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Pregnancy with Pruritus: Our Experince.

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Abstract: *Pruritus effects about 15% of pregnancy and is distressing for the women and also carry additional risk to the foetus. Careful clinical evaluation supported by appropriate laboratory investigation will help in the differential diagnosis of the specific skin condition such as scabies and systemic disorders with associated dermatological manifestations.*
Aim: *Aim of the study is to evaluate outcome of pregnancy with pruritus.*
Material and method: *A total number of 270 pregnant women who attended antenatal clinic of a defence hospital were monitored for the symptom of pruirtus during the period of Jul 2005 to Aug 2006. There were 35 patients who had symptoms of pruritus.*
Result : The incidence was about 14.5 % at the age group below 30 years and about 10% in older patients. The incidence in primigravida was 14 % and in multigravida was 12%. 80 % of patients were in third trimester. A varied aetiology of pruritus was observed such as 24 (68.5%) IHCP, 39 (3.8%) skin infection, 2 (5.7%) allergic drug reaction , 2 (5.7%) polymorphic eruption of pregnancy, 3 (5.85%) idiopathic, 2 (5.7%) allergic drug reaction and 1 (2.8%) scabies. The site of pruritus was predominantly abdomen (77%). The pregnancy complications was observed in the form of IUGR in 9 (25.7%), gestational diabetes in 3 (13%), jaundice in 7 (20%) of cases, preterm labour in 8(22.8%), foetal distress in 19(54.2%), meconium stained liquor in 21(60%). Operative deliveries LSCS n 11 (31.4%), vacuum delivery in 3 (8.5%) , forceps delivery in 2 (5%) , PPH in 7 (19%) and neonatal admission in NICU in14(40%)
Conclusion: Pruritus in pregnancy is often encountered in ante natal period. Intra hepatic cholestasis of pregnancy is an important cause of pruritus, which is associated with adverse obstetrical and foetal outcomes. Therefore, close monitoring of maternal and foetal conditions as well as timely delivery on reaching term is advisable.
Key words*: pruritus in pregnancy, obstetric cholestasis, fetal compromise.*

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I. Introduction

Pruritus effects about 15% of pregnancy and is distressing for the women .(1) It may be very stressful for the women and also carry additional risk to the foetus. Careful clinical evaluation supported by appropriate laboratory investigation will identify the specific skin condition such as scabies and systemic disorders with associated dermatological manifestations. In patients with itching and rash one should consider other systemic disorders such as lymphoma, liver and thyroid disorder. In the remaining women where rash is present a pregnancy specific dermatosis such as polymorphic eruption of pregnancy, pruritic folliculitis of pregnancy, prurigo of pregnancy, pemphigoid (herpes) gestationis, impetigo herpetiformis may occur.(2) One study has proposed that an over active placenta as measured by excessive elevated human chorionic gonadotrophin (HCG) levels can be associated with pruritus provided other causes have been excluded.(3)

The women who have neither rash nor systemic disorder and no pregnancy specific dermatosis should be considered to have pruritus gravidarum-obstetric cholestasis also called intrahepatic cholestasis (IHCP). Obstetric cholestasis is associated with cholesterol gallstones is associated with raised transaminases. Clinical studies reported that IHCP may lead to premature birth in upto 60%, meconium staining of amniotic fluid in 30-40% , risk of obstetrics hemorrhage in 10-22% due to hypoprothrombinemia, fetal distress in upto 33% and intrauterine foetal death in upto 2-15% of patients.(4,5,6) The cause of foetal death is acute anoxia.(7) the incidence of obstetrics cholestasis varies from 0.1-1.5% of pregnancies in Europe and 9.2-15.6% in South American countries such as Bolivia or Chile . It is particularly high in the native Araucanian population in Chile, where the proportion of affected pregnancies reach nearly 28% . (8) The aetiology of obstetrics cholestasis is undoubtedly multifactorial , with genetic , environmental, and hormonal factors having important roles.

Aim

Aim of the study is to evaluate outcome of pregnancy with pruritus.

II. Material And Method

A total number of 270 pregnant women who attended antenatal clinic of a defence hospital were monitored for the symptom of pruirtus during the period of Jul 2005 to Aug 2006. There were 35 patients who had symptoms of pruritus. They were evaluated and the findings of clinical examination , ultrasonography and appropriate laboratory investigations in the antepartum, intrapurtum and postpartum periods were recorded.They were managed by standard obstetrics practice. The incidence of meconium stained liquor, neonatal health status , NICU admission were observed and data was analysed.

