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Research Article

Prevalence and complication of Intrahepatic Cholestasis of Pregnancy

Magda M Helmi*

Private Consultant, Department of Obstetrician and Gynecologist, El hedaia Center, Giza, Egypt

***Corresponding Author:** Magda M Helmi, Private Consultant, Department of Obstetrician and Gynecologist, El hedaia Center, Giza, Egypt.

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a temporary condition caused by maternal liver dysfunction during pregnancy. It is characterized by intense generalized pruritus (itchiness). It is a relatively rare condition affecting pregnant women. Though it has been reported to occur in as many as 4% of pregnancies in Chile, and in over 1% of pregnancies in Scandinavia, the rate of occurrence in the U.S. is believed to be less than 1 in 1,000 (0.1%). It appears to be genetically linked. Its prevalence in Egyptian pregnant population is not well defined. Therefore, detailed schematic investigation was carried out on 6900 pregnant cases until delivery of the baby. 79 patients showed high levels of bile acids and hepatic enzymes (20 cases with itching and 20 cases as control were reassessed for liver function test twice: at 30 and at 36 weeks and followed up to delivery). Highly significant correlation between high levels of bile acids, hepatic enzymes in blood and obstetric complications (preterm labor, operative delivery, fetal distress and lower than average apgar scoring).

Keywords: Intrahepatic Cholestasis; Pregnancy; Obstetric; Complications

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a temporary condition caused by maternal liver dysfunction during pregnancy. To understand the link between ICP, bile acid levels and stillbirth [1], analysed more than 170,000 pregnancies from 40 international studies. The work was funded by ICP Support, Tommy's, Genesis Research Trust, Wellcome Trust and the NIHR. Severe Intrahepatic cholestasis of pregnancy is associated with adverse pregnancy outcome. Levels of BA correlate between mother and fetus [2]. This condition is characterized by intense generalized pruritus (itchiness) which usually begins in the third trimester. Though it may cause extreme discomfort, cholestasis of pregnancy is generally regarded as benign to the mother (Feldman M., *et al*). It has, however, been associated with an increased incidence of stillbirth [3-5].

The condition resolves shortly after delivery Intrahepatic cholestasis of pregnancy (ICP) is also known as obstetric cholestasis (OC) cholestatic jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum [3]. Cholestasis of pregnancy is a relatively rare condition affecting pregnant women. The rate of occurrence in Egypt is not accurately determined. The poCreams, such as aqueous cream with menthol, are safe to use in pregnancy and can provide some relief from itching.

There are some medications, such as ursodeoxycholic acid (UDCA), that help reduce bile acids and ease itching.

The purpose of the study is evaluating the incidence of obstetric cholestasis with pregnancy in Egyptian population/The danger from ICP is eliminated when the child is safely delivered. When cholestasis of pregnancy was first described, it was viewed as a benign condition. Since then, it has been widely established that ICP poses a significantly increased risk to the fetus.

Some specialists might advise earlier induction than this if the condition is severe (defined as bile acids over 40μmol/L). Nevertheless, many physicians still perceive this condition as harmless

and merely adopt a "watch and wait" policy. Because many obstetricians may see very few pregnancies with ICP in their careers, and most of those end without complication (even without treatment), they may be reluctant to induce labor when fetal monitoring shows no abnormalities. It is hoped, however, that they learn from the sad experience of other physicians who have published their data that the condition indeed poses serious risks and should be treated accordingly.

Aim of the work

Evaluation of incidence of obstetric cholestasis in Egypt.

Methods and Material

Source of population

Health insurance unit in 6 October city (between years, 1995 - 2001), Antenatal clinic. There were no other obstetric services within this area at this time and therefore the great majority of pregnant women use the services of this obstetric unit.

Selection of participants

All of the participants 9600, were followed up during pregnancy. (They are all employed mid social class residence of Sixth October city). 79 out of 9600 pregnant women, complaining of pruritus (itching without a rash) with the current pregnancy.

