Severe intrahepatic cholestasis in pregnancy – case report and literature review

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Abstract
Intrahepatic cholestasis of pregnancy (ICP), a common hepatic disease in pregnancy, sometimes can result in adverse fetal outcome. We present the case of 37-year old woman in 34 gestational week of her second pregnancy with ICP, schizophrenia and anaemia. The patient was admitted to hospital with the worsening pruritus of palm and feet since 3 weeks. Current pregnancy also was complicated with upper respiratory tract infection in 32 gestational week and anaemia. The pregnant woman was treated with risperidonum because of schizophrenia. On admission ultrasound examination of the abdomen was within normal limits, the evaluation of umbilical artery and mean cerebral artery flows were correct. The cardiotocographic test did not raise any doubts. The biochemistry shows the elevated AlAT (180 IU/l) as well as AspAT (205 IU/l) levels in serum. The fasting total bile acids (TBA) level was 113.3 μmol/l. The tests into direction of liver infection diseases such as HBS, HCV test were negative. The therapy of ursodeoxycholic acid, enoxaparin, vitamin K was implement and steroids for fetal lung maturity were administered. Because of the TBA augmentation (up to 183 μmol/l), reduced fetal movements and worsening of cardiotocographic tests the pregnancy was ended with elective caesarean section. The live male baby with birth weight 2500 g and Apgar score 9, 9 in 1 and 5 minutes, respectively was delivered. The early detection of hepatic problem in pregnant women and implementation of proper treatment is crucial. In some cases of ICP the immediate termination of pregnancy by delivery induction or by cesarean section should be considered. The appropriate postpartum care of the mother and newborn is also important. The cooperation of medical experts team is required to improve the perinatal outcomes in women with ICP.

Key words: intrahepatic cholestasis of pregnancy, total bile acids, perinatal outcome

Introduction
Intrahepatic cholestasis of pregnancy (ICP), with impaired hepatocytes and bile ducts function, is the most common hepatic disease in pregnancy. The disorder affects 1-4% of Caucasian population and up to 16-25% Indian populations in South America. In the 20th century up to 10% of ICP complicated pregnancies ended with intrauterine fetal death but currently this fatal event occurs in 0.57% [1, 2]. The etiology of ICP is unknown. The intra-liver bile stasis as well as dysfunction of bile compounds transport in hepatocytes can play role in its etiology. In mother it results in the increased concentration of bile acids, liver enzymes, and with or without bilirubin elevation usually after 30 weeks of gestation [2, 3]. It is believed that ICP is the multifactorial disorder with hormonal components contribution. The prevalence of ICP is increased in multiple pregnancies, where the concentration of estrogens is higher. Moreover, probably progesterone metabolites can take part in bile excretion dysfunction. Additionally first clinical symptoms usually occur in the third trimester, when the highest hormone concentration is observed. There was also indicated that the environmental, dietary and genetic factors are strongly associated with ICP etiology [4]. Thus ICP is observed more often during winter time, and moreover selenium deficiency may be a trigger factor in its pathophysiology. Furthermore higher familiar ICP occurrence in sisters and mothers, as well as in some ethnic groups is observed. It was shown the strong involving of multidrug resistance protein 3 mutations in the etiology of ICP [5-7].

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The main ICP clinical symptoms are pruritus. Pruritus, in the skin rash absence, usually occurs in the II or III trimester (usually after 30 gestational week), it usually intensify at night and it is confined mainly to palms and feet. Escalated pruritus may lead even to insomnia. The laboratory signs are total bile acids (TBA) increasing (more than 10 μmol/l), alanine transaminase (ALAT) as well as aspartate transaminase AspAT, gamma-glutamyltranspeptidase (GGTP) elevation. Alkali phosphatase (ALP) is not a specific cholestasis marker, because it is also produced by placenta. Total bile acids are the main liver cholesterol degradation product and useful marker of proper liver function. In histological examination hepatocytes apoptosis is observed. TBA increasing also is observed at patients with viral hepatitis, cirrhosis, and liver cancers. TBA rising (norm 0-10 mmol/l) is also noted at almost each pregnant women with cholestasis [8]. Moreover, TBA high concentration is a severe threat for a fetus life [3, 9, 10]. Clinical and biochemical symptoms usually subside within few days after delivery. In other case comprehensive diagnosis as to other liver dysfunction should be started [11].

