International Journal of Public Health Asia Pacific

Open Access: e-Journal
ISSN: 2822-0587(Online)

Factors associated with obstetric cholestasis in a tertiary hospital in Nepal: A case control study

Sweta Mahato[1*], Tulika Mahato [2], Sanjeev Younjan[3], Anamika Mahato[4], Adarsh Mahaseth[5], Resham Gautam[6], Sajana Adhikari[7]

[1]Department of Obstetrics and Gynaecology, Dhulikhel Hospital, Nepal
[2]Department of Emergency Medicine, Grande City Hospital, Nepal
[3]Department of Obstetrics and Gynaecology, Scheer Memorial Adventist Hospital, Nepal
[4]Department of Paediatrics, Dhulikhel Hospital, Nepal
[5]Department of Orthopaedics, Armed Police Hospital, Nepal
[6]Department of Internal Medicine, Lumbini Medical college, Nepal
[7]Nursing Instructor, Tulsipur City Hospital, Nepal

*Corresponding author: Sweta Mahato, swetakusms@gmail.com

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder in pregnancy and is associated with an increased risk of adverse obstetrical outcomes like sudden fetal demise. It frequently develops in third trimester in pregnancy. It commonly occurs in individuals who are genetically predisposed. It is characterized by generalized itching, with no other skin manifestations. Maternal outcomes for patients diagnosed with ICP mild however, fetal outcomes are serious.

Objectives: To evaluate pregnancy outcomes and fetal complications associated with women with Obstetric cholestasis.

Methods: A retrospective case control study was conducted among women with Obstetric Cholestasis in Dhulikhel hospital in Nepal from April 2022 to April 2023. All the patients in the obstetrics and gynaecology labour room (Dhulikhel Hospital) with the diagnosis of Obstetric cholestasis in a given time frame were included. Secondary research data such as existing medical records and database were used for this study. Odds Ratio and its 95% CI was calculated by using unconditional logistic regression. P-value of <0.05 was considered as significant.

Results: The incidence of ICP was 4.2%. Majority of women with obstetric cholestasis belonged to age group 26-30 years. Majority of them were primigravida. This study identified that maternal and fetal complications were higher in women with obstetric cholestasis. The complications like Primary Postpartum Haemorrhage (PPH) (OR=2.43, 95%CI:1.03-5.76, p 0.042), meconium stained liquor (OR=4.44, 95%CI:2.26-8.72, p <0.001), abnormal Cardiotocography (CTG) (OR= 3.88, 95%CI: 1.83-8.23, p <0.001), Intrauterine Growth Retardation(IUGR) (OR=6.73, 95%CI: 3.06-14.78, p <0.001), Neonatal Intensive Care Unit (NICU) admission (OR=3.49, 95%CI: 1.61-7.61, p 0.002), low APGAR score (OR=2.31, 95%CI: 1.09-4.92, p 0.029) and neonatal Death (OR=3.16, 95%CI: 1.083-9.22, p 0.035) were associated with pregnancies complicated with obstetric cholestasis.

Conclusion: The women with obstetric cholestasis were found to have adverse pregnancy outcome compared to pregnant women without obstetric cholestasis. However, perinatal outcome is good in actively managed women.