All attendees were followed up included ordinary antenatal care up to delivery with regular antenatal laboratory profile and regular ultrasonic assessment of pregnancy. One biochemistry laboratory serves all of these health unit, We endeavored to trace all abnormal liver tests occurring in pregnant women in this geographical area using the computer database of the biochemistry laboratory. The principal biochemist flagged up all abnormal liver tests which originated from the antenatal clinic of our health unit.

Exclusion criteria

All patients were referred to internist in the same unit to be clinically laboratory and ultrasound assessed to exclude the following patient.

1. Any coincidental diseases.
2. Any organic or infectious liver diseases, including viral hepatitis.
3. Any, dermatological condition.
4. Patients with hypertension and/or proteinuria.
5. Patients with acute fatty liver with pregnancy.
6. Twins and multiples.

The following laboratory tests (Pubmed-indexed for Medline) were done for 40 cases (20 cases with a history of itching, without a rash, and 20 cases without any complaint):

- Total bilirubin; Unconjugated bilirubin; Indirect bilirubin; Conjugated bilirubin; Direct bilirubin (Normal Values direct bilirubin: 0 to 0.3 mg/dl total bilirubin: 0.3 to 1.9 mg/dl Note: mg/dl = milligrams per deciliter (Pub Med –indexed for Med line).
- ALT in serum SGPT; Serum glutamate pyruvate transaminase; Alanine transaminas. (Normal Values Normal range can vary according to a number of factors). This test is used to determine if a patient has liver damage (Pub Med –indexed for Med line).
- AST; Aspartate aminotransferase; Serum glutamic-oxaloacetic transaminase; SGOT; (Normal Values the normal range is 10 to 34 IU/L.m Note: IU/L = international units per liter (Pub Med –indexed for Med line).
- Bleeding time (Normal Values the bleeding stops within 1 to 9 minutes) this is a test that measures the speed at which small blood vessels close off to stop bleeding (the condition of the blood vessels) and platelet function (Pub Med –indexed for Med line).

Abnormal liver function tests (LFT) were defined as: bilirubin >25 μmol/l; aspartate aminotransferase (AST) > 40 iu/l; gamma glutamyl transpeptidase (γGT) >35 iu/l. It should be stressed that liver function was not assessed as routine in all pregnancies.

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Diagnostic criteria for obstetric cholestasis of pregnancy were based on clinical findings and investigations (Itching and elevated hepatic enzymes).

Results

Prevalence of Cholestasis of pregnancy

The prevalence of the condition in the chosen sample was (79 out of 6900) 1.14%.

Mild jaundice: occurred in only 2 pregnant cases with itching ('yellow' coloration of the skin, dark urine and pale faeces).

n%

Cases with itching 79 1.14

Cases without itching 6821 98.85

Total 6900 100

Pregnancy outcome

Outcome Total -n Normal-n% OC-n%
Preterm labor
Operative delivery
Fetal distress
A Still birth
Meconium
280
689
347
417
6
273
681
341
409
5
4
9.98
5
5.99
0.07
7
8
6
8
1
35%
40%
30%
40%
5%
Apgar scoring>5
689
681
9.98 8
40%

Apgar score at 5 min was satisfactory in all neonates.

Liver function tests (32 Weeks pregnancy)

Test r Normal % n. Abnormal % Total
Total bilirubin
ALT
AST
Bleeding time
6
1
18
40
15
2.5
45
100
34
39
22
0
85
97.0
55
0
40
40
40
40

Liver function tests (36 Weeks pregnancy)

Test n. Normal % n. Abnormal % Total
Total bilirubin 2 5.1 37 94.8 39
ALT 0 0 40 100 39
AST 22 56.4 17 43.58 39
Bleeding time 39 100 0 0 39

ALT values

Variable Mean SD SE N P
ALT 30 W 1st group 39.550 3.649 0.816 20 0.098
ALT 36 W 1st group 40.400 3.218 0.720 20
ALT 30 W 2nd group 70.900 8.638 1.932 20 0.350
ALT 36 W 2nd group 73.667 9.387 2.213 18

