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Obstetric outcome of pregnancies complicated with intrahepatic cholestasis

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Abstract

The incidence of intrahepatic cholestasis of pregnancy is estimated to be 0.5% of all deliveries, with great geographic variations. Clinical onset of this condition is represented by intolerable pruritus dominant on the palms and soles of the feet with the emphasizing of symptoms during the night. Regarding the risks for the fetus, the main complications are prematurity, intrauterine demise, meconium-stained amniotic fluid and a greater incidence of neonatal respiratory distress syndrome. Our retrospective study aimed to analyze the incidence of intrahepatic cholestasis of pregnancy for a period of five years in Bucharest Emergency University Hospital, fluctuations of the incidence depending on maternal age and parity, also, related neonatal risks. Secondly, we present a literature review regarding maternal and fetal follow-up and the possibilities for preventing the potential related complications. During the studied period, the incidence of intrahepatic cholestasis of pregnancy was 0.3%. Fetal status at birth was influenced by this condition, being reflected by an Apgar score lower than 8 in 34% of cases. Also, meconium stained fluid was associated in a higher proportion (14%) comparing to uncomplicated pregnancies in which fetal demise was showed not to be a direct consequence of intrahepatic cholestasis of pregnancy. The major purpose of management of these pregnancies consists in a rigorous fetal surveillance and early delivery guided by the comparison of the risk of fetal death and potential risks of prematurity. There is no ideal method for fetal surveillance in intrahepatic cholestasis of pregnancy yet.
Keywords: *pregnancy, intrahepatic cholestasis, management*

Introduction

Occurrence in the second and third trimester, specifically after 28 weeks of gestation of incontrollable pruritus accompanied by the elevation of serum bile acid concentration reflects intrahepatic cholestasis of pregnancy[1]. Just several cases of onset in the first trimester are reported[2]. Intrahepatic cholestasis of pregnancy has also been known as recurrent idiopathic jaundice of pregnancy, obstetric cholestasis or pruritus gravidarum and is characterized by the implicit potential for maternal morbidity, significant risk for fetal morbidity and mortality and the implication for future health of the fetus[3]. The challenge of a clear diagnosis rests in the interpretation of present modification in the context of normal physiologic changes of pregnancy and the decision of a therapeutic approach considering the implication for both the mother and the fetus. Cholestasis of pregnancy along to acute fatty liver of pregnancy are liver diseases specific to pregnancy, but signs of hepatobiliary disease can appear in multisystem disease characteristic to pregnancy such as preeclampsia together with hemolysis, elevated liver enzymes and low platelet count syndrome, in the worsening due to pregnant state of diseases present in non-pregnant women, as cholelithiasis, thrombotic diseases and hepatitis E virus infection, or in cases of illness occurred during pregnancy, like acute viral hepatitis or pre-existing chronic liver disease. Through all these encountered pathologies, obstetric cholestasis is the most common pregnancy-specific liver disorder. Women who manifest this condition presents also altered immunity, abnormal hormone metabolism, genetic predisposition and confirm a certain environmental influence[4]. The reported incidence of this condition presents great differences varying from 0.1 to 15.6%[5], the most relevant reason being the geographic and implicitly the ethnic factor. Other risk factors are multiple gestation, assisted reproductive techniques, maternal age over 35, environmental factors like dietary selenium and vitamin D levels, viral infections in pregnancy, family or personal history of intrahepatic cholestasis of pregnancy or preeclampsia[6].

The association of gallstones and prolonged emesis are frequent. The etiology of obstetric cholestasis is not completely understood, the most relevant theory being the influence of increased estrogen and progesterone levels during pregnancy of genetically predisposed women resulting a slower bile excretion with increased serum bile acid and elevated liver enzymes. Fetal and maternal complications result from the vasoconstriction of the placental vessels caused by the metabolites of the serum bile acids[7]. The risk of fetal death associated with intrahepatic cholestasis of pregnancy is reported to be 10-15%; other fetal complications are chronic distress, preterm delivery, heart rate abnormalities and meconium stained fluid. Associated comorbidities worsen the prognosis. Geenes et al.[7] conducted in 2014 a prospective study on 669 women

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with sever cholestasis, in comparison with uncomplicated pregnancy in the study group increased risk of spontaneous and iatrogenic preterm birth, neonatal unit admission and stillbirth was found. Associated maternal conditions are mild jaundice in 10-15% of cases, anorexia, malaise, abdominal pain, acute fatty liver and gestational diabetes[8,9].

