Pruritus in pregnancy

Our patient had excoriations all over her body—but no blistering. What do you suspect was causing her itching?

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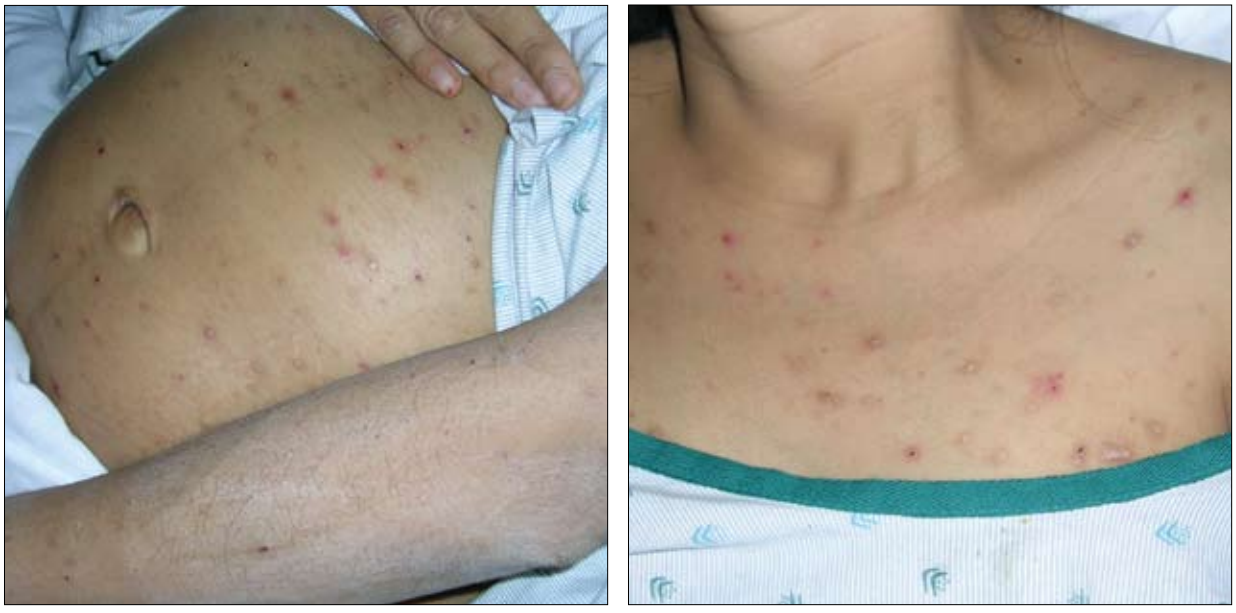
A 32-year-old mother of 2 came into our facility during her 31st week of pregnancy and told us that she couldn't stop itching. She said that her whole body was itchy and it got worse at night. She was unable to get a good night's sleep. Up until this point, her pregnancy had been uncomplicated and she had no past history of medical problems.

An examination revealed excoriations—but no blistering—on her abdomen, chest, arms, and legs (**FIGURES 1 AND 2**). She had no jaundice or scleral icterus. The fundal height was 31 mm and the fetal heart tones were 150 bpm.

- **What is your diagnosis?**
- **How would you manage this condition?**

FIGURES 1 & 2

Excoriations on the abdomen and chest



A 32-year-old woman in her 31st week of pregnancy with excoriations on her abdomen and arm, as well as her chest.

Diagnosis: Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is caused by maternal intrahepatic bile secretory dysfunction.[1] The disorder, which is also referred to as obstetric cholestasis and pruritus gravidarum, has no primary skin lesions. Patients have generalized pruritus and secondary excoriations (**FIGURE 3**). In about 20% of cases, patients are also jaundiced.[2]

The sudden onset of generalized pruritus, which is the hallmark of ICP, starts during the late second (20%) or third (80%) trimester, followed by secondary skin lesions, namely linear excoriations and excoriated papules caused by scratching.[3] These excoriations are typically localized on the extensor surfaces of the limbs, but may also be found on the abdomen and back. The itching may involve the palms and soles, as well. The severity of the skin lesions correlates with the duration and degree of pruritus.[3]

According to one study, ICP occurred in 0.5% of 3192 pregnancies. The disorder resolves after delivery, and recurs with subsequent pregnancies.[4]

