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ORIGINAL ARTICLE

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Cholestasis of pregnancy

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OBJECTIVE(S) : To study the nature and outcome of pregnancy in obstetric cholestasis.

METHOD(S) : This prospective study included 32 women booked for delivery and diagnosed as having obstetric cholestasis. Medical treatment for symptomatic relief was offered to all; protocol for antenatal check-ups and induction of labor was as per obstetric indications.

RESULTS : Incidence was 1.2% (32/2668). Symptoms appeared after 30 weeks in 84.3% (27/32). 66.6% (6/9) of the multiparous women had a previously affected pregnancy. The cesarean section rate was 31.2% (10/32). Elective cesarean section was done in one woman for gestational diabetes. Intra-partum abnormal cardiotocography (CTG) was noted in 9 / 31 (29.03%) and thick meconium in 10 / 31 (32.2%). Women delivering after 38 weeks had a higher incidence of thick meconium (45% vs 11.1%), abnormal CTG (35% vs 11.1%), neonatal nursery admission (45% vs 11.1%), and perinatal mortality (105 per 1000 vs none) than women delivering between 35 and 38 weeks. The difference regarding thick meconium and neonatal nursing admission was statistically significant though that regarding abnormal CTG was not. Post partum hemorrhage was noted in 8 / 32 (25%).

CONCLUSION(S) : Obstetric cholestasis is associated with increased perinatal morbidity and mortality if delivered after 38 weeks. An attempt to deliver prior to 38 weeks may improve perinatal outcome.

Key words : obstetric cholestasis, pregnancy outcome

Introduction

Obstetric cholestasis is a liver disease unique to pregnancy. Once assumed to be a benign condition, its significance has been highlighted only recently due to the associated maternal morbidity and perinatal mortality. The prevalence, presentation, and severity of the condition vary worldwide. A low incidence of 0.2% in Europe and a high incidence of 4 -14% in Chile have been reported [1,2]. The disease course is also known to be more severe in Chile than in other parts of the world. Hence, it may not be appropriate to extrapolate the outcome across different populations. We, therefore, undertook this study to determine the nature and outcome of obstetric cholestasis amongst women attending our antenatal clinic.

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Methods

From April 2003 to March 2004, women with obstetric cholestasis (n=32) were recruited for the study from amongst antenatal booked women attending our antenatal clinic.

The diagnosis of obstetric cholestasis was based upon the clinical symptom of persistent pruritus without a skin rash associated with biochemical evidence of mild to moderate cholestasis in the absence of other liver disease, which resolved postnatally. Abnormal liver function was defined as at least two to four fold increase in transaminase not exceeding 250 IU/L with or without mild increase in serum bilirubin not exceeding 5 mg/dL. Alkaline phosphatase, which is a good marker of cholestasis in the non pregnant state, is not of much help because of its pregnancy associated

increase coming from placenta. Women with a positive serology for hepatitis A, B or C, previous history or sonographic evidence of gall bladder disease, pregnancy induced hypertension, and those in whom liver function test did not normalize within two weeks of delivery were excluded from this study. Once identified, the women were asked regarding the nature and severity of pruritus which was measured using a scoring system from 0 (no itching) to 5 (severe itching) [2]. All women were offered palliation initially with topical emollients with or without chlorpheniramine (maximum of 4 mg thrice daily). Ursodeoxycholic acid (UDCA) was given at a starting dose of 8 - 12 mg/kg/day in divided doses only when severe pruritus persisted. In all women, liver function tests (LFT) were repeated every 2 weeks. Protocol for antenatal care with respect to interval between clinical examination, ultrasonography, cardiotocography (CTG), and induction of labor was decided on the merit of obstetric indication.

Obstetric notes were reviewed to determine the maternal and fetal outcome with respect to intrapartum events such as abnormal CTG patterns or meconium staining, the mode of delivery, apgar score, need for nursery admission in the new born, and maternal postpartum complications. Symptomatic relief of pruritus and liver function test was determined in all women two weeks after delivery.

Results

During the study period, out of the 2668 antenatal registered women, 32 with a mean age of 24.7 years were diagnosed as having cholestasis of pregnancy giving an incidence of 1.2%. Twenty-three (71.8%) were primigravidas. Six out of nine (66.6%) multiparous women with intrahepatic cholestasis in the present pregnancy had a previously affected pregnancy. The cardinal symptom of obstetric cholestasis was pruritus, which appeared after 30 weeks of gestation in 27 / 32 (84.3%) with a range of 26 weeks 2 days to 36 weeks 4 days (Figure 1). Twenty-two women (68.7%) graded their symptom severity as 4 and above on at least one occasion. When asked to list all parts where pruritus was perceived 24 / 32 (75%) reported it to be all over. When asked about the single site where pruritus was most severe 15 / 32 (46.8%) women answered palms and soles. (Figure 2).