Pruritus is the typical symptom of intrahepatic cholestasis of pregnancy, its intensity increases along to pregnancy advances and grade ofdeteriorated liver function with no associated rash. Additional signs of elevated bile acids like dark urine, pale stools and jaundice in rare cases may appear[10].

Elective early delivery was proposed and adopted by several units in order to reduce the risk of late stillbirth, the efficiency of this practice being limitedly investigated. In our days, ursodeoxycholic acid is the essential pharmacologic treatment having proved safety for both the mother and the fetus. The most suggestive study on the effects of ursodeoxycholic acid implied 111 women with intrahepatic cholestasis of pregnancy and a significant reduction in pruritus and important reductions in alanine aminotransferase, gamma-glutamyl transferase and bilirubin were reported[11]. The second line of treatment is represented by a choleretic antibiotic with some effects on reducing the pruritus enhancing bile acid excretion, namely rifampicin.

No method of fetal monitoring proved a real prediction or reduction of the risk of adverse perinatal outcomes. Even if there were no reported results on the effects of early delivery in intrahepatic cholestasis of pregnancy, this strategy seems to be correlated with a major decrease of reported stillbirth cases in women with intrahepatic cholestasis of pregnancy, complication thatis appreciated at the present to be 1.5%. According to Lo et al. the optimal time for delivery is immediately after 36 weeks of gestation[12]. The results of a large cohort study showed that the risk of fetal, infant or neonatal mortality was significantly lower in comparison to expectant management.

Laboratory tests associated with intrahepatic cholestasis

In addition to physical examination, laboratory test can offer a certainly diagnosis. Suggestive laboratory finding are increased values of bile acids, cholic acid, chenodeoxycholic acid, total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, prothrombin time, and partial prothromboplastin time[13]. The most sensitive diagnostic finding in women with intrahepatic cholestasis of pregnancy is elevation of total serum bile acids. Bile acids result from the cholesterol catabolism, representing its end products; main human bile acids are cholic acid and chenodeoxycholic acid. During their synthesis bile acids are conjugated with either glycine or taurine, for finally to be exported and storage in the gallbladder. The gut bacteria play a special role in the terminal ileum and colon and subsequent to the enterohepatic circulation through which 95% of bile acids are reabsorbed and returned to the liver[14]. Each step from the metabolism of these products is essen-