III. Result

A total no of 270 pregnant women had been observed during the study period and 35 patients had symptoms of pruritus with variable intensity . The incidence of pruritus was about 15% in pregnant women who were below 30 years of age and 9.7% in those of older age. (Table 1)

Table1. Age of patients with pruritus

	<20 yrs	20-25 yrs	26-30	>30 yrs
Number of patients with pruritus	07	13	11	04
Total no of pregnancies	65	89	75	41
Percentage %	15	15.7	14.7	9.7

The incidence of pruritus in primigravida was 14%, second and third gravida were 12 %, and in fourth gravida and above was about 10.7%. (Table 2)

Table2. Parity of patients with pruritus

	Primi gravida	Second gravida	Third gravida	Fourth gravida & above
No of patients with pruritus	12	10	6	6
Total number of pregnant patients	85	80	49	56
Percentage	14.1	12.3	12.2	10.7

Pruritus was experienced at different gestational age, 7 (20%) pregnant women had in second trimester and 28 (80%) had in third trimester.(Table 3)

Table 3. Gestational age of patients with pruritus

	First trimester	Second trimester	Third trimester
Number of patients with pruritus	00	07	28
Percentage	00	20	80

The causes of pruritus evaluated were: IHCP in 24 (68.5%), skin eruptions (bacterial infections) in 03 (8.5%), allergic rashes and drug reaction in 02(5.7%) and scabies in 01 (2.8%).(Table 4)

Table 4. Aetiology of patients with pruritus

Aetiology	Number of pregnancy with pruritus	Percentage
Intra hepatic cholestasis(IHCP)	24	68.5
Skin eruption (bacterial infection)	03	8.5
Poly orphic eruption of pregnancy	02	5.7
Idiopathic	03	8.5
Allergic rash and dru reaction	02	5.7
Skin infection with scabies	01	2.8

The predominant site of pruritus were 27 (77%) in abdomen, 13 (37.1%) limbs , 10 (28.5) back and chest and 17 (48%) in whole body. (Table 5)

Table 5. The site of pruritus

Site of pruritus	No of pregnancy with pruritus	Percentage
Abdomen	27	77
Limbs (palm & sole)	13	37.1
Back and chest	10	28.5
Whole body	17	48.5

Pregnancy complication observed were IUGR in 9 (25.7%) gestational impaired glucaose tolerance in 03(8.5%), and jaundice in 07(20%) .(Table 6)

Table 6. Pregnancy complications

Complications	No of pregnancy with pruritus	Percentage
IUGR	9	25.7
Gestational Impared Glucose tolerance	03	8.5
Jaundice	07	20

Abnormal liver function test were observed in the form of raised serum biliruibin 0.8 mg/dl in 10 (28.5%), SGOT>40 iu in 24 and SGPT >40 in 24 patients. (Table 7)

Table7. Abnormal Liver Function Test

Test	No of pregnancy with pruritus	Percentage
Serum bilirubin > 0.8 mg/dl	10	28.5
SGOT>40 iu	24	68
SGOT>40 iu	24	68

Complication at delivery were observed as preterm labour in 8(22.8%), foetal distress in 19(54.2%), meconium stained liquor in 21(60%). Operative deliveries LSCS in 11 (31.4%), vacuum delivery in 3 (8.5%) , forceps delivery in 2 (5%) , PPH in 7 (19%) and neonatal admission in NICU in14(40%).

Table 8 Complications of delivery

Complications	No of pregnancy	Percentage
Pre term delivery	08	22.8
Foetal distress	19	54.2
Meconium stained liquor	21	60
PPH (modeate)	05	14
PPH (severe)	02	5
NICU admission	14	40
Vaccum delivery	03	8.5
Forceps delivery	02	5
LSCS	11	31.4
Neonatal death	0	00

Observation

A total of 35 (12.9%) pregnant women complained of pruritus amongst 270 women who had delivered during the study period. The incidence was about 14.5 % at the age group below 30 years and about 10% in older patients. The incidence of pruritus in primigravida as 14 % slightly above than multipara which was about 12%. About 80 % of patients had the onset of pruritus in third trimester. A varied aetiology of pruritus was observed such as 24 (68.5%) IHCP, 39 (3.8%) skin infection, 2 (5.7%) allergic drug reaction , 2 (5.7%) polymorphic eruption of pregnancy, 3 (5.85%) idiopathic, 2 (5.7%) allergic drug reaction and 1 (2.8%) scabies. the site of pruritus was predominantly abdomen (77%). The pregnancy complications was observed in the form of IUGR in 9 (25.7%), gestational diabetes in 3 (13%), jaundice in 7 (20%) of cases .Liver function abnormality was observed as raised serum biluribin in 10 (28.5%) and raised SGOT/SGPT in 24 (68%) of cases. The delivery was complicated by foetal distress in 19 (54.2%) ,preterm labour in 8 (22.8%), forceps delivery in 2 (5%), vacuum delivery 3 (8.5%), LSCS 11 (31.4%), meconium stained amniotic fluid in 21 (60%), PPH 7 (19%) and neonatal NICU admission in nursery 14(40%).

