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OBSTETRIC CHOLESTASIS: A RETROSPECTIVE STUDY IN A TERTIARY CARE MATERNITY CENTRE

Ufaque Muzaffar*[1] and Farhat Jabeen[2]

[1]Senior Resident, Department of Obstetrics and Gynaecology, GMC Srinagar, India.
[2]Professor, Department of Obstetrics and Gynaecology, GMC Srinagar, India.

***Corresponding Author: Dr. Ufaque Muzaffar**

Postgraduate, Department of Obstetrics and Gynaecology, GMC Srinagar.

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ABSTRACT

Objective(s): To study the epidemiology and outcome of pregnancy complicated by obstetric cholestasis (OC). **Methods(s):** Retrospective case control study of 45 women with OC at a tertiary private hospital from November 2016 to November 2017. A p value <0.05 was considered statistically significant. **Results:** The incidence of OC was 8.2%. The most common symptom was generalized pruritus which appeared after 28 weeks in 73.3% cases. The cesarean section rate was 93.3%. 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 pa- rameter - pathological cardiotocography, 1-5 minute Apgar score <7, intrauterine growth restriction, neonatal intensive care ad- mission or perinatal mortality. There was no case of postpartum hemorrhage. **Conclusion:** The incidence of OC is high in the Indian population. Perinatal outcome is good in actively managed women, although at the cost of a high intervention rate.

KEYWORDS: Obstetric cholestasis, perinatal outcome, meconium.

INTRODUCTION

Obstetric cholestasis (OC), also known as intrahepatic cholestasis of pregnancy is a hepatic disease unique to pregnancy which presents with intense generalized pruritus without any skin rash.[1] It is a temporary condition caused by maternal liver dysfunction during pregnancy and blood tests reveal increased levels of one or more of the liver enzymes.[2] The pathophysiology of intrahepatic cholestasis is poorly understood.[3] Alternative causes of itching and abnormal liver function tests (LFTs) should be excluded.[1,2] Postnatal resolution of pruritus and abnormal LFTs should be confirmed to establish the diagnosis.[2]

The importance of OC lies in the associated adverse pregnancy outcome. The potential risks are intrauterine fetal death, prematurity (usually iatrogenic), fetal distress and postpartum hemorrhage (PPH).[3-6] It is also associated with significant maternal morbidity due to persistent itching and consequent sleep deprivation.[2]

Our study was aimed at determining the incidence of OC in our hospital, studying the course of pregnancy and evaluating the pregnancy outcome in these women.

METHOD

This retrospective case control study was conducted at the Department of Obstetrics and Gynecology, GMC Srinagar, India The medical records of all women with OC who delivered between November 2016 and November 2017 were reviewed. Two women were chosen as control for each case of OC; the women delivering immediately before and after each case of OC were chosen as control. From the case records the patient profile, complaints, associated medical and ob- stetric complications were noted. The records of investigations, treatment and the pregnancy outcome were studied.

The diagnosis of OC was secured on the basis of the symptom of persistent generalized pruritus, biochemical evidence of altered LFTs and the remission of both following delivery. Pregnancy specific ranges of LFTs were used. For the transaminases, gamma glutamyl transferase (GGT) and bilirubin in pregnancy, the upper limit of normal value is 20% lower than that in the non-pregnant state. Alkaline phosphate (ALP) is raised normally in pregnancy and is considered abnormally high if there is at least a three fold increase over the non-pregnant normal value (upper limit of normal range). Other causes of altered LFTs were excluded by hepatitis serology, hepatobiliary sonography and liver autoimmune screen (for primary biliary cirrhosis) wherever indicated.

The monitoring of women with OC included regular

prenatal visits with LFTs every 10–14 days. Fetal surveillance was done with daily maternal recording of fetal movements, regular sonography including amni- otic fluid index (every 7-14 days depending on the pe- riod of gestation) and twice weekly nonstress test (NST) beginning at 34 weeks of gestation. Control group had regular prenatal visits and NST when indi- cated by obstetric conditions.

We noted the occurrence of complications of pregnancy including preterm premature rupture of membranes (PPROM), (defined as the occurrence of spontaneous rupture of membranes before the onset of labor in pregnancies <37 weeks of gestation) and preterm delivery (defined as delivery at <37 completed weeks of gestation). We also noted the mode of delivery, the cardiotocographic findings during fetal surveillance, the presence of meconium during delivery, Apgar score at 1 and 5 minutes, intrauterine growth restriction (IUGR) (defined as birth weight <10th percentile for gestational age according to the normal tables for our population - Intrauterine weight chart, AIIMS), need for neonatal intensive care (NICU) admission and perinatal mortality.

