Intrahepatic cholestasis of pregnancy: Case series of a rare disease in an African setting

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Abstract
Intrahepatic cholestasis of pregnancy commonly presents in the second and third trimester with unexplained pruritus sine materia, abnormal liver function tests, and/or elevated serum total bile acid concentration. Its incidence ranges from less than 1% to 27.6%, with Araucana Indians from Chile being the highest affected. Intrahepatic cholestasis of pregnancy complicates pregnancy, hence influencing its outcomes. Our series involves three cases of pruritus in pregnancy ending with one elective cesarean delivery and two emergency cesarean deliveries without any significant complications to babies as well as immediate resolution of maternal symptoms. High index of suspicion for intrahepatic cholestasis of pregnancy is of paramount importance among clinicians even in primary care setup. Prompt treatment and intervention will prevent poor perinatal outcome.

Keywords
Intrahepatic cholestasis pregnancy, bile acids, pruritus

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Introduction
Intrahepatic cholestasis of pregnancy (ICP) is a heterogeneous condition of pregnancy characterized by unexplained pruritus sine materia, abnormal liver function tests, and/or elevated serum total bile acid concentration.1 It commonly presents in the second and third trimester; however, a few cases have been reported during the first trimester.2 The incidence varies worldwide, ranging from less than 1% to 27.6%, with Araucana Indians from Chile being the highest.3 It is more common in multiple gestation and in women with advanced maternal age. Other recognizable epidemiological contributing factors include prior or family history of ICP.3 The etiology of ICP is unclear, however, hormonal and environmental factors, as well as genetic susceptibility contribute to the condition.4 The classic presentation is mild to severe pruritus predominantly in the soles and palms, which worsens during the night. There are no primary skin lesions associated with the disease other than scratch marks which result in prurigo nodules and excoriations. Other clinical presentations may include right upper quadrant pain, steatorrhea with poor appetite.4,5 ICP complicates pregnancy, hence influencing its outcomes. It is associated with stillbirth with little or no warning at gestation age of 38 weeks or above, preterm birth, meconium-stained amniotic fluid, and neonatal intensive care unit admission.3 Management goals include reduction or elimination of troublesome symptoms and perinatal morbidity/mortality.6 Despite lack of definitive treatment, the current approach advocates the use of ursodeoxycholic acid.6 Fetal wellbeing assessment as well as relevant laboratory tests for a pregnant woman are important and may influence the decision to deliver a woman.3,7 Skin conditions during pregnancy are not uncommon, however, clinical judgment and close follow-up is indispensable because some conditions have adverse neonatal outcomes.

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Table 1. Features associated with the cases.

| Case | Age | Ethnicity | Family history of ICP | Parity | Gestation age at onset | Gestation age at delivery | Reasons and mode of delivery | Outcome |
|------|-----|-----------|-----------------------|--------|-----------------------|--------------------------|-----------------------------|---------|
| 1    | 24  | Asian     | NONE                  | PRIME  | 34                    | 35                       | Non-reassuring fetal status. Emergency-Cesarean delivery | 2.2 kg APGAR SCORE: 61st min, 95th min Pruritus resolved immediately after delivery |
| 2    | 36  | African   | NONE                  | PRIME  | 35                    | 35+3                     | Non-reassuring fetal status. Emergency-Cesarean delivery | 3.25 kg APGAR SCORE: 81st min, 95th min Pruritus resolved immediately after delivery |
| 3    | 35  | African   | NONE                  | P0+2   | 25                    | 37                       | Elective cesarean delivery. | 2.6 kg APGAR SCORE: 61st min, 95th min Pruritus resolved immediately after delivery |

Case series

**Clinical course of the cases**

**Case 1.** She presented with 1-week history of generalized body itching without skin rash, more on palms and soles. Her medical history was remarkable for being on metformin 500mg because of polycystic ovarian syndrome (PCOS). Her laboratory investigation showed alkaline phosphatase 147.10 (35–104) IU/L, albumin 60.94 (66–87) g/L, and bile acids 40 µmol/L (0–14 µmol/L). Her management involved ursodeoxycholic acid 300 mg every 8 h, intramuscular dexamethasone (for fetal lung maturation) 6 mg every 12 h for 48 h with continuation of metformin, and multivitamins tablets (Table 1).

**Case 2.** She presented with 1-day history of generalized body itching with dark urine and normal stools. Her medical history was remarkable for asymptomatic cholelithiasis. She was managed clinically without laboratory confirmation of ICP because reagents for bile acids were out of stock. Urseodeoxycholic acid 300 mg every 8 h, intramuscular dexamethasone (for fetal lung maturation) 6 mg every 12 h for 48 h with continuation of metformin, and multivitamins tablets were prescribed.

