# Intrahepatic Cholestasis of Pregnancy: Review of the rare perplexing problem

## *GEBELİĞİN İNTRAHEPATİK KOLESTAZI NADİR ŞAŞIRTICI BİR PROBLEMİN DERLEMESİ*

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**Summary**

We are presenting a case with a puzzling disorder of intrahepatic cholestasis of pregnancy and reviewing its etiopathogenesis, clinical features, diagnosis, management and outcome in the light of the literature in this report.

**Key Words:** Intrahepatic cholestasis of pregnancy, Pruritus, Obstetric cholestasis

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**Özet**

Bu yazıda şaşırtıcı bir bozukluk olan intrahepatik kolestazlı bir gebeyi sunuyor ve literatür ışığı altında etiyopatogenezini, klinik özelliklerini, tanısını, tedavisini ve sonucunu gözden geçiriyoruz.

**Anahtar Kelimeler:** Gebeliğin intrahepatik kolestazı, Pruritus, Obstetrik kolestaz

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We have been recently encountered a perplexing problem of intrahepatic cholestasis of pregnancy. Although this is not unique to pregnancy, we wish to review this issue in the light of the literature, since the differential diagnosis and management of this enigma is important during pregnancy because of intense pruritus and the increased risk of fetal asphyxia (1).

### Case

The case was a thirty-five year-old woman with gravida 1, para 0 had complaint of "itching" especially affecting her palms and soles at 35 weeks of gestation, so severe that she had sleep disturbances due to this terrible itching. She had no clinical findings except some scratch marks on those areas. Until that time she had completely normal pregnancy at follow-ups. Blood levels of transaminases and bilirubins were checked. Aspartate amino transferase (AST) and Alanine amino transferase (ALT) were 40 U/L and 60 U/L, respectively and bilirubins were in normal limits. These tests were checked again after 7 days. The results were slowly raising for AST and ALT as 80 U/L and 120 U/L, respectively. Complaint of itching was reported as "unbearable" by that time. Serum markers of Hepatitis A, B, C, and E were ordered, all were normal. Abdominal ultrasonography showed normal liver and gall bladder, and also no other abnormality. Five days later AST and ALT levels were again found gradually raising, and the level of total bilirubin was 1.4 mg/dL, just above the normal. We have discussed the case with gastroenterologists and hospital-stay was suggested to the patient. Other clinical findings were all normal such as blood pressure, hepatic size, fetal well-being. Depending on the benign clinical picture with pruritus and raising transaminases, the diagnose of intrahepatic cholestasis of pregnancy was made. At 37 weeks of gestation, when her serum levels of AST and ALT were 480 U/L and 632 U/L, the pregnancy was terminated by cesarean section, and healthy girl baby weighed 2900 g was delivered. Approximately after 6 hours, the blood levels of transaminases were sharply fell to 120 U/L and 243 U/L for AST and ALT respectively. On postoperative first day, AST and ALT levels were more decreased to 60 U/L and 120 U/L, respectively. On day 2 postoperatively, levels of transaminases were in normal limits and she had no complaint. She and her baby was discharged from hospital on day 5 postoperatively. Her late postpartum control on day 40 was also normal.

### Discussion

Liver diseases specific -at least partially- to pregnancy are hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, preeclampsia/eclampsia, HELLP syndrome and hepatic rupture (2,3).

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Intrahepatic cholestasis of pregnancy (ICP), a rare, puzzling disorder is also known as "recurrent jaundice of pregnancy", "icterus gravidarum", "cholestatic hepatosis", "obstetric cholestasis". In fact, it is not unique to pregnancy because this may recur after pregnancy by using hormonal contraception. In addition, some males may also exhibit cholestasis when exposed to estrogen products (4). It is also known that apart from pregnancy, drugs, total parenteral nutrition, sepsis, graft-versus-host disease, and some systemic disorders like sarcoidosis, amyloidosis, Hodgkin's disease are etiological factors in intrahepatic cholestasis (5).

The reported incidence varies between 1 in 500 to 1000 pregnancies (6,7) Two areas in the world have the striking incidences comparing the rest of the world: Chile and Sweden. In Chile, 14% of deliveries in 1975 and 4% in 1995 has been complicated with this disorder (8).

Etiopathogenesis is yet not totally understood. Various findings lead the authors to suggest different theories. Increased serum levels of human chorionic gonadotropin, estrogen, progesterone in susceptive women is proposed (1,4,9). It has been suggested that an impaired sulphation capacity provoked by high circulating estrogen levels might be the explanation in the pathogenesis of ICP (10). Some drugs -azothioprine as an example- may decrease the canalicular transport of bile acids. When bile acids can not be completely cleared by the liver, then accumulate in the plasma. In women with ICP, serum selenium levels and glutathion peroxidase enzyme activity were also found significantly lower during the last trimester and postpartum period, and suggested as a contributor in pathogenesis (11). Why only some women are affected is another question is to be answered. Genetic predisposition is also involved. Studies on familial inheritance pointed out "Mendelian dominant type" of inheritance (12,13), although X-linked inheritance can not be excluded (12). Male expression of the phenotype seemed to be inhibited from the observations of unhelpful information -opposite to the useful information in women- when unmasking carriers in the kindred by normal challenge applied to male obligate carriers (13). HLA communication was also studied for susceptibility for ICP. However, a study on genomic DNA was unable to show a communication between the disorder and HLA-DPB1 alleles (14). In a previous study it has been noted that among the 37 the HLA system, only HLA-BW16 showed a tendency to be more frequent in women with ICP comparing with controls, however, that finding was related to ethnicity rather than ICP (15).

