IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 2 Ver. V (Feb. 2015), PP 01-04
www.iosrjournals.org

Intrahepatic Cholestasis in Pregnancy and Its Response to Ursodeoxy Cholic Acid

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Abstract: *Pregnancy is a special clinical state with several normal physiological changes that influence body organs including the liver. Liver disease can cause significant morbidity and mortality in both pregnant women and their infants. In our study, four cases were studied to test the efficacy of ursodeoxycholic acid in intrahepatic cholestasis of pregnancy, in relation to maternal pruritis, the biochemical abnormalities and the outcome of pregnancy. Patients with intrahepatic cholestasis of pregnancy,with intense pruritus and were assigned to receive ursodeoxycholic acid, 15mgs/KG body wt/ twice a day, orally with a drug free interval of ten days, till delivery. The follow-up was extended for 3 months after delivery. No adverse effects were detected in the mothers or in their babies. After 3 weeks of treatment, patients receiving ursodeoxycholic acid had a clinical improvement in pruritus, serum bilirubin, aspartate aminotransferase. All babies born alive, but with LBW, and were thriving normally 3 months after delivery*

Keywords: *abnormal liver function tests, cholestasis of pregnancy, pruritis, vitamin K', ursodeoxycholic acid.*

I. Introduction

Pruritus affects up to 20% of the pregnant women. Pruritis can be sufficiently severe to affect sleep and quality of life, and might lead to or worsen depression.[1] It affects 0.7% of Pregnancies in multiethnic populations and 1.2–1.5% of women of Indian–Asian or Pakistani –Asian origin.[1]

Although pruritis is commonly caused by dry skin, it can also indicate an underlying condition unique to pregnancy. The causes of pruritis in pregnancy include pruritic urticarial papules of pregnancy, (PAPPP), intra hepatic cholestasis of pregnancy (IHCP), phempigoid gestationosis, (PG), and atopic eruptions of pregnancy.[2] Clinical history and physical examination are the most important diagnostic clues when evaluating pruritus in pregnancy. Intrahepatic cholestasis of pregnancy (IHCP), also known as obstetric cholestasis, cholestasis of pregnancy, jaundice of pregnancy, and prurigo gravidarum is a medical condition in which cholestasis occurs during pregnancy.[3] It is caused by the disruption of hepatic bile flow during pregnancy. It runs in families and tends to recur in subsequent pregnancies. It typically presents with troublesome intractable itching, and can lead to complications for both mother and fetus.[4] It recurs in 40-60% of future pregnancies. The intensity of pruritis and the laboratory alterations fluctuate during one pregnancy and also vary in subsequent affected pregnancies. Associated biochemical cholestasis of mild to moderate severity appears during pregnancy at different times and disappears after delivery. Here we are reporting relatively rare cases of intrahepatic cholestasis and its response to Ursodeoxy cholic acid.

Abbreviations: IHCP- intra hepatic cholestasis of pregnancy**,** LFT: liver function tests**,** FT, ND: full term, normal delivery. PPH: post partum hemorrhage**,** LSCS: lower segment caesarean section.

II. Materials And Methods

We studied 10 cases of pruritus of pregnancy of variable severity, out of which four cases were due to intrahepatic cholestas is of pregnancy.

In all cases

1. Most common complaint was intractable pruritis.
2. There was no significant family, medical, or personal history. No h/o taking oral contraceptives, or alcohol intake.
3. Admitted to hospital at 30- 32 weeks till delivery, Physician's and dermatologist's opinion was taken when ever required.
4. Serum bilirubin and alkaline phosphatase were raised (Serum biluribin ranges from 2-20 mg %).
5. Investigations to exclude other causes of pruritus and of abnormal LFTs performed, weekly till delivery.
6. USG showed normal liver without evidence of obstructive Jaundice.
7. Liver biopsy was not done in any case.