A S T values

Variable Mean SD SE N P
AST 30 W 1st group 22.100 8.290 1.854 20 0.580
AST 36 W 1st group 23.550 8.159 1.825 20
AST 30 W 2nd group 46.350 7.707 1.723 20 0.117
AST 36 W 2nd group 50.944 9.879 2.328 18

Total bilirubin

Variable Mean SD SE N P

BD 30 W 1st group 0.121 0.100 0.022 20 0.804

BD 36 W 1st group 0.129 0.103 0.023 20

BD 30 W 2nd group 0.238 0.214 0.048 20 0.221

BD 36 W 2nd group 0.329 0.244 0.056 19

Bleeding time

Variable Mean SD SE N P

BT 30 W 1st group 0.540 0.219 0.049 20 0.942

BT 36 W 1st group 0.535 0.216 0.048 20

BT 30 W 2nd group 0.885 0.669 0.150 20 0.976

BT 36 W 2nd group 0.879 0.563 0.129 19

Normal total bilirubin Values: 0.3 to 1.9 mg/dl. Abnormal total bilirubin Values: 2:6.8mg/dl.

Normal ALT Values: 35 to 45 IU/L. Abnormal ALT Values: 45:92 IU/L. Normal AST Values: 10 to 34 IU/L. Abnormal AST Values: 34:79 IU/L.

Discussion

The incidence of obstetric cholestasis in the sample examined were 1.14% Egyptian pregnant woman. It varies from 0.1% to 1.5% of pregnancies in Europe and 9.2%-15.6% in South American countries such as Bolivia or Chile [6]. It is particularly high in the native Araucanian population in Chile, where the proportion of affected pregnancies reaches nearly 28%. 3 and in over 1% of pregnancies in Scandinavia [7].

It appears to be genetically linked; more than one-third of patients have a family history of the disease e.g. mothers or sisters [5]. When the condition occurs in a pregnancy, it recurs in 60-70% of future pregnancies and occurs in every pregnancy of about 25% of affected women. However, the severity of ICP may vary from one pregnancy to the next and may skip pregnancies entirely.

The condition is also up to four times more common in twin or triplet pregnancies than in singleton pregnancies ICP has a mild association with previous miscarriage while it has been shown to have no association with obesity, infertility, maternal diabetes, or chronic illness [5].

Itch

This is the most common and typical symptom. The itching associated with OC usually begins during the last ten weeks of pregnancy, although it can start much earlier. Women describe it as constant and sometimes as intolerable. The itch can be 'all over', but it is often worst on the hands and feet. Commonly, itch is the only symptom. Hillman., *et al*. [8], Considered intrahepatic cholestasis of pregnancy in all women who have itching during pregnancy.

OC can present with severe itching and normal liver/bile acids. Normal serum markers of liver function and/or bile acids at the onset of pruritus do not exclude the later development of OC. There is a need, therefore, to identify early and specific serum marker(s) of OC. Several other disorders were considered to be excluded. For example the absence of hypertension and proteinuria, ALT is a simple bile acid blood test could tell risk of stillbirth [1] Locatelli and colleagues [9] have shown a significantly higher rate of cholestasis in otherwise asymptomatic women seropositive for hepatitis C. In our study all the patients were seronegative for viral hepatitis C and were checked up by the Internist before admission to the study.

It may be extremely stressful for the mother but also carries risks for the baby [6].

Creams, such as aqueous cream with menthol, are safe to use in pregnancy and can provide some relief from itching.

There are some medications, such as ursodeoxycholic acid (UDCA), that help reduce bile acids and ease itching.

Complications

Though cholestasis of pregnancy appears to have no serious health risks to the mother, it has been shown to be associated with somewhat increased risks to the fetus. Total serum bile acid concentration is an important laboratory investigation in any woman with itching in the absence of a rash during pregnancy [10]. In obstetric cholestasis, the most common selected liver function tests are total serum bile acids and transaminases particularly ALT [4].