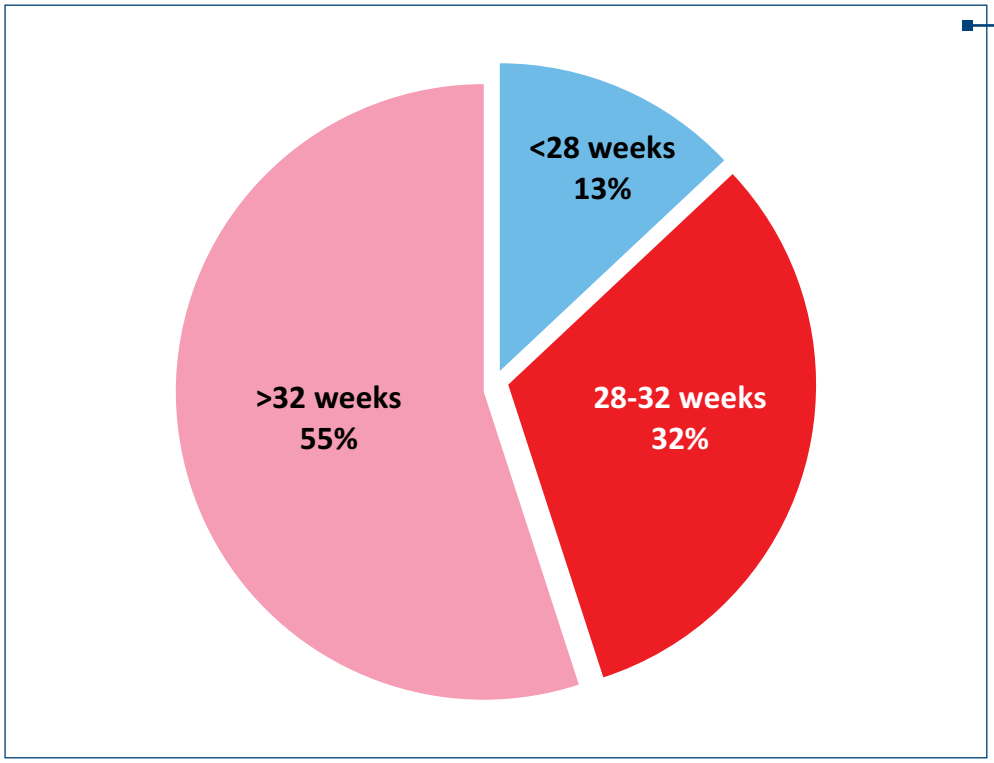

Figure 1. The onset gestational age of intrahepatic cholestasis of pregnancy

tial and the homeostasis of bile acids is imperative to be highly regulated, the toxicity of bile acids increase proportionally to their level in serum. Their accumulation influences a variety of metabolic processes like lipid and glucose metabolism and inflammation. It is speculated according to several studies that sulfated progesterone metabolites are potential agonist for the main hepatic bile acid receptor, farnesoid X receptor[15]. This action results in impaired homeostasis by inhibiting the induction of its target genes and inhibiting hepatic uptake and efflux of bile acids. Referring to liver transaminases, it should be noted that usually occur after the rise of bile acids and the correlation between this two parameters is poor. Royal College of Obstetricians and Gynecologists affirm that intrahepatic cholestasis of pregnancy may be over-diagnosed in the absence of bile acids tasting[16]. It is mandatory that tests for other causes of cholestasis to be taken for a clear diagnosis.

Methods

We conducted a retrospective study aimed to analyze the incidence of intrahepatic cholestasis of pregnancy for a period of five years in Bucharest Emergency Uni-