Although varies from pregnancy to pregnancy, typical clinical picture of ICP is intense pruritus with or without jaundice. Pruritus is often generalized, but it especially affects palms and soles (16). Most patients are apparently well, but increasing pruritus may disturb so much that insomnia may occur. Accompanying skin changes are absent except excoriation due to pruritus. Nutrition of the mother may be affected by the cholestatic state due to fat malabsorption. Deficiencies of vitamin K and some trace minerals have been reported (16). Only a minority -10%- of women with ICP may develop jaundice (1).

In diagnosis, intense pruritus without troubled clinical appearance may suggest ICP. In ICP, hyperbilirubinemia is not prominent, and also AST and ALT levels show a slow but steady raising trend. These serum aminotransferases usually are moderately elevated. Absence of hypertension, proteinuria will help to differentiate ICP from liver diseases associated with preeclampsia or eclampsia. Viral hepatitis is another disease that must be excluded. Serologic tests are available for all types. In addition, smooth-muscle antibodies -though not common in practice- may be helpful in differentiating ICP, in which it is frequently positive, from viral hepatitis (17). Acute fatty liver of pregnancy has a more troubled clinical appearance with malaise, nausea, vomiting, anorexia, epigastric pain and jaundice (1). "Pruritus gravidarum" is a unique skin disorder in pregnancy and it can be viewed as a variant of ICP. In women with pruritus gravidarum, there is not either transaminase changes nor hyperbilirubinemia, and obstetric outcome is not affected. Pregnant women with pruritus should not be given a simple explanation before exploring for other disorders by biochemical tests. Liver biopsy is no longer suggested (6,16).

Therapy of ICP aims to reliewe the major symptom of pruritus. Unfortunately until now, there is no effective treatment for this troublesome symptom. There has been several drugs proposed, but the results of different studies are all conflicting. Cholestiramine is one of the drugs suggested for the treatment, as 12-16 g/d (1,16). It is an anion-binding resin. Although it has been declared to be effective recent reports show no beneficial effect on pruritus (1). Besides, this drug my affect the absorption of other drugs and also fat-soluble vitamins. Phenobarbutal is another drug, but has not proved to be satisfactorily effective (16). Dexamethasone is also suggested as 12mg/d. It has been thought that dexamethasone might suppress the fetoplacental estrogen production. The study on 10 women with ICP, treatment with dexamethasone showed complete relief of itching (18). However, dexamethasone therapy is also controversial in the literature. The presentation of a dexamethasone-treated case with ICP reveals worsening of clinical picture (19). In the last decade studies on the therapy of ICP have been focused on S-adenosyl-L-Methionine (SAMe), as 800-1000 mg/d intramuscularly or intravenously and ursodeoxycholic acid (UDCA), as 450-1000 mg/d orally (1,20-24). The synopsis of results is not totally conclusive, however UDCA seems to be beneficial, though the mechanism of action was not totally understood (1). Oral guar gum, a dietary fiber, which relieves cholestasis, has also been shown to be effective in relieving pruritus in ICP, although indicators of cholestasis are only partially reduced (25). Obviously the management depends on the age of gestation, since all problems in ICP reversed to normal after delivery, as in our case.

Prognosis of ICP is good for the mother when monitorization for prothrombine is normal and vitamin K deficiency is absent, but the same is not true for the fetus. Indeed, according to the studies on women with ICP, fetus has been found at risk of distress, preterm delivery, and the need of good neonatal care (1,26) There has been found 3-4 times increased risk of having meconium aspiration according to the studies (27,28). The reason for the intrauterine fetal distress is not totally understood. There did not found any significant fetal blood flow parameters by Doppler examination (29). An interesting study by Ma et al (30), showed that the serum nitric oxide (NO) levels in women with ICP was significantly lower comparing with normal pregnant women. Fetal hypoxia, premature delivery and growth retardation of the fetus, thus may be explained by decreased NO concentrations in women with ICP. It is also interesting to note that perinatal outcome is suggested not to be predictable by conventional fetal surveillance like NST and amniotic fluid assessment (27). Perhaps the best way of management in ICP is delivering the fetus as soon as the fetus gets maturity.

Intrahepatic cholestasis recurs in 40-60% of subsequent pregnancies and also when using oral contraceptives containing estrogen (1,4). Thus, women with ICP should be warned against the recurrence.

In conclusion, ICP is puzzling disorder with unclear etiology. It may be more often than reported. The symptom of troublesome pruritus in pregnant woman, especially in the last trimester would better be explored, since poor perinatal outcome may occur with ICP.

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