Statistical analysis was performed using the z test when appropriate. A p value <0.05 was considered statistically significant.

RESULTS

During the study period 550 deliveries were performed at our institution. Of these women, 45(8.2%) were diagnosed with OC. The mean age of these women was 28.7 years (20-37 years). Thirty one were nulliparous and of the 14 parous women nine (64.3%) had a previous history of cholestasis. Women in the study group and the control group were similar in age and parity (Table1).

Generalized pruritus worsening at night, causing variable degree of sleep deprivation was the principal symptom seen in all the women with cholestasis. The palms and the soles were worst affected by the pruritus in 17/45 (37.8%) women. Five women complained of dark colored urine (11.1%). There was no case of clinical jaundice.

In 33/45 (73.3%) women the gestational age at diagnosis of OC was after 28 weeks with the maximum number being diagnosed between 32-36 weeks. In only 8/45 (17.8%) women the symptom started before 20 weeks (Fig 1).

Using pregnancy specific ranges for the LFTs it was found that the most frequent abnormality encountered in OC was elevated transaminases (97.8%) and GGT (42.9%). The peak value of alanine aminotransferase (ALT), aspartate aminotransferase (AST) in our study ranged from 37-631 U/Land 49-603 U/L respectively. The value of ALP in these women varied from normal to as high as 986 U/L. Mild hyperbilirubinemia was present in 18.4% of the women and the highest bilirubin level noted was 2.8mg% (Table 2).

Topical emollients and oral antihistaminics were offered to all the subjects for symptomatic relief of pruritus. 9/45 women (20%) had partial relief; 36/45 (80%) women were given ursodeoxycholic acid (UDCA) in a dose of 600-1800 mg/day. All the women reported partial or complete relief of pruritus and there was biochemical improvement in 34/36(94.4%) women. 19/45 (42.2%) women were prescribed parental vitamin K.

The incidence of PPROM was significantly higher in the study group compared to the control group (8.9% vs 1.1%, p<0.05). The mean gestational age at delivery in the OC group ranged between 32-39 weeks with most.

Table 1: General profile of subjects and controls.

Maternal Characteristics	Cholestasis of pregnancy (n=45)	Control (n=90)
Mean age (Range)	28.7 yrs (20-37)	28.5 yrs (18-40)
Primiparous (%)	68.9	68.2
Multiparous (%)	31.1	31.8

Table 2: Liver function tests in obstetric cholestasis.

LFT	Results (range)	Normal value non-pregnant value (Upper limit)	Normal value in pregnancy (Upper limit)	Raised in (%)
SGOT (iu/L)	30-631	40	30	97.8
SGPT (iu/L)	24-603	40	32	97.8
GGT (iu/L)	11-956	50	41	42.9
ALP (iu/L)	76-986	130	418	15.8
SB (mg%)	0.3-2.8	0.8	0.8	18.4

Table 3: Complications of pregnancy.

Complications	Obstetric Cholestasis (n=45) (%)	Control (n=90) (%)	p value <0.01
Preterm premature rupture of membranes	4/45 (8.9)	1/90 (1.1)	
Preterm delivery	10/45 (24.4)	14/90 (15.6)	>0.05
Total Cesarean section	42/45 (93.3)	69/90 (76.7)	>0.05
Elective Cesarean section	32/42 (76.2)	45/69 (65.2)	---
Postpartum hemorrhage	0	0	---