8. Patients were given bed rest, folic acid supplementation, soothing lotions for purities.
9. Management was conservative and symptomatic.
10. Ursodeoxycholic acid a choleretic agent, was given in present pregnancy when serum bilirubin was raised > 5g% in a dose of 15 mg/kg body wt/ daily is administered till delivery.
11. Fetal monitoring done weekly by clinical means, USG, and Biweekly biophysical profile.
12. IUGR, low birth weight, and still birth are seen.
13. Blood transfusion given in one patient for PPH.
14. Prophylactic vitamin K is given before delivery.
15. Postnatal resolution of pruritus and abnormal LFTs confirmed after 2- 3weeks.
16. All three babies were normal at the age of 3months, and at six months follow up.

III. Results

There is rapid clinical improvement in pruritus and resolution of deranged biochemistry while taking ursodeoxy cholic acid, and also improved perinatal outcome.
Presentation of four cases is shown below.

Case 1: 25years G3, P3.

ANC registration		1st pregnancy	2nd pregnancy	3rd pregnancy
1	Booked/ non booked	Booked	Booked	Booked
2	Specific symptoms	--	Pruritis at 9months.	Pruritis at 6 months, jaundice at 8th month with loss of fetal movements, admitted with labor pains.
3	Specific investigations	-	Serum bilirubin 2. 2 mg%	. Serum bilirubin 7.2 mg%,
4	Treatment received	-	Ursodeoxycholic acid 15 mg/kg daily 15 days prior to delivery, and 7 days after delivery.	Ursodeoxycholic acid 15 mg/kg daily/bd 7 days after delivery.
5	Mode of delivery	FT,ND	FT,ND,	Preterm, still birth, vaginal delivery.1. 2kg
6	Complications	--	--	Severe PPH.
7	Fetal outcome	FA/H/ 6years	2.5 kg,M/A., 3yrs,	Still birth
8	Disappearance of manifestations	-	S. biluribin became normal after 15 days.	Serum bilirubin became normal after 15 days

Case 2: 30years G3, P3

ANC registration		1st pregnancy	2nd pregnancy	3rd pregnancy
1	Booked/ non booked	Booked	Booked	Booked
2	Specific symptoms	-	Pruritus at 4months. Jaundice at 7months.	Pruritus at 4months and jaundice at 7 months.
3	Specific investigations	-	Serum bilirubin 1.2 mg in 5th month rose to 10mg% on follow up at 36 weeks.	Serum bilirubin 1mg% at 3 months & raised to 18 mgs at 6months and persisted till term.
4	Treatment received	-	Ursodeoxycholic acid 15 mg/kg daily for 7 days.	Ursodeoxycholic acid 15 mg/kg /bd/daily for 21 days, with a drug free interval of 10 days, till delivery.
5	Mode of delivery	FT,ND	FT,LSCS	FT, LSCS at 37 wks, severe IUGR .
6	Complications	--	--	--
7	Fetal outcome	F,A/H/ 7years	IUGR, M/A. 3yrs,	IUGR at 37 wks, 1.6 kg.
8	Disappearance of manifestations	No relevant history	Jaundice disappeared within 1 week .S. biluribin became normal after 3 weeks.	Serum bilirubin became normal after 3 weeks.

Case 3:19 years G1, P1

ANC registration		1st pregnancy
1	Booked/ non booked	Booked
2	Specific symptoms	Developed jaundice and purities' at 4 months
3	Specific investigations	S. bilirubin rises to 14 mg%, but after taking udiliv comes to 2.2 mg% within 6weeks, 7 mg% at 36weeks.
4	Treatment received	Ursodeoxycholic acid 15 mg/kg, BD daily for 21 days, with a drug free interval of 10 days, till delivery.
5	Mode of delivery	Vaginal delivery at 36 weeks.
6	Complications	Developed PROM at 36 weeks.
7	Fetal outcome	Preterm delivery 2.2 kg,Alive/ healthy
8	Disappearance of manifestations	Pruritus disappeared within 2 days of delivery, S. bilirubin came to normal within 7 days of delivery

