus were normal. Meconium passage was observed in 22(7.3%) fetus. Remaining 278(92.67%) fetus were not observed with meconium passage. Fetal loss was seen in 5(1.7%) cases. **(Table-2)**

**TABLE-1: AGE OF PATIENTS**

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25</td>
<td>63</td>
<td>(21%)</td>
</tr>
<tr>
<td>26-30</td>
<td>121</td>
<td>(40.3%)</td>
</tr>
<tr>
<td>31-35</td>
<td>105</td>
<td>(35%)</td>
</tr>
<tr>
<td>36-40</td>
<td>11</td>
<td>(3.7%)</td>
</tr>
</tbody>
</table>

**TABLE-2: OUTCOME**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Bradycardia</td>
<td>18</td>
<td>6.0%</td>
</tr>
<tr>
<td>Meconium Passage</td>
<td>22</td>
<td>7.3%</td>
</tr>
<tr>
<td>Fetal Loss</td>
<td>5</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
DISCUSSION:
ICP is a liver disease of as yet undefined etiology and pathogenesis. ICP is characterized by pruritis, which typically occurs in the third trimester, starts in the palms and soles and resolves postpartum. The diagnosis is confirmed by the demonstration of raised liver transaminases and/or serum bile acids. Its pathogenesis is likely to involve a genetic hypersensitivity to estrogen, and autosomal transmission has been suggested [15,16].

From the maternal viewpoint, it is essentially benign. In contrast, ICP is a condition with possible lethal outcome for the unborn child if not handled with care. Reported perinatal mortality fell from 9.2–11% in older studies to 2.0–3.5% in the more recent series, perhaps because most women were delivered by 38 weeks of gestation. Animal studies have implicated bile acids in the pathophysiology of intrauterine death and spontaneous prematurity [17,18]. Bile acids have been shown to have direct effect on fetal cardiomyocytes, on placental chorionic veins and on gut motility. Their presence in meconium may explain the observed umbilical vein constriction that meconium causes [5,18,19].

Spontaneous preterm delivery affects 12–44% of pregnancies. Interestingly, meconium passage has been reported in 86% of cholestasis associated fetal deaths [5,20]. At present, it is not possible to predict which pregnancies are at the risk of fetal complications due to obstetric cholestasis. It has also not been established whether absolute levels of maternal total serum bile acids or the severity of maternal disease can be used to predict adverse pregnancy outcome in obstetric cholestasis or whether the treatment can reduce the risk of fetal complications. Elective delivery at 37 weeks is currently suggested as the best strategy for prevention of intrauterine fetal death. However, the risk of respiratory distress syndrome when delivered at 35 weeks is 1.4% and 0.2% at 37 weeks. If future prospective studies support the correlation of deranged liver profile to fetal outcome in cholestasis, it may be justifiable to defer delivery to a later gestation than 37 weeks in women who have responded to treatment biochemically [21,22].

Although recent studies have improved understanding of the underlying pathophysiological disturbances and their association with specific symptoms in obstetric cholestasis, the pathogenesis and prognosis of pregnancy have remained obscure. Various strategies have been proposed to improve obstetric outcome. Nevertheless, in several studies, the investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance, and that delivery after establishment of fetal lung maturity may reduce fetal mortality rate [23].

A review of the series which reported the rate of meconium stained amniotic fluid in cases of fetal deaths associated with obstetric cholestasis reveals that meconium passage precedes fetal death in 86% of cases. Such rate is significantly higher than that of meconium passage associated with fetal death in general obstetric population. The overall rate of meconium passage was 7.46%. Although likely to be significantly increased, these rates are much less than previously reported (25–58%) [17,20,24]. ICP increases the risk of preterm delivery (up to 19–60%) [17,20,25], meconium staining of amniotic fluid (up to 27%) [26], fetal bradycardia (up to 14%) [20], fetal distress (up to 22–41%) [20,23] and fetal loss (up to 0.4–4.1%) [12,20,24].

In this study fetal bradycardia was observed in 18(6%) fetus, meconium passage was seen in 22(7.3%) fetus and fetal loss was seen in 5(1.7%) mothers. Keeping in mind the reported results in literatute reagding adverse events reagding fetal outcome results of this stuyd showed less coaplications regadng fetal outcome with active mangement of ICP. Reenu Jain studied the nature and clinical outcome of pregnancies with obstetric cholestasis on active management and to correlate perinalaloutcome to gestational age at delivery. In his results she reported that no episode of fetal asphyxia or bradycardia was observed. The overall rate of meconium passage was 7.46% (5/67). However, there was no case of meconium aspiration syndrome [14].

Results of our study is consistent with the results reported by Reenu Jain. However in this study fetal bradycardia was seen in 6% patients which was high as caomprred to that of reported by Reenu Jain as 0%, fetal loss was seen in 1.7% mothers which was also a bit high as that of reported by Reenu Jain while meconium passage rate was almost similar. These results indicate that with the active management of Intrahepatic Cholestasis of pregnancy fetal complications can be minimized.

M Padmaja in his study studies the epidemiology and outcome of pregnancy complicated by obstetric cholestasis. Results of the study showed that a higher incidence of meconium staining in amniotic fluid at delivery (17.1% vs 1.1%, p<0.005) and preterm premature rupture of membranes (8.9% vs 1.1%, p<0.01) was noted without an increase in preterm delivery rate (24.4% vs 15.6%, not significant). There
was no statistically significant difference in the following parameter — pathological cardiotocography, 1–5 minute Apgar score <7, intrauterine growth restriction, neonatal intensive care admission or perinatal mortality. There was no case of postpartum hemorrhage [27].

The results of the current study demonstrate that with active intervention of such pregnancies, the perinatal outcome improves in comparison with previous reports and results in successful outcome, similar to those observed in the general obstetric population.

CONCLUSION:
Results of current study demonstrate that with active management of the patients with obstetric cholestasis good fetal outcome can be achieved with minimized complications for the fetus [bradycarida [18/300: (6%)], meconium passage [22/300: (7.3%)] and fetal loss [5/300:(1.7%)].

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