Fig 1 Gestational age at diagnosis in Obstetric Cholestasis

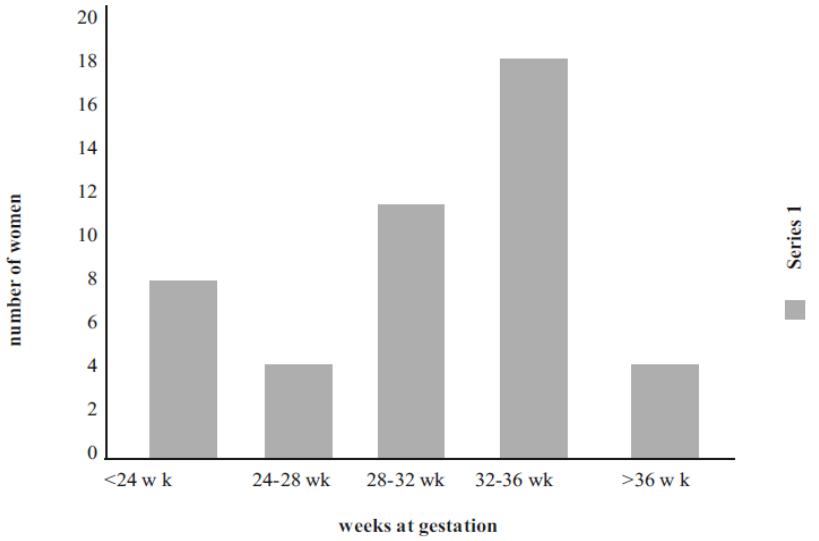

Fig 2 Gestational age at delivery in Obstetric Cholestasis

Table 4: Perinatal outcome.

	Cholestasis of pregnancy (n=45) (%)	Control (n=90) (%)	p value
Meconium staining of amniotic fluid	8/45 (17.8)	1/90 (1.1)	<0.005
Abnormalcardiotocography	2/45 (4.4)	5/90 (5.6)	>0.05
Apgar <7 at 5 mins	2/45 (4.4)	2/90 (2.2)	>0.05
Intrauterine growth restriction	4/45 (8.9)	7/90 (7.8)	>0.05
Neonatal intensive			
care admissions	7/45 (15.6)	14/90 (15.6)	>0.05

Table 5: Perinatal mortality.

	Cholestasis of pregnancy (n=45)	Control (n=90) (%)
Stillbirths	1	4
Stillbirth rate (per 1000 total births)	22.2	44.4
Neonatal deaths	0	2
Neonatal mortality rate (per 1000 live births)	0	23.2
Perinatal deaths*	1	6
Perinatal mortality rate (per 1000 live births)	22.7	69.7

*Excluding congenital malformations of the women delivering at 37-38 weeks (Fig 2). Al- though the incidence of preterm delivery was higher in the study group (24.4% vs 15.6%) this did not attain statistical significance (p> 0.05). It is important to men- tion that many of the preterm deliveries were planned elective deliveries. The cesarean section (CS) rate was higher in the study group (93.3% vs 76.7%), but even this did not attain statistical significance (p> 0.05).The higher CS rate was mainly due to a higher elective CS (76.2% vs 65.2%). There was no case of PPH in either group (Table 3). Perinatal outcome is shown in Table 4. In the OC group there was a higher incidence of meco- nium staining of amniotic fluid (17.7% vs 1.1%, p<0.005). There were no significant differences in the incidence of abnormal cardiotocography, Apgar score at 1 minute and 5 minutes, incidence of IUGR or NICU admissions.

Perinatal mortality is shown in Table 5. No significant differences were observed in the fetal, neonatal or perinatal mortality rates between the groups. A single still- birth and no neonatal deaths were observed in the OC group while in the control group there were four still- births and two neonatal deaths.

DISCUSSION

The prevalence of OC is influenced by genetic and environmental factors and varies between populations.[3] It is most common in Chile where 2.4% of all pregnancies are affected with 5% prevalence in women of Araucanian-Indian origin.[2] The incidence of OC among Indian women has been reported as about 1%.[4,7] We found an incidence of 8.2% in our study. However it is prudent to mention that our hospital is a tertiary referral private hospital and the incidence of high risk pregnancy is higher. Hence the incidence of OC is expected to be higher than that in the community.

Some authors have reported that women of relatively advanced age (>35 yrs) are at increased risk of developing OC8 but we found that the mean age was 28.7 years (range 20-37yrs) and there was no significant difference between the two groups in maternal age or parity. OC tends to recur in subsequent pregnancies in upto 60-70% of the women.[3] In the present study the recurrence rate was 64.3% among multiparous women.