Keywords: Fetal complications, Maternal complications, Obstetric cholestasis

1. Introduction

Intrahepatic cholestasis of pregnancy, commonly known as 'obstetric cholestasis' is a liver disease characterised by generalised pruritis that appears in the latter half of pregnancy, and resolves in the puerperium [1]. In one study, a perinatal mortality rate of 110/1000 livebirths were attributed to it [2]. In a later study, it was reported that intensive fetal surveillance, including induction of labour before term, and amniocentesis for meconium staining of liquor, was associated with a perinatal mortality of 35/1000 livebirths. The prevalence of the condition varies worldwide as does its presentation. A low incidence has been reported from European countries; from 0.2% in France to 2% in Scandinavia [3]. In Chile the prevalence in 1975 was reported to be as high as 14% of deliveries, although more recently this has been lower (4% in 1995) [4]. The disease course also varies worldwide with less severe forms of the disease described in Scandinavia than in Chile [5]. Such worldwide variations and the observed clustering of the condition within families suggest a genetic aetiology [6, 7]. In Nepal, it has been reported up to 1.15% [8]. In most old and recent series in Nepal, approximately 50% of obstetric cholestasis pregnancies were complicated by fetal distress, defined as fetal heart rate abnormality or meconium-stained amniotic fluid [9]. There have been no large studies on the clinical features of obstetric cholestasis pregnancies complications. The two largest prospective cohort studies, and several smaller series, have demonstrated that obstetric cholestasis are associated with increased rates of spontaneous and iatrogenic preterm labor, meconium-stained amniotic fluid, fetal hypoxia and stillbirth [1]. The major consequences of ICP are premature births in 19% to 60% of affected pregnancies [9, 10]. A high rate of intraportal fetal distress in 22% to 33% of deliveries [11, 12] and stillbirths in 1% to 2% of ICP pregnancies [13, 14]. Women with ICP have slightly higher long term risks of liver cancer and biliary tree as well as higher rates of other hepatobiliary diseases [15]. We undertook a retrospective study to determine the nature and outcome of obstetric cholestasis in a population when actively managed. Our study aimed at determining the pregnancy outcome in population complicated with obstetric cholestasis.

2. Methods

2.1 Study Area

This study was conducted among women with Obstetric Cholestasis in Obstetrics and Gynaecology (OBGYN) Department in Dhulikhel hospital in Nepal from April 2022 to April 2023.

2.2 Study Design

A retrospective case control study with the ratio of one control to one case (1:1) was conducted.

2.3 Sample size and sampling

The World Health Organization calculator was used to determine the sample size with a 95% confidence interval. The percentage of exposed cases with respiratory distress was 17.1%, whereas the percentage of exposed controls was 4.6%. The study involved the enrollment of 84 patients, with a 1:1 case-to-control ratio. A total of 84 cases were diagnosed as Obstetric Cholestasis in the given time frame. Women with pruritus of unexplained cause were included in the study. A control was chosen for each case of obstetric cholestasis who delivered immediately after each case of Obstetric Cholestasis. The control were women with normal pregnancy without intrahepatic cholestasis of pregnancy and any other comorbidities. The diagnosis of Obstetric Cholestasis was made on the basis of the symptom of generalized itching, biochemical evidence of altered LFT.

2.4 Data Collection

All the patients present in the OBGYN labour room (Dhulikhel Hospital) with the diagnosis of Obstetric cholestasis in a given time frame were included. Secondary research data such as existing medical records and database were used for this study. A total of 84 cases were diagnosed as Obstetric Cholestasis in the given time frame. Control was chosen for each case of Obstetric Cholestasis who delivered immediately after each case. From the case records the patient profile, complaints associated with medical and obstetric complications were noted. The records of investigations, treatment and the pregnancy outcome were studied. The diagnosis of Obstetric Cholestasis was made on the basis of the symptom of generalized itching and biochemical evidence of altered LFT.

2.5 Data Analysis

Data were entered into a Microsoft Excel spreadsheet. Data analysis was done using SPSS-21 and was depicted in tables. Odds

Ratio (OR) and its 95% Confidence Interval (95% CI) was calculated by univariable analysis using simple unconditional logistic regression. P-value of<0.05 was considered as significant.

2.6 Ethical Clearance

The Institutional Review Committee (Protocol approved number 156/23), Kathmandu University School of Medical Sciences, Dhulikhel, Nepal, approved this study.