IV. Discussion

Pruritus of variable intensity is commonly encountered in pregnant women. It is an unpleasant cutaneous sensation provoking scratching also known as itch. The pathophysiological origin of itch is within skin free nerve endings involving unmyelinated C fibers to dorsal horn in spinal cord. Scratching is spinal reflex response it ascends to cerebral cortex via spinothalamic tract. The chemical mediators are substance P, opioid and non opioid peptides, somatostatin, neurokinin A, histamine, serotonin, prostaglandins. External mediators are skin inflammation environmental heat or dryness, vasodilation, psychological concerns.

Pregnancy specific dermatological lesion such as pruritic urticarial papules and plaques of pregnancy also called polymorphic eruption of pregnancy are also seen. It occurs more commonly in primigravidas, more common in third trimester; with an incidence of 0.4- 0.6% of pregnancies and it may be related to abdominal distention. Increased meternal weight gain, foetal macrosomia, and twin gastation are risk factor. Affected locations are at the onset over abdomen in 90% of case (especially striae), symmetric spread to thigh and

buttock, may also involve upper arm, back, and hand. Usually does not involve face or periumbilical area. The lesion appears as red 1-2 mm papule with surrounding pale halo. The lesions may coalesce into urticarial plaques and few vesicle may also be seen. The management is nonspecific management of pruritus such as cool compresses, oatmeal bath, antithistamines. The refractory cases of intolerable itching may need topical conrticosteroids even consider short course of Prednisone 40 mg. The severity decreases within one week of onset. Rash and symptoms persist on average 6 week and resolves with delivery .

The obstetrics cholestasis has relatively very low incidence of approximately 0.7% of pregnant women in the UK and 0.2–2% of pregnant women worldwide with adverse maternal and foetal implication increased risk of adverse perinatal outcomes associated with severe ICP, such as spontaneous preterm birth, meconium staining of the amniotic fluid and stillbirth. (10) Historically obstetric cholestasis has been associated with the cholestatic effect of oestradiol metabolites, in practicular 17-β oestradiol glucuronide. Progesterone metabolites, however, play an ever more important part in its pathogenesis. Patients with obstetric cholestasis have a siginificantly increased ratio of 3 α to 4 β hydroxysteriods and large amount of mono or disulphated progesterone metabolites excreted in their urine. (11) Excess of these metabolites in the urine in obstetric cholestasis may be related to malfunction of biliary canalicular transporters normally responsible for their secretion from hepatocytes into bile. Several of these transporters have recently been characterized and include proteins responsible for bile canalicular secrection of bile acids (bile salt export pump), organic anions (multidrug resistant protein 2) or phospholipids (multidrug resistance protein 3).

Recent findings have shown that obstetric cholestasis occurs more commonly patients whose mothers have rare, inborn cholestatic disoders such as progressive familial intrahepatic cholestasis type 3 or recurrent familial intraheptic cholestasis, both related to dysfunction of biliary transporters. This suggests that mothers heterozygous for mutation in genes coding for transporter proteins are predisposed to obstetric cholestasis. For example, in the family of an infant with progressive familial intrahepatic cholestasis type 3 both maternally and paternally related women who were heterozygous for the multidrug resistance protein 3 mutation suffered from obstetric cholestasis. (12) The infants condition was caused by a mutation associated with dysfunction of the bile canalicular phospholipid transporter multidrug resistance protein 3, which cause raised levels of gamma glutamyle transpeptides,

In other patients with obstetric cholestasis and raised mamma glutamyl transpeptidese but without a family history of progressive familial intrahepatic cholestasis, it was found that a single amino acid substitution disrupted multidrug resistance protein trafficking to the membrane of transfected cell. (13) A recent study from Finland showed a significantly higher incidence of obstetric cholestasis among mother and sister of patient with obsestric cholestasis, confirming a genetic predisposition to this condition. (14)

Thus it is plausible to speculate that mild malfunction of canalicular transporters, which cause no problem outside pregnancy, may lead to clinical symptoms of cholestasis when the capacity of transporters to handle substrates is exceeded—as occurs with high levels of sex hormones produced in pregnancy. It is possible that fetal inheritance of the " loss of function" mutation in a gene that codes for a protein which transports bile acids across the placenta to the mother could predispose it to be the effect of raised serum bile acids. Animal studies have implicated bile acids in the patho-physiology of intrauterine death and spontaneous prematurity in obstetric cholestasis. (15,16) Therefore inheritance of such a mutation would predispose the fetus to these complications.