**Case 3.** She presented with 1-month history of body itching that worsened with time despite using cetirizine. Her medical history was unremarkable. Because reagents for bile acids were out of stock, she was managed based on clinical symptoms. Urseodeoxycholic acid 300 mg every 8 h for 2 weeks, daily calamine lotion application and intramuscular hydrocortisone 100 mg every 8 h for 3 days were prescribed leading to significant reduction in symptom severity. She continued with her multivitamin tablets. She was managed as an outpatient with weekly antenatal clinic follow-up till delivery.

**Discussion**

ICP has unique epidemiological distribution with variation observed in different geographical areas.9 While reported to be common in South Asia, South America, and among Scandinavian countries, data from Africa are limited.

These epidemiological factors3 may not be applicable all the time, and careful assessment is important. Our cases had some of the above outlined risks, hence detailed assessment prompted heightened suspicion of these cases despite its rarity in our context.

Pruritus during pregnancy represents a spectrum of dermatoses that might be either physiological or pathological due to infections, infestations, and inflammatory conditions occurring coincidentally. In Black skin individuals, the inherent structure and molecular features are known to exacerbate pruritus. This brings about atypical presentation of pruritic conditions leading to difficulties in diagnosis and management.10 In Africa, pruritic conditions are common with infestations as well as skin water contact being the contributors, however, ICP is seldom encountered. However, when pruritus is intense and involves soles and palms, ICP should be suspected.11 Having generalized body pruritus provides a wide differential diagnosis with different management strategies. The less common signs of ICP include nausea, dark urine, light-colored stool, fatigue (extreme tiredness), decreased appetite, pain in the upper right belly, and jaundice (yellowing of the skin and eyes). However, one needs to individualize each case according to the presentation and risk factors to come up with a specific diagnosis as it was in our cases. ICP if not properly identified may cause substantial adverse effects, especially to the fetus. The Royal College of Obstetricians and Gynecologists agrees that ICP is diagnosed in the presence of unexplained pruritus, especially involving soles and palms in pregnancy associated with
abnormal liver function tests and/or elevated serum bile acids as per pregnancy specific ranges, and both resolve after delivery.\textsuperscript{7}

Ursodeoxycholic acid has now been proven to be the most effective medication in treating ICP. In two meta-analyses by Kong et al.\textsuperscript{12} and Zhang et al.\textsuperscript{13} ursodeoxycholic acid was reported to improve pruritus, as well as liver functions in ICP. The findings correlated with reduction in adverse perinatal outcomes. In a case series by Diac et al., where 12 women with ICP presenting with persisting pruritus and deranged liver functions despite the use of ursodeoxycholic acid were put on dexamethasone resulting in clinical and biochemical improvement within 7 days. However, it was concluded that dexamethasone is not the mainstay treatment for ICP but can be used carefully in intractable cases.\textsuperscript{14} The use of cholestyramine, hydrocortisone, antihistamines, and phenobarbitone has not shown to influence relief in ICP on their own; however, they can be used in combination with ursodeoxycholic acid.\textsuperscript{3} We started treatment with ursodeoxycholic acid on all our patients, with two of them also receiving dexamethasone and one hydrocortisone as steroids. Dexamethasone was given in anticipation of preterm delivery which occurred. There was an improvement in symptoms, but two patients ended up delivering prematurely because of non-reassuring fetal status. The symptoms were completely resolved after delivery.

The definitive treatment in ICP involves a planned delivery preferable around 37 weeks to avoid serious fetal adverse effects, such as fetal distress and sudden intrauterine demise. Other management strategies as mentioned earlier with the use of ursodeoxycholic acid are considered but warned against being routinely utilized.\textsuperscript{15,16}

Delivery may be indicated earlier in the case of serious fetal adverse effects such as non-reassuring fetal status.\textsuperscript{4,6} The existing literature also shows that the risk of stillbirth is increased in women with intrahepatic cholestasis of pregnancy and singleton pregnancies when serum bile acids concentrations are 100 µmol/L.\textsuperscript{17} Moreover, levels of bile acids can assist in determining risks for an adverse event for the fetus such as (spontaneous preterm deliveries, asphyxia events, and meconium staining of amniotic fluid, placenta, and membranes) which were found to increase by 1%–2% per additional µmol/L of serum bile acids with the same report reckoning that no increase in fetal risk among ICP patients with bile acid levels <40 µmol/L.\textsuperscript{18} These aid in follow-up and delivery decision in these clients. In cases of clinical suspicion without laboratory confirmation of ICP as it was for our two cases, symptomatic management while monitoring mother as well as fetal wellbeing closely should ensue. For our cases, two had preterm deliveries because of fetal distress and one had an elective C-section at 37 weeks of gestation, with all babies ending up with no significant complications.

**Conclusion**

High index of suspicion of ICP is of paramount importance among pregnant women regardless of their race in primary care setup. Prompt treatment and intervention will prevent poor perinatal outcome.

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**Ethical approval**

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**Informed consent**

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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