The most concerning complication in ICP is increased rate of fetal death. 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 [6]. One review of over 1,000 reported cases showed a rate of stillbirth and fetal death at delivery to be 10%. Virtually all of the deaths occur at 36 weeks gestational age or more (normal term delivery is at 40 weeks) [3]. It has been associated with a high incidence of stillbirth and perinatal complications. Meconium staining occurred in 45%, spontaneous preterm labour in

44%, and intrapartum fetal distress in 22%. Of 86 infants two were stillborn and one died soon after birth in a study by Fisk and Storey [5].

In our clinical study it is clearly shown that when obstetric cholestasis complicates pregnancies it lead to premature births in up to 35%, fetal distress in up to 30%, and intrauterine death in up to 1% of patients.

In a study by Kenyon, AP., *et al*. [11] 36% women required caesarean section. In our study 40% women required caesarean section.

The etiology of obstetric cholestasis is undoubtedly multifactor, with genetic, environmental, and hormonal factors having important roles. Although OC remains the commonest liver disease in pregnancy (>60% of all cases after 22 weeks gestation) the etiology of the disease is unknown.

Because of the presence of meconium associated with the stillbirths, it is thought that the meconium itself may cause a decrease in oxygen available to the fetus. In our study the incidence of meconium stained liquor was high (40%0) in pregnancy with obstetric cholestasis. Some authors have thought that the deaths may be related to an increased incidence of postpartum hemorrhage. The cause of fetal death is acute anoxia [6]. Regardless, it is widely accepted that the deaths are due to a sudden episode of decreased oxygen rather than a chronic or long-term deficiency most probably the cause of fetal death is acute anoxia [5].

Treatment

There are two primary objectives in treating cholestasis of pregnancy: alleviating the pruritis and ensuring that the child is born safely.

Until the pathophysiology of obstetric cholestasis is understood more clearly, it seems appropriate to offer all women the same policy of active management.

More active management of obstetric cholestasis pregnancies has reduced the associated fetal and prenatal mortality. (More, frequent antenatal visits, at least twice weekly, visiting professional nutritionists as early as we discover the condition).

Regardless of the severity of the abnormality in liver function [11].

The alternative treatments available are

Systemic treatment

Cholestasis often does not respond to medical therapy of any sort. Some reports indicate success with the use of ursodeoxycholic acid (20-30 mg/kg/d), which acts to increase bile formation and antagonizes the effect of hydrophobic bile acids on biological membranes. Phenobarbital (5 mg/kg/d) may also be useful in some cases [12,13].

Anti-Histamines, Dexamethasone, Vitamin K, S-AdenosyI Mmethionine, Cholestyramine [11]. A diet that is rich in carbohydrates and proteins can be substituted for a diet containing long-chain triglycerides., fat-soluble vitamin formulation A, D, E, and K supplementation is safe and potentially effective in patients with cholestasis [12].

Topical treatments

If the skin is well moisturized, pruritus may be relieved. Despite the use of all of the above medication there was no conclusive evidence of their curative effects.

Conclusion

Cholestasis of pregnancy appears to have serious health risks to the fetus, It increases the risk of preterm labor, operative, fetal distress and stillbirth. It manifests itself in the second or third trimester of pregnancy with generalized pruritus, most pronounced in palms and soles. It is characterized by increased hepatic enzyme (ALT) Jaundice is relatively uncommon, complicating only the most severe and prolonged episodes. To avoid complication, routine liver function tests should be done for all pregnant patients with itching without a rash.

Summary

A controlled trial performed at 6th October Health Insurance Unit, to evaluate the incidence of obstetric cholestasis, in the sample examined it was 1.14% pregnant woman cholestasis of pregnancy appears to have serious health risks to the fetus, It increases the risk of preterm labor, operative, fetal distress and stillbirth.. Total serum bile acid concentration increases in pregnant woman with cholestasis of pregnancy. Liver function is getting worse with progress of pregnancy.

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