In 71.1% women, OC was diagnosed in the third trimester which is similar to that seen in other studies.[4,7] Generalized pruritus was the cardinal symptom in all and was most pronounced in the palms and soles in 37.8% women. It has been reported that severe pruritus of the soles of the feet maybe particularly suggestive of this condition.[4] We found no case of clinical jaun- dice. However it has been reported in upto 10% women.[5]

Abnormalities in one or more of the transaminases, GGT, bilirubin and/or bile salts are consistent with a diagnosis of OC. The most commonly elevated LFTs have been reported as transaminases and total serum bile acids1 and typically the transaminases range from just normal to several hundreds.[2] In our study the transaminases were raised in 97.8% of the women and the maximum value encountered in our study was twenty times the normal value in pregnancy. Various studies have reported that elevated levels of GGT and bilirubin have been noted in upto 50% and 22-56% patients respectively but clinical jaundice is rare1. In our study we found raised levels of GGT in 42.9% patients and hyperbilirubinemia in 18.4% women. There was no case of jaundice. As bile salt assessment is not available we could not determine the levels in our patients.

The efficacy of topical emollients like calamine lotion and oral antihistaminics like chlorpheniramine has not been tested in clinical trials but their use is safe in pregnancy and for some women may provide mild temporary relief of pruritus.[2] In our study 20% of the women reported partial relief. Several studies demonstrate that in addition to providing safe and effective relief of pruritus and improving LFTs, UDCA may improve the prenatal outcome[9,10] by preventing the accumulation of biliary constituents of maternal origin in the fetus, which may contribute to the risk of fetal distress and even stillbirth. In our study UDCA was prescribed in 80% of the women and there was partial or complete relief of pruritus in all with biochemical improvement in 94.4% women. Kenyon et al[4] found a high incidence of PPH in women with OC who did not receive vitamin K compared to those who did (45% vs 12%), but we found no case of PPH though only 42.2% of the women on our study received vitamin K.

The disease has been related to a high incidence of perinatal complications including an increase in perinatal mortality rate (35/1000), a high incidence of meconium stained amniotic fluid (upto 45%), preterm labor (upto 44%), and fetal distress (upto 22%).[5,6] Our study shows a significant increase in the incidence of PPROM and meconium staining of amniotic fluid in the OC group. It

has been suggested that both fetal distress and in- creased stimulation of colonic motility by bile acids is the cause of increased incidence of meconium staining on OC.[6] Unlike other studies we did not find a signifi- cant increase in preterm deliveries, fetal distress, NICU admissions or perinatal mortality. No association with IUGR has been reported[4,5,11] and in this study also we found no significant increase in growth restriction.

As the pathophysiological basis of the fetal risks in OC is not clear, conventional fetal surveillance is not al- ways helpful in determining the risk of fetal compro- mise.[11] Increased perinatal mortality rate (1.3-3.5%) and increased stillbirth rate ranging from 2.5-11% has been reported5. intrauterine fetal demise appears to be an acute anoxic event and the high concentrations of fetal bile acids may contribute to this acute event. The risk of fetal death increases near term and most deaths occur after 37-38 weeks. To avoid the risk many hospi- tals adopt a policy of active management with antenatal surveillance and early elective delivery at 37-38 weeks1. In our study active management including in- tensive fetal surveillance with delivery between 37-38 completed weeks of gestation was used.

The only stillbirth in the OC group in our study was an unbooked woman who came in at 39 weeks gestation with the complaint of loss of fetal movements and ultra-sonography on admission confirmed fetal demise. The mother did not have other complications of pregnancy and the fetus was grossly normal with appropriate weight for gestational age. All the stillbirths in the con- trol group were in unbooked women who presented with intrauterine fetal death. The two neonatal deaths were due to extreme prematurity and IUGR.

Apart from the significant morbidity due to the intense pruritus, OC does not seem to have serious health con-sequences for the mother. There is an increased risk of delivery by CS (25.9-36%)[5] though it is not clear whether the high rates are due to active management or because of complications as a result of the disease or both. PPH has been observed in 2-25% patients in some studies.[4,7] In our study the CS rate of 93.3% was high but not significantly higher than that in the control group. The CS rate in our hospital is high in view of the higher incidence of complicated pregnancies.

CONCLUSION

The incidence of OC is high in our hospital, a tertiary care private hospital unit. Larger studies are needed to assess the correct incidence in the general population. Cholestasis of pregnancy has an adverse effect on the fetal outcome and hence early diagnosis with careful clinical examination and biochemical testing is essen-tial. Affected women should be offered treatment with UDCA. This provides symptomatic relief, improvement of liver function and may contribute to improvement in the perinatal outcome. The obstetric intervention rate is high in our study as we adopted a policy of active man-agement with close antenatal surveillance and elective delivery after 37 completed weeks to improve the peri-natal outcome.

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