The target of ICP treatment is to reduction of abnor-
mal laboratory tests and distressing maternal symptoms as well as improve fetal outcomes. The management of ICP with ursodeoxycholic acid is indicated as it normalizes biochemical tests [10, 12]. Cholestasis recurrence is observed in 60-70% consecutive pregnancies. So far, there are no methods that would allow to predict the cholestasis recurrence. In children from ICP complicated pregnancies in their adult life usually no dysfunctions are observed.

The aim of this study was to introduce the pregnant complicated by severe intrahepatic cholestasis (ICP) and briefly summarize the current knowledge of this intriguing disease.

Case report

37-year old pregnant woman was admitted into the hospital with diagnosis: second pregnancy, 34 gestation- nal week, intrahepatic cholestasis of pregnancy. The additional disease in the patient was schizophrenia and anaemia. In obstetrical anamnesis uncomplicated course of the first pregnancy has been noted. In the familial anamnesis the history ICP or the other hepatic disorders have not been observed.

On admission obstetric examination revealed single pregnancy, breech presentation of the fetus, amniotic membranes intact, no cervical dilatation and no vaginal bleeding. In the ultrasound examination estimated fetal weight was 2450 g, amniotic fluid index (AFI) 13 cm, placenta with no abruption signs, the evaluation of umbilical artery and mean cerebral artery flows were correct. Ultrasound examination of the abdomen was within normal limits. The cardiotocographic test did not raise any doubts.

The main symptom in the patient was the pruritus of palm and feet. The worsening of pruritus and life comfort was noted since 3 weeks. Current pregnancy also was complicated with upper respiratory tract infection in 32 gestational week (treated with amoxicillin 2 × 1.0 g po. through 6 days) and anemia (Sorbifer Durules 2 × 1 tab. po.). The pregnant woman was treated with risperido- num because of schizophrenia (25 mg/day). Earlier psychiatric consultation revealed no abnormalities.

The laboratory tests results were as follows: morphology HGB 10.3 g/dl, HCT 0.32 L/l, WBC 8.6 G/l, RBC 3.39 T/l, PLT 392 G/l, coagulation test INR 1.17, PT 86.4%, APTT 29.9 sec. D-dimers 1798.71 ng/ml. The biochemistry shows the elevated ALAT (180 IU/l) as well as AspAT (205 IU/l) levels in serum. The fasting total bile acids (TBA) level was 113.3 μmol/l and bilirubin level in serum was on the upper level 1.1 mg/dl, CRP level was 2.81 mg/l. The test into direction of liver infec-
tion diseases such as HBS, HCV test were negative. Bacteriological vaginal swab was also negative.

Following drugs were administered: fluid therapy iv., ursodesoxycholic acid 3 × 500 mg po., betamethazon 2 × 12 mg im. every 24 h, enoxaparin 1 × 40 mg sc, and vitamin K 1 × 10 mg po. Because of the TBA augmentation (up to 183 μmol/l), reduced fetal movements and worsening of cardiotocographic tests the pregnancy was ended with elective caesarean section. The live male baby with birth weight 2500 g and Apgar score 9, 9 in 1 and 5 minutes, respectively was delivered.

After delivery in the newborn partial parenteral nu-
trition was used. Ultrasound of the brain and heart was normal. In newborn the hypoglycaemia and jaundice with no treatment requirement has been confirmed. In the puerperium in the mother serum fasting TBA assay was slightly return to the normal level. The lactation was blocked and risperidolum treatment because of schizophrenia was maintained. She left the hospital in 5th day after delivery, after psychiatric consultation. It was recommended the gynaecologic, psychiatric and gastroin-
testinal examinations as well as the treatment with low fat to improve lipid state and liver function.

Discussion

The background of ICP remains unclear and possible involved different components such as environmental,
hormonal and genetic factors. In cholestasis could be also seen the disturbances of lipid metabolism particular in early onset or in relapsed form of disease [13]. The likelihood of defects of bile acid transport should be considered in patients of familiar cholestatic disorder in this history of ICP [7, 14].

The presence of ICP in current pregnancy could underlay the possibility of ICP occurrence in subsequent pregnancy even the metabolic disorders and serious cholestatic defects of liver function in later life. The many observations indicated that the women with hepatic disorders are in higher risk to be fertile. Moreover in this group the intrauterine death and preterm birth have been noted in higher rate [15, 16]. Thus the vigilant clinical anamnesis, accurate physical examination, the excluding of viral hepatic disorders (by serologic tests), and appropriate biochemical analysis allow to make the precise diagnosis [12, 17].