3. Results

During the study period, 2100 deliveries were performed at our institution. Of these women, 84 (4.2%) were diagnosed with ICP. Majority of women with obstetric cholestasis belonged to age group 26-30 years. Majority of them were Primigravida. In this study 28 (33.3%) of female with Obstetric Cholestasis were illiterate, 31 (36.9%) of female had completed primary level of education, and 25 (29.7%) females had completed secondary level of education. Similarly, 53 (63.1%) of women with Obstetric Cholestasis were housewife, 12 (14.2%) were worked in office, and 9 (10.7%) of them were student. Therefore, the majority of the female in this study were illiterate and house wife. Women with age group less than 20 were considered as teen-age pregnancy and intrahepatic cholestasis was seen in 25% of them. This study also identified that the majority of women with ICP had more than 8 Antenatal Care (ANC) visits which concluded that ICP was diagnosed if women had frequent ANC visits. Thus, this study also recommends more than 8 ANC visits which is recommended by WHO.

Table 1: Characteristics of cholestatic and non-cholestatic pregnant females (84 Cases: 84 Controls)

Maternal characteristics	Cholestatic female		Non-Cholestatic female	
	Number	Percentage	Number	Percentage
Age (years)				
< 20	15	17.86	21	25.00
21-25	19	22.62	16	19.05
26-30	27	32.14	27	32.14
31-35	23	27.38	20	23.81
Education				
Illiterate	28	33.34	25	29.76
Primary	31	36.90	33	39.29
Secondary	25	29.76	26	30.95
Occupation				
Housewife	53	63.10	51	60.71
Office job	12	14.29	21	25.00
Student	9	10.71	8	9.53
No job	10	11.90	4	4.76
OBS presentation				

Maternal characteristics	Cholestatic female		Non-Cholestatic female	
	Number	Percentage	Number	Percentage
Cephalic	66	78.57	62	73.81
Breech	13	15.48	15	17.86
Transverse	5	5.95	7	8.33
ANC visit				
≤8	40	47.62	30	35.71
≥8	44	52.38	54	64.29

This study identified that maternal and fetal complications were higher in women with Obstetric Cholestasis. The complications like Post-partum Haemorrhage (PPH) (OR =2.43, 95%CI: 1.03-5.76, p 0.042) , Meconium Stained Liquor (OR=4.44, 95%CI :2.26-8.72, p <0.001), Abnormal Cardiotocography (CTG) (OR=3.88, 95%CI: 1.83-8.23, p <0.0001) , IUGR (OR=6.73, 95%CI: 3.06-14.78, p <0.001), Neonatal Intensive Care Unit (NICU) admission (OR=3.49, 95%CI: 1.61-7.61, p 0.002), low APGAR score (OR=2.31, 95%CI: 1.09-4.92, p 0.029) and Neonatal Death (OR=3.16, 95%CI: 1.083-9.22, p 0.035) were associated more with pregnancies complicated with Obstetric Cholestasis (Table 2).

Table 2: Complications of cholestatic and non-cholestatic pregnant female (84 Cases:84 Controls)

Factors	Cholestatic female		Non cholestatic female		Odds ratio	95% CI	P-value
	Number	%	Number	%			
Abnormal CTG	33	39.30	12	14.30	3.88	1.83-8.23	<0.001
PPH	19	22.60	9	10.70	2.44	1.03-5.76	0.042
Meconium-stained liquor	46	54.80	18	21.40	4.44	2.26-8.72	<0.001
IUGR	40	47.60	10	11.90	6.73	3.06-14.78	<0.001
Low APGAR	25	29.80	13	15.50	2.31	1.09-4.92	0.029
NICU admission	29	34.50	11	13.10	3.49	1.61-7.61	0.002
Neonatal death	4	16.70	5	6.00	3.16	1.08-9.22	0.035