ICP has been linked to fetal distress (20%–30%), stillbirths (1%–2%), and preterm delivery (20%–60%).[3] Autopsies of the placenta have shown signs of acute anoxia. Fetal complications in ICP may be caused by decreased fetal elimination of toxic bile acids.[3]

Hormones, genes, and even the weather may play a role

Increased hormone production during pregnancy plays a role in ICP. Estrogen, which increases 100-fold during pregnancy, interferes with bile acid secretion across the basolateral and canalicular membrane of the hepatocyte. Particularly noteworthy is the fact that estriol-16 α-D-glucuronide, the estrogen metabolite that increases most during pregnancy, is cholestatic, according to animal studies.[3] In addition, progesterone metabolites play an important part in the pathogenesis of ICP. Progesterone inhibits hepatic glucuronyl transferase, thereby reducing the clearance of estrogens and amplifying their effects.

Familial clustering and geographical variation indicate that there is a genetic predisposition for ICP. There is a high prevalence of ICP in Chile (14%), especially among Araucanian Indian women (24%), and in Bolivia.[3] ICP patients may have a family history of cholelithiasis and a higher risk of gallstones. There is a family history of cholelithiasis in 50% of ICP cases.[2]

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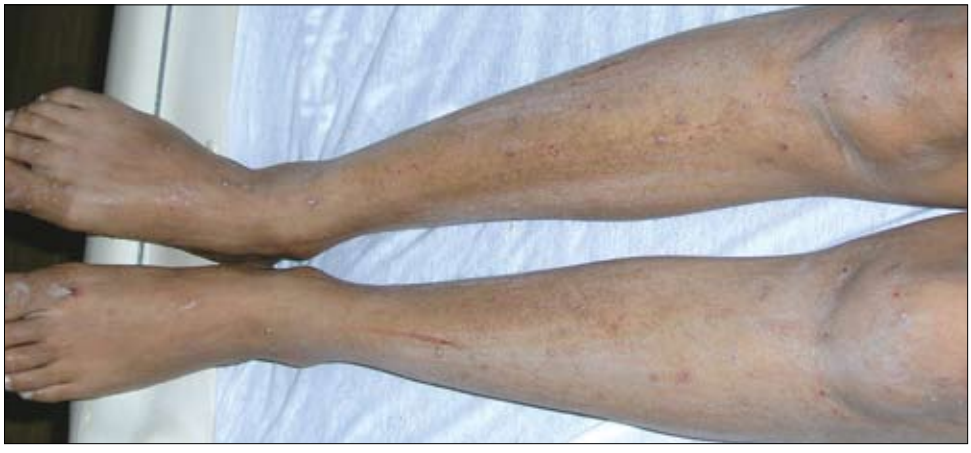
FIGURE 3

Excoriations down the legs



Patients with intrahepatic cholestasis of pregnancy have generalized pruritus, as evidenced by the excoriations down the patient's legs.

Exogenous factors have been implicated in the pathogenesis of ICP. There is a higher incidence of ICP during the winter. Low selenium levels have also been linked to ICP. This suggests that the environment and nutritional factors play a role.[2]

The differential Dx includes scabies

Itching has been reported to occur in 17% of pregnancies,[2] so it is important to differentiate ICP from the conditions listed below.

- **Pruritic urticarial papules and plaques of pregnancy**—also known as polymorphic eruption of pregnancy—is a dermatosis of pregnancy. Unlike the excoriations of ICP, this condition involves papulovesicular or urticarial eruptions on the trunk and extremities. It is particularly pronounced around the abdominal striae, and is more common in nulliparous women.
- **Pemphigoid gestationis,** also known as herpes gestationis because of its appearance, is a bullous or blistering disease that is associated with pregnancy. It is often periumbilical and can also have target lesions, which are absent in ICP.
- **Atopic eruption of pregnancy** is a new term used to include previous nonspecific diagnoses such as prurigo of pregnancy and pruritic folliculitis of pregnancy. Prurigo of pregnancy, which is also called Besnier's prurigo gestationis, involves bite-like papules that resemble scabies. Pruritic folliculitis of pregnancy is characterized by red, follicle-based papules. These 2 conditions differ from ICP in that there is no cholestasis and liver studies are normal. (In ICP, there is an elevation in liver enzymes and serum bile acids.)
- **Scabies infestation** can occur during pregnancy. The mite burrows in the skin and produces severe itching between the fingers and in skin folds. Look for burrows and the typical distribution between the fingers, on the wrists, in the axilla, and around the waist. A positive scraping viewed under the microscope will show mites, eggs, and mite feces.