On initial treatment with emollients and chlorpheniramine 17/32 (53.1%) had good relief. The remaining 15/32 (46.8%) who had mild or no relief were advised UDCA. Of 15 who had poor relief only eight agreed to take the drug. All of them had good symptomatic relief and six out of eight (75%) reported complete relief. There was also biochemical improvement with reduction in the serum bilirubin and transaminase levels in all of the eight women.

Figure 1. Weeks of gestation at onset of pruritus.

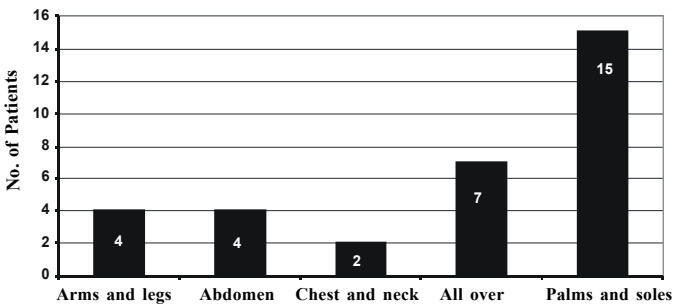

Figure 2. Site of most severe pruritus (n=22).

Thirty-one women went into labor either spontaneously or after induction. In 7 / 32, (21.8%) it was preterm. Elective cesarean section was done in one case of gestational diabetes on 40 units of insulin daily in divided doses. Most women went into labor spontaneously 22 / 32 (68.75%). In the spontaneous group, 16 / 22 (72.72%) delivered vaginally with a cesarean section rate of 6 / 22 (27.27%) (Table 1).

Table 1. Weeks of gestation at onset of spontaneous labor (n=22).

Weeks of gestation	Number
< 30	0
30 – 32	1
32 – 34	2
34 – 36	4
36 – 38	2
38 – 40	11
> 40	2

Vaginal delivery 16/22 (72.72%) Cesarean Section 6/22 (27.27%)

Nine women (28.1%) underwent induction of labor, all of them beyond 37 completed weeks. The method of induction depended on the cervical score, amniotic fluid index and

CTG pattern prior to induction. The two most common indications were post-dated pregnancy and worsening symptoms (3 women in each category). The cesarean section rate in this group was marginally higher than that in the spontaneous onset group (3/9,33.33% vs 6/22, 27.27% (Table 2).

Table 2. Indications for induction of labor (n=9).

Weeks of gestation	Number (n=9)	Indications
37-38	3	Worsening symptoms - 2 Less fetal movements - 1
38-39	1	Gestational diabetes on diet control with one previous spontaneous abortion - 1
39-40	2	Decrease in amniotic fluid index -1 Worsening symptoms -1
>40	3	Postdated pregnancy -3

Vaginal delivery 6/9 (66.6%), Cesarean section 3/9 (33.3%)

During labor an abnormal CTG was noted in 9 / 31 (29.03%) while 14 / 31 (45.1%) had meconium staining of liquor, of whom 10 / 31 (32.2%) had thick meconium. The cesarean section rate in our study was 10 / 32 (31.2%). Of the nine emergency cesarean sections, four were for fetal distress (Table 3). The instrumental delivery rate was 8 / 32 (25%) of which six were for fetal distress.

Table 3. Indications for cesarean section.

Elective cesarean section	1
Gestational diabetes on insulin	1
Emergency cesarean section	9
Fetal distress	4
Meconium stained liquor in early labor	3
Failure to progress	2

Cesarean section rate 10/32 (31.2%)

Birth weights were appropriate for gestational age for all infants. An apgar score of < 7 at 5 minutes was seen in 6 / 32 (18.7%). Thirteen newborns required admission in the neonatal care unit (40.6%). There was one intrauterine fetal demise (IUFD) at 38 weeks 6 days and one early neonatal death (NND) 2 days after delivery. In the latter case, the woman had undergone emergency cesarean section for thick meconium stained liquor with loss of beat-to-beat variability in CTG at 40 weeks 5 days of gestation. The only maternal morbidity of significance apart from emergency surgical intervention was post partum hemorrhage seen, in 8 / 32 (25%) women. In four, it was severe enough to require blood transfusion.

Discussion

This prospective study describes the nature and outcome of obstetric cholestasis. The incidence was 1.2% (32/2668), which is comparable to the incidence of 1.24% in the Indian population reported by Kenyon et al [2]. 84.3% of women presented after 30 completed weeks of pregnancy, which is similar to that seen in other studies [2, 3]. In 15 / 32 (46.8%) women, the most severe site of pruritus was palms and soles. Indeed, pruritus that is most severe on the soles and feet may be particularly suggestive of this condition [2].