Obstetric cholestasis classically manifests itself in the second or third trimester of pregnancy with generalized prupritus, most pronounced in palms and soles. Jaundice is relatively uncommon, complicating only the most severe and prolonged episodes. Routine liver function tests show raised transaminases in 60% of patient and raised bilirubin concentrations in only 20%, bile acids were raised in the vast majority of patients.

The recent demonstration of an association between obstetric cholestasis and mutation of multidrug resistance protein 3 (causing raised levels of serum gamma glutamyl transpeptidase) had prompted to determine the proportion of patients with obstetric cholestasis who had raised gamma glutamyl transpeptidase values: these were a third of all patient with obstetric cholestasis. Ursodeoxycholic acid, is increasingly used in patients with obstetric cholestasis (17,18,20) This hydrophilic bile acid was found to normalize the ratio of 3α to 3β hydroxysteriod in patients with obstetric cholestasis and decrease the accumulation of bile acids, in particular cholate, in the fetus. (11,18,21) Ursodeoxycholic acid is effective in reducing abnormalities in liver function test. (17, 18) No concerns have emerged about potential adverse events, and the only side effect noted so far is occasional, mild diarrhoea.

The occurance of pruritus in pregnant women should be the subject of routine inquiry, and when present acted on. Confirmation of obstetric cholestasis with blood tests should alter management. Affected patients can be offered treatment with ursodeoxycholic acid, not only to relieve pruritus but also to protect against accumulation of biliary constituents of maternal origin in the fetus, which may contribute to risk of fetal distress of even stillbirth.it should prompt a search for underlying liver disease. (20, 21)

Intra hepatic cholestasis typically resolve rapidly following delivery; occasionally abnormalities in liver function tests persists for 34–82 weeks. Liver function and serum bile acid level should be estimated 6 weeks postpartum. Persistently high transaminases or serum bile acids levels after 6 weeks postnatal period need a check for other causes for hepatic dysfunction such as viral hepatitis, primary billiary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, drug induced, biliary obstruction, veno occlusive diseases etc. In spite of rapid resolution, emerging data indicates association of future morbidity in both women and their children. There is a higher incidence of hepatobiliary diseases (hazard ratio, HR 2.62; 95% CI 2.47–2.77), including hepatitis C (HR 4.16; 95% CI 3.14–5.51), chronic hepatitis (HR 5.96; 95% CI 3.42–10.33), hepatic fibrosis (HR 5.11; 95% CI 3.29–7.96) and gallstones (HR 2.72; 95% CI 2.55–2.91) in effected women. (22)

A recent study of 2015 has also reported increased risks of liver and biliary tree cancer (HR 3.61; 95% CI 1.68–7.77 and HR 2.62; 95% CI 1.26–5.46, respectively), immune-mediated disease (HR 1.28, 95% CI 1.19–1.38) and cardiovascular disease (HR 1.12, 95% CI 1.06–1.19) in women with ICP. (23) Another study had opined that children of women who had ICP during pregnancy are also at increased risk of metabolic disease later in life. (24)

The use of bland topical ointments, calamine lotion, and aqueous cream with menthol and systemic treatment – cholestyramine - a poorly tolerated acid chelating agent had reported relief in some women ,but associated with exacerbating vit K deficiency . There is insufficient evidence to recommend Gaur Gum, activated charcoal, S- adenyl –methionine .UDCA alone or in combination shows improvement in treating women with cholestasis of pregnancy. Delivery should be considered after 37 completed weeks of pregnancy. (25)

A recent Cochrane review in management of IHCP ,has described as insuffinient evidence to use S-adenyl –methionine, guar gum, activated charcoal, dexamethasone, cholestyramine , Salvia, Yinchnghao decocton(YCHD), Danoxioling and Yiganling or Yiganling alone or in combination are effective in treating women with cholestasis of pregnancy.(26)

V. Conclusion

Pruritus in pregnancy is often encountered in ante natal period though often not given adequate attention and not evaluated. Intra hepatic cholestasis of pregnancy is an important cause of pruritus, which is associated with adverse obstetrical outcome as well as indicator of hepatic dysfunction,cancer and metabolic disorders in offspring . Continuation of pregnancy beyond the 37th week of gestation is associated with risk of foetal distress and even stillbirths. In affected mother the symptoms classically disappear within a day to two after delivery, with rapid normalization of liver function values and serum bile acid concentrations. Persistent abnormalities should prompt a search for underlying liver disease.

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