4. Discussion

The aim of the present study was to summarize the available evidence regarding complications in Obstetric Cholestasis. Our study found that the obstetric and neonatal complications were higher among women with Obstetric Cholestasis. Clinical studies clearly show that when obstetric cholestasis complicates pregnancies it may lead to premature births in up to 60%, fetal distress in up to 33%, and intrauterine death in up to 2% of patients [15]. In most old and recent series, approximately 50% of obstetric cholestasis pregnancies were complicated by fetal distress, defined as fetal heart rate abnormality or meconium-stained amniotic

fluid, and this has not changed despite early delivery [16]. At present, it is not possible to predict which pregnancies are at risk of fetal complications of obstetric cholestasis. Twenty-nine (34.5%) neonates were admitted to NICU with the most frequent cause being RDS or TTN in 50% of the admitted neonates followed by neonatal sepsis in 27.8%. The rate of NICU admission was lesser than that previously reported from Nepal by Pokhrel et al in which meconium stained liquor (32.5%) was the main reason for NICU admission [10]. Bile acids are known to cause an increase in colonic motility, which could be a possible explanation for meconium passage. Some studies have demonstrated an abnormal fetal heart rate [4]. Recently, Rioseco et.al found that intrahepatic cholestasis was associated with a two-fold increase in the incidence of AF meconium and a three-fold increase in the incidence of preterm delivery [5] which was similar to our study. Women delivering after 38 weeks had a higher incidence of thick meconium as compared to the study of Ray et.al (45%) [17]. Abnormal CTG was 33% as compared to 35% in Ray et.al series which was consistent to our study. Obstetric cholestasis is associated with increased maternal morbidity and perinatal morbidity and mortality. Risk to the fetus increases as pregnancy advances and particularly after 38 weeks. Continuous monitoring of fetus with USG and CTG may not prevent sudden fetal distress and Intrauterine Fetal Death (IUFD). Roncaglia N et al and Fisk NM et al have reported good outcomes with a policy of induction of labour at 37- or 38-weeks' gestation [2, 18, 19]. Many clinicians in the UK have adopted this practice as the IUFD appear to cluster at later gestations [19]. However there have been very few reports of the gestational week at which the IUD occurs [20]. Alsulyman OM et.al also found that risk of meconium passage was higher in the cholestasis group [11]. It has been suggested that both fetal distress and increased gut motility by bile acids is the cause of raised incidence of Meconium-stained liquor [21]. Williamson C et.al observed 38% preterm delivery rate in cholestasis patients [15]. According to Heinonen S et.al intrahepatic cholestasis increases the need for intensive neonatal care in general population [5]. According to Rasheed S et.al postnatal resolution of pruritus and liver function test occurred within 5-14 days with a mean of 8 days [22]. Large therapeutic trials are required to establish management strategies effective at reducing the rates of adverse maternal and fetal outcomes. In this study, the sample size was small, and the time

period was limited, it therefore may not reflect the true magnitude of the problem. However, early diagnosis and active maternal and fetal surveillance is of utmost importance to avoid adverse outcomes.

5. Conclusion

Our study suggests that there is a significant risk for maternal post-partum complications, fetal morbidity and mortality in ICP with evident implications for future health of the offspring. The currently available evidence on risk factors of ICP is still limited in quantity and remains inconclusive given the lack of robustly conducted studies. The dreaded consequences of this condition do not relate to the mother but rather to the fetus. Scientific evidences, including the risks and benefits of the available management options, should be presented to the patient in a clear manner by the health care providers. ICP remains a common, dangerous, and poorly understood complication of pregnancy for which continued investigation is certainly warranted. Our data are consistent with the low perinatal mortality reported in more recent series with active management. It is unknown whether the Nepali population is at lower risk. Further work is needed to better identify those fetuses at risk. If such identification are possible, unnecessary surveillance and intervention in low-risk obstetric cholestasis cases and the associated morbidity can be avoided. The consequences of intrahepatic cholestasis primarily affect the mother, with discomfort from pruritus and mild jaundice. Although there is no long-term hepatic injury to the mother, it is advisable that patients with intrahepatic cholestasis to be monitored for fetal effects. Careful timing of delivery is usually the only active therapy required in singleton pregnancies to achieve a normal outcome.

Acknowledgement

We are grateful to all the staff of OBGYN department of Dhulikhel Hospital for helping us conduct this study.

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