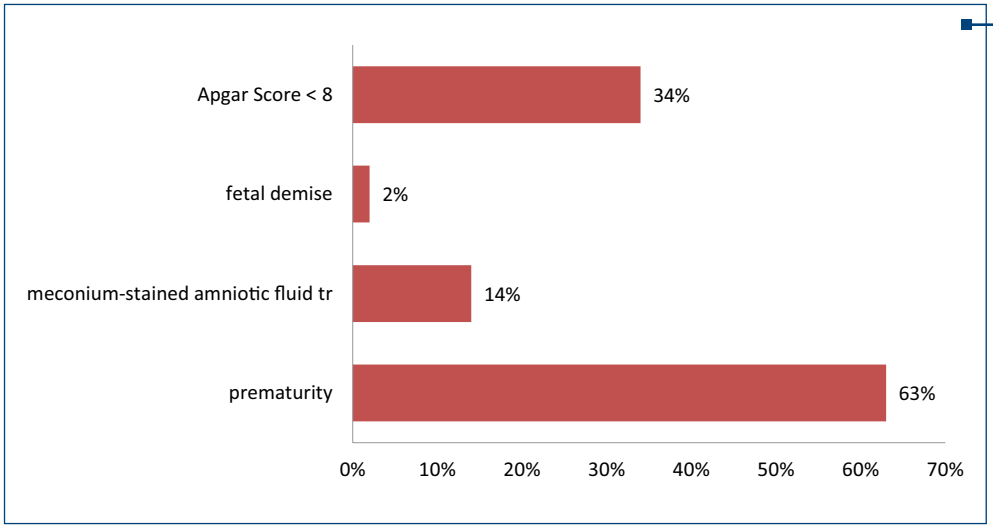

Figure 2. Fetal consequences of intrahepatic cholestasis of pregnancy

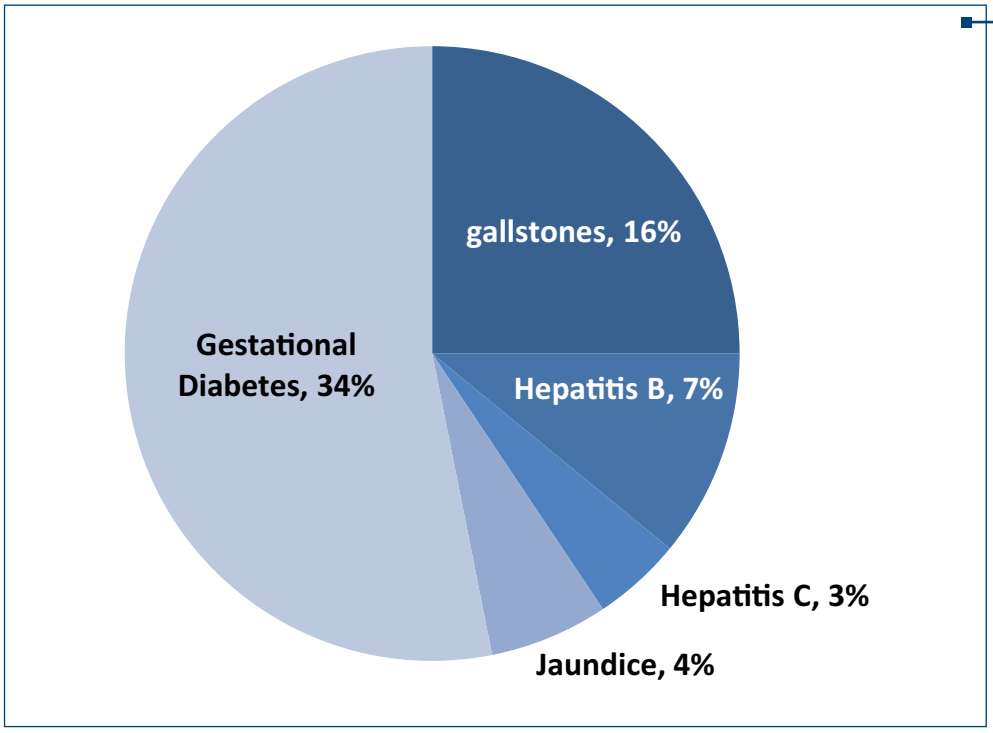

Figure 3. Associated maternal conditions

versity Hospital, fluctuations of the incidence depending on maternal factors and associated conditions, also, related neonatal risks. During the studied period, the incidence of intrahepatic cholestasis of pregnancy was 0.3%. An important parameter related to intrahepatic cholestasis of pregnancy is the onset gestational age.

Results

Only one case presented symptoms at 25 weeks of gestation. At over 85% of women with intrahepatic cholestasis of pregnancy the disease started in the third trimester, at the gestational age higher than 28 weeks. More than half of the cases (55%) had the onset at over 33 weeks of gestation (Figure 1).

The dominant symptom that the patients had was the intense itching (86%) started on the palms of the hands and soles of the feet accompanied by disturbed sleep and fatigue due to the intense pruritus at night. Only 14% of cases had an exclusively laboratory based diagnosis by finding at routine analyses elevation of bile acids or/and elevated aminotransferase levels.

We intended to quantify the main fetal consequences overlaid and related directly or indirectly with intrahepatic cholestasis of pregnancy. There was a significant rate of prematurity among the studied cases. It was impossible for us however to determine what proportion of this prematurity cases was spontaneously and what proportion was iatrogenic.

The most preterm newborns resulted from pregnancies complicated with intrahepatic cholestasis of pregnancy (64%) were born at gestational age of 33-37 weeks. Fetal status at birth was influenced by this condition, being reflected by an Apgar score lower than 8 in 34% of cases. Also, meconium stained fluid was associated in a higher proportion (14%) comparing to uncomplicated pregnancies. Fetal demise was not a direct consequence of intrahepatic cholestasis of pregnancy; important maternal conditions like gestational diabetes and preeclampsia had been associated in these cases (Figure 2).

It is unusual the development of intrahepatic cholestasis of pregnancy as a solitary, independent pathology. We extracted the main associated maternal condition which we consider that had some impact on the outcome of pregnancy. The frequency of gestational diabetes among the studied cases was high, 34% of patients with intrahepatic cholestasis of pregnancy had this condition superimposed. As we expected, the association of pre-existing liver disease was common (Figure 3).

Discussion

Intrahepatic cholestasis of pregnancy is characterized by a rapid postnatal resolution, but the impact on the fetus reflects on its future outcome. For the mother instead, this condition has an increased risk of recurrence in future pregnancies and a higher incidence of hepatobiliary diseases like hepatitis, hepatic fibrosis and gallstone[17,18]. The risk of recurrence in subsequent pregnancies is quantified to be up to 90%. As a personal observation considering the obtained results, we emphasize the need for counseling pregnant women regarding the first signs of this disease, the appropriate diet during pregnancy and about the medication and importance of a correct and complete treatment. Also, pregnant women with high risk of intrahepatic cholestasis of pregnancy should be informed about the possible associated condition, especially prematurity. Data obtained from our study corresponds with other results reported in literature. The frequency of this pathology in our hospital was not alarming.

Conclusions

In our study, higher association with prematurity confirms that preterm birth was preferred often in order to reduce the risk of fetal death which increase exponentially after 38 weeks of gestation. In this context information of women with intrahepatic cholestasis of pregnancy on the risks and benefits of preterm birth and on the risk that the infant may necessitate neonatal intensive care is imperative. ■

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