UDCA was used in only a minority of cases who had severe pruritus failing to respond to emollients and antihistaminics. UDCA was very effective in reducing both pruritus and improving biochemical parameters [3-5]. However no study has had a large enough series of patients to establish whether its use improves outcome in pregnancies complicated by obstetric cholestasis [2, 6, 7].

On further analyzing the data, we found that the period of gestation at the time of delivery greatly affected intrapartum events and perinatal outcome. Women delivering after 38 weeks had a higher incidence of thick meconium stained liquor (45% vs 11.1%), abnormal CTG (35% vs 11.1%) and need for neonatal nursery admission (45% vs 11.1%) compared to those delivering between 35 and 38 weeks of gestation. The differences between the two groups regarding thick mecomium stained liquor and nursery admission were more than twice the standard error of difference between the two proportions viz., 15.26, and hence statisticaly significant. However, the difference regarding abnormal CTG was less than twice the standard error of difference between the two proportions viz., 14.90, and hence statistically not significant. Based on a benchmark of 0.05 alpha, the difference in perinatal mortality rate (PMR) is statistically significant ($P<0.0001$). The difference regarding nursery admission rate was greater than twice the standard error of difference between the two proportions viz, 8.7, and hence statistically significant. One case of IUFD and one of early NND also belonged to the group delivering after 38 weeks giving PMR of 105 / 1000 live births (Table 4).

Unfortunately, in the woman having IUFD, the amniotic fluid index and CTG tracing were normal 14 hours prior to detection of fetal demise. The cause of IUFD is uncertain in obstetric cholestasis. An acute anoxic event due to direct cardiotoxic effect of bile acid on fetal cardiomyocytes seems to be the likely mechanism, rather than a chronic placental

insufficiency. Therefore, it is not surprising that sonography and CTG tracing may both be normal and not always helpful in preventing sudden fetal demise [2, 8].

Table 4. Pregnancy outcome with respect to period of gestation at the time of delivery.

	> 38 weeks n=20	35-38 weeks n=9	< 35 weeks n=3
Thick meconium stained liquor	9/20 (45%)	1/9 (11/1%)	0
Nonreactive CTG	7/20 (25%)	1/9 (11.1%)	1/3 (33.3%)
Apgar < 7	5/20 (25%)	1/9 (11.1%)	3/3 (100%)
Neonatal nursery admission	9/20 (45%)	1/9 (11.1%)	3/3 (100%)
IUFD	1/20 (5%)	0	0
NND	1/20 (5%)	0	0
PMR	105/1000 live births	0	0
PPH	5/20 (25%)	2/9 (22.2%)	1/3 (33.3%)
LSCS	6/20 (30%)	4/9 (44.4%)	0

CTG - Cardiotocography, LSCS - Lower segment cesarean section
IUFD - Intra-uterine fetal death NND - Neonatal death
PMR - Perinatal mortality rate PPH - Post-partum hemorrhage

Three women delivered between 31 weeks 5 days and 32 weeks 2 days. Although all three neonates required nursery admission, none had an apgar score of < 7 and there was no perinatal mortality. It is interesting to note that perinatal consequences of gravid cholestasis may be minimized if a reasonable premature delivery is accepted [9]. The overall perinatal mortality rate (PMR) and nursery admission rate in the study group were much higher than those for all booked women during the same period (PMR 64.5 vs 14.5 per 1000 live births and nursery admissions 40.6% vs 13.05% respectively).

The cesarean section rate of 31.2% is comparable to that in other studies [2, 3]. Women who went into labor spontaneously had a lower cesarean section rate than that in the induced labor group (27.2% vs 33.3%). The difference was not statistically significant.

Most studies recommend antenatal prophylactic vitamin K to all women with obstetric cholestasis to prevent coagulation disorders [1,2,9]. We administered vitamin K intramuscularly to all women who had PPH after delivery and to three women 24 hours prior to induction. All three who receiving vitamin K prior to delivery had serum bilirubin level >2.5 mg/dL. PPH occurred in eight women (25%). Of these, one had received vitamin K 24 hours prior to induction of labor. A high incidence of PPH (41.6%) was reported by Kenyon et al [2] in those who did not receive vitamin K compared to 10% in those who received a daily dose of 10 mg orally from 34 weeks or after diagnosis.

Obstetric cholestasis occurs mainly in the final months of pregnancy with pruritus as the cardinal symptom and has a high recurrence in future pregnancies. It is associated with increased maternal morbidity, and perinatal mortality and morbidity. Risk to the fetus rises progressively till term especially beyond 38 completed weeks regardless of serum levels of bilirubin and transaminase, or the symptoms. Close monitoring in the antenatal period with sonography and CTG may not prevent sudden fetal distress and IUFD. Induction of labor between 37 – 38 weeks may improve perinatal outcome.

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