Case 4: 26years G2, P2

ANC registration		1st pregnancy	2nd pregnancy
1	Booked/ non booked	Booked	Booked
2	Specific symptoms	Purities at 4 months and jaundice at 6 months	Purities and jaundice at 5months.
3	Specific investigations	Serum.biluribin 6mg%	Serum biluribin raised to 12mg%.
	Treatment received	No history	Ursodeoxycholic acid 15 mg/kg BD/daily for 21 days, with a drug free interval of 10 days, till delivery.
4	Mode of delivery	Terminated at periphery for jaundice.	Preterm vaginal delivery at 36 weeks.
5	Complications	Preterm	Preterm, 2 kg.
6	Fetal outcome	Still birth	M/A, 6months old.
7	Disappearance of manifestations	Within2- 3 weeks.	Serum. biluribin became normal after 15 days.

IV. Discussion

Intrahepatic cholestasis of pregnancy presents in the second or third trimester with the sudden onset of severe pruritis that starts on the palms and soles and quickly becomes more generalized. The pruritis persists throughout pregnancy and is worst at night. The secondary lesions involve linear excoriations and excoriated papules and develop secondary to scratching. Jaundice occurs in about 10% of patients and is due to concomitant extra hepatic cholestasis, often accompanied by dark urine and clay-colored stools. These patients are at risk of developing steatorrhea with malabsorption of fat-soluble vitamins, including vitamin K, which might lead to bleeding complications and cholelithiasis.[4] The clinical importance of obstetric cholestasis lies in the potential fetal risks.

Mechanism: Causes of intrahepatic cholestasis of pregnancy are still not fully understood.[5] Clustering of cases of IHCP in families, geographic variation in rates of IHCP and recurrence of IHCP in 45-70% of subsequent pregnancies all suggest a genetic component to the disease.[4]A number of features of the disease suggest a link to hormones:[6] IHCP occurs in the third trimester at the time when hormone levels are at their highest.Twin and triplet pregnancies, which are associated with higher hormone levels, show a higher incidence of IHCP.[7] IHCP resolves quickly after delivery, when placental hormone production ceases. High-dose estrogen oral contraceptive pills could cause features of IHCP. Women should be informed of the inability to predict stillbirth, increased risk of perinatal morbidity from early intervention (after 37+0 weeks of gestation).

If the ALT level is elevated, along with pruritus of palms and soles, could be considered as diagnostic of IHCP, but only with elevated bile acid levels (however LFTs are not always elevated in IHCP patients). The serum bile acid blood test for IHCP is a quantitative measurement of bile salts.

Mode of action : Ursodeoxycholic acid regulates cholesterol by reducing the rate at which the intestine absorbs cholesterol molecules while breaking up micelles containing cholesterol. Because of this property, ursodeoxycholic acid is also used to treat gallstones non-surgically. ursodeoxycholic acid thought to be chemo preventive, perhaps by inducing cellular differentiation and/or cellular senescence in colon epithelial cells. In obstetric cholestasis, the proposed mechanism of action of UDCA is displacement of more hydrophobic endogenous bile salts from the bile acid pool. This may protect the hepatocyte membrane from the damaging toxicity of bile salts; enhance bile acid clearance across the placenta.

V. Conclusion

Cholestasis of pregnancy though benign, is associated with perinatal mortality, and morbidity. Pruritus is the cardinal sympom, and might not have other clinical features. Administration of ursodeoxy cholic acid provides a significant improvement in maternal purities' and biochemical abnormalities, but with low birth weight babies at the time of delivery, but normal post natal development. Delivery by 35-37 completed weeks may be important to fetal outcome as a recent study demonstrated that in severe ICP (defined as bile acids greater than 40 umol/L) the risk of stillbirth was 1.5% compared to 0.5% of uncomplicated pregnancies. This risk rose further if bile acids doubled.[9]

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