If you suspect ICP in a patient who is also jaundiced, you'll also need to rule out several other conditions. These include:

- acute liver disease of pregnancy
- preeclampsia complicated by increased liver enzymes
- hyperemesis gravidarum
- viral hepatitis
- drug reaction
- obstructive biliary disease, such as a gallstone lodged in the common bile duct.

Order a blood chemistry or liver profile

If you suspect that your patient has ICP, start by ordering a blood chemistry or liver profile. If any of the liver tests are elevated, order a total bile acid level (which is the most sensitive indicator of ICP) and a hepatitis panel (or specific hepatitis tests based on the patient's history of exposures and vaccinations). If there is laboratory evidence of cholestasis, a right upper quadrant ultrasound will help you to spot gallstones and evidence of obstruction.

In ICP, there will be mild abnormalities of the liver function tests, including transaminases, alkaline phosphatase, and bilirubin. Bilirubin may be mildly to moderately elevated (2–5 mg/dL). (Jaundice is seen only at the higher levels of bilirubin.) Our patient's tests, for instance, revealed that her ALT and AST were both over 300; her total bilirubin was elevated at 2.1.

Serum levels of bile acid correlate with the severity of pruritus. Our patient's bile acids were elevated and her hepatitis panel was negative. Her ultrasound showed gallstones, but we saw no obstruction. An ICP patient's lipid profile may show mild elevations in total cholesterol and triglycerides, as was the case for our patient.

Malabsorption of fat may cause vitamin K deficiency resulting in a prolonged prothrombin time. Liver biopsy is

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A total bile acid level is the most sensitive indicator of intrahepatic cholestasis of pregnancy

unnecessary in suspected cases of ICP, but would show cholestatic changes such as dilated bile canaliculi, bile pigment in the parenchyma, and minimal inflammation.

Skin biopsy is not helpful in ICP

In suspected cases of ICP, skin biopsy will only reveal a spectrum of nonspecific findings. It is, however, helpful if you suspect pemphigoid gestationis, since it will reveal subepidermal blisters. Similarly, biopsy for direct immunofluorescence is nonspecific in ICP, but helpful in pemphigoid gestationis.

Soothing baths can help, ursodiol is most effective

Mild cholestasis responds to symptomatic treatment with soothing baths, topical antipruritics, emollients, and primrose oil, among others. Antihistamines are rarely effective. Anion exchange resins, such as cholestyramine, can be helpful, too; they bind bile acids and decrease their enterohepatic circulation.[2]

Patients who do not respond to cholestyramine, or who cannot tolerate it, may be treated with ursodeoxycholic acid (ursodiol). The research indicates that ursodiol works faster than cholestyramine, has a more sustained effect on pruritus, and is more effective in improving the biochemical abnormalities of ICP (strength of recommendation [SOR]: **A**, based on good-quality patient-oriented evidence). Ursodiol is considered safe for both mother and fetus.[5] For all of these reasons, ursodiol has replaced cholestyramine as the first-line agent for ICP.

Doses range from 1 g/day to high doses of 1.5 to 2.0 g/d.[6] The dose is maintained until delivery. Davies et al[5] suggest that the use of ursodiol can reduce fetal mortality associated with ICP (SOR: **C**, based on consensus, usual practice, opinion, disease-oriented evidence, case series).

Weekly non-stress tests beginning at the 34th week of gestation are advisable (SOR: **C**).[2] Labor may need to be induced in the 38th week in mild cases of ICP, and in the 36th week in severe cases (SOR: **C**).[2]

Ursodiol for our patient, labor was induced

We treated our patient with oral ursodiol and topical 1% hydrocortisone cream. Her bile acids and transaminase levels dropped and her pruritus improved—though it did not completely resolve until after delivery. Our obstetrics department recommended weekly non-stress tests starting at the 34th week of gestation. The non-stress tests were reactive. Due to the severity of her condition, labor was induced at 36 weeks.

Our patient had a healthy baby girl without complications. After delivery, the itching went away completely and her skin began to heal from all of those excoriations. Our patient is planning an elective cholecystectomy in the coming months because she doesn't want to take a chance that she might have problems with her gallstones in the future. ■

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Ursodiol has replaced cholestyramine as the first-line agent for intrahepatic cholestasis of pregnancy

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The authors reported no potential conflict of interest relevant to this article.

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