Pruritus is the classical symptom of cholestasis presence during pregnancy. The diagnosis of ICP can be confirmed by abnormal liver function tests. The central problem is the proper recognition the cause of pruritus. There also was described the cases of pregnant women with severe pruritus appeared after the administration of amoxicillin for upper respiratory tract inflammation [18].

TBA measurement is one of the main diagnostic criterion. It is worth remarking that TBA concentration increases after food consumption, so it is important to measure it fasting. Moreover, TBA concentration higher than 40 μmol/l is a severe threat for a fetus life. TBA causes choriionic vessel contraction. Increased maternal serum TBA concentration results in increased TBA concentration in amniotic fluid umbilical blood and meconium. TBA enhances fetal bowel movements and prostaglandin synthesis what leads to drastic umbilical flow reduction. There are also some suggests about direct toxic influence of TBA into fetal heart cells, what may probably end with sudden fetal cardiac arrest [19, 20, 21].

The presented case of pregnant women with severe ICP included two important suggestions. Firstly the early onset ICP is the severe form of cholestasis that appears most often after 20 weeks of gestation but could also appear in late third trimester of gestation [22]. Thus in this period the increased attention is essential. Secondly adequate monitoring and early treatment with high doses of ursodesoxycholic acid are required to improve the maternal and fetal state [23, 24].

There were described the serious consequences for the fetus in the course of ICP. Fetal distress is observed in 21-44% cases, fetal bradycardia in 14% cases and meconium-stained amniotic fluid in 27% cases [2, 25]. The risk of preterm delivery at pregnant woman with cholestasis is 19-60% and it is even higher in multiple pregnancies. Intrauterine fetal death affects 0.44.1% patients with cholestasis and it usually takes place at the end of pregnancy. The reasons of intrauterine fetal death are not fully understood, the fetal autopsy usually reveal acute hypoxia [2]. The ICP appearance typically is not connected with the severe maternal consequences. The coagulopathy could occurred because of vitamin K deficiency that is the cause of postpartum hemorrhage. To avoid this complication the administration of 10 mg of vitamin K/day orally should be considered. The other problem in the mother is gallstones formation after pregnancy complicated by ICP. Moreover in subsequent pregnancy ICP could reappeared in 40-60% cases [10, 25].

The ursodesoxycholic acid (UDCA) seems to be the most important in the management of ICP. It is well tolerated and any adverse effects on the mother and fetus have been not observed. It protects hepatic cells from toxic effects through displacing hydrophobic bile salts and decreased the intestinal absorption of toxic bile acids. Although the many drugs were used in ICP treatment (cholestyramine, benzodiazepines, opioid antagonists, Sadenozyll-L-methionine) the UDCA seems to be most efficient in clinical practice [10, 26, 27]. On the other hand in the ICP coagulation tests reveal the prolonged prothrombin time because of vitamin K deficiency, thus administration of vitamin K doses orally should be individually consider in each case. At present the opinions are differed as to recommendations for delivery induction and fetal surveillance [4, 10]. The experts discuss also whether is the increased risk of stillbirth between 37 and 39 gestational week [28]. On the basis of meta-analysis of 18 studies Lo et al. indicated that labour induction at 36 weeks of gestation in women with ICP is the best possible delivery strategy [29].

Relating to ICP the early assessment of situation severity and early admission to the hospital for detailed assessment of mother and fetus state is very important. In the hospital the proceedings oriented to the diagnosis of mother status and liver function monitoring as well as the proceedings oriented to the assessment of status of the fetus and stimulation of respiratory system maturation could be immediately implemented. No less important is the exact evaluation of TBA and aminotransferases concentration as well as the presence of factors influencing the liver function from the anamnesis. The essential is the dynamic estimation of liver function and decreasing of biochemical disturbances in mother. The
most vital is to minimize the risk of fetal distress, preterm birth and fetus sudden death considering the risk of immaturity by preterm birth in relationship to the risk of intrauterine fetal death. What is crucial all decisions should be make individual in each patient with ICP [2, 11, 18, 30].

Conclusions

The early detection of hepatic problem in pregnant women and implementation of proper treatment is crucial. In some cases of ICP the immediate termination of pregnancy by delivery induction or by cesarean section should be considered. The appropriate postpartum care is also important. The cooperation of medical experts team is required to improve the perinatal outcomes in women with ICP.

References


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