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Obs and Gynae PG Focus Series

Liver Disorders in Pregnancy



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CHAPTER

Physiology of Liver and Changes in Pregnancy

Changes in the value of certain serum liver function tests occur during normal pregnancy and an understanding of these physiological changes is necessary for the management of liver diseases. Because of the phenomenon of hemodilution, the albumin level decreases as early as the first trimester. Serum alanine and aspartate aminotransferase activity levels remain within the normal limits established for nonpregnant women. Measurement of serum aminotransferase levels thus remains the most useful test for the routine diagnosis of liver diseases during pregnancy. Serum total and free bilirubin concentrations are lower in pregnant women than in nonpregnant controls during all three trimesters, as are concentrations of conjugated bilirubin during the second and third trimesters. Serum alkaline phosphatase activity increases in late pregnancy, due both to the production of the placental isoenzyme and to the increase in bone isoenzyme. Consequently, measurement of serum alkaline phosphatase levels is not a suitable test for the diagnosis of cholestasis during pregnancy. Serum gamma-glutamyl transferase activity levels decrease during the second and third trimesters, and serum 5'-nucleotidase activity increases slightly in the second and third trimesters. Serum total bile acid concentrations during pregnancy are not different compared to levels in nonpregnant women. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits. In summary, according to the clinical setting, an increase in values of serum aminotransferase activity, serum GGT activity, serum bilirubin or fasting total bile acid concentrations during pregnancy should be considered pathologic.

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INTRODUCTION

The pregnant woman experiences physiological changes to support fetal growth and development. The levels of estrogens (estradiol) and progesterone increase progressively during pregnancy. These sex hormones have effects on hepatic metabolic, synthesis, and excretory functions. The biliary excretion of bromosulfophthalein decreases during late pregnancy and the clearance of some compounds that are secreted into bile may therefore be impaired. The phenomenon of hemodilution secondary to the increase in plasma volume decreases the serum protein concentrations. Consequently, certain changes in values of liver function tests occur during normal pregnancy.

In this chapter, we review the liver-related clinical and biochemical changes that occur during normal pregnancy, with emphasis on liver function tests that are used for the management of liver diseases in pregnancy.

LIVER-RELATED SYMPTOMS AND PHYSICAL EXAMINATION IN PREGNANCY

Nausea and vomiting are common symptoms of early pregnancy and occur in over half of all pregnant women. The symptoms frequently persist throughout the day, although this condition was traditionally named "morning sickness". By contrast, *Hyperemesis gravidarum*, usually defined by severe vomiting beginning in early pregnancy and requiring hospitalization, is much less frequent. As discussed in Chapter 3, *Hyperemesis gravidarum* may be associated with liver involvement. Nausea or vomiting occurring during the second or third trimester should be considered pathologic and should require investigations including the measurement of serum aminotransferase activity. It should be noted that jaundice and generalized pruritus should never be considered normal features in pregnancy. Vascular spiders and palmar erythema are commonly associated with chronic liver disease and pregnancy.

In the United States of America, vascular spiders were found in 14% of white women by the 2nd month of pregnancy and in 66% by the 9th month of pregnancy. The frequency of these vascular spiders was noted to be lower in black women with 8% occurring in the 4th month of pregnancy and 14% in the 9th month. In this study, about three-quarters of the women had lost these vascular spiders by the 7th week after delivery. In the same study, palmar erythema was observed in 63% of the white women and 35% of black women. By the time of the postpartum consultation, palmar erythema had faded in all but 9% of the women. During pregnancy, these cutaneous vascular changes are not usually associated with hepatic dysfunction but may be related to sex steroids circulating in the blood over a long period. Physical examination of the liver is normal although it is difficult in late pregnancy because of the expanding uterus. In the postpartum period, after normal delivery, the liver and spleen may be palpable because of ptosis of these organs.

HEPATOBILIARY ULTRASONOGRAPHY IN PREGNANCY

Ultrasonography of the liver and biliary tract is widely used in the management of liver diseases outside pregnancy and is safe during pregnancy. In normal pregnancy, ultrasonographic examination reveals no dilatation of the biliary tract, but fasting gallbladder volume and residual volume after contraction are increased. The lithogenic or cholesterol saturation index of bile increases during pregnancy, which is considered a cholelithogenic state. Indeed, biliary sludge frequently occurs during pregnancy but is generally asymptomatic and often disappears spontaneously after delivery.

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Gallstones are much less frequent (2% in an Italian study, 12% in a Chilean study) and may be associated with biliary pain. In the absence of suggestive symptoms, systematic ultrasound examination of the gallbladder as an extension of the routine pelvic ultrasound is not justified because silent stones in pregnant women need no treatment.

BLOOD VOLUME AND HEMODYNAMICS IN PREGNANCY

Plasma volume increases steadily from 6th to 36th week of gestation by about 50%. The red cell volume also increases, but the increase is moderate (about 20%) and delayed. Consequently, the total blood volume increases with hemodilution. The hematocrit decreases by the 24th week and becomes stable. Plasma and red cell volume decrease rapidly after delivery. This phenomenon of hemodilution should be kept in mind during the interpretation of all serum concentrations during pregnancy.

Cardiac output increases (about 40%) until the second trimester, then decreases and normalizes near term. Absolute hepatic blood flow remains unchanged, but the percentage of cardiac output to the liver decreases.

SERUM PROTEIN AND LIPID LEVELS IN NORMAL PREGNANCY

Serum albumin levels decrease during the first trimester, and this decrease becomes more accentuated as the pregnancy advances. The decrease in serum concentration is explained by the hemodilution phenomenon. Indeed, the intravascular mass of albumin is normal in pregnancy and the rates of synthesis or catabolism are unaltered in normal pregnancy compared to controls. By contrast, there is an increase in serum concentration of some proteins such as alpha-2-macroglobulin, alpha-1-antitrypsin, and ceruloplasmin. Fibrinogen and most coagulation factors (II, VIII, IX, and XII) increase when protein S levels decrease and fibrinolysis is inhibited. These physiological changes in hemostasis limit bleeding during delivery but are associated with an increased risk of thromboembolism during pregnancy and the postpartum period. Any change in the prothrombin time, which is widely used in the routine evaluation of chronic and acute liver failure, should be considered pathologic.

Serum cholesterol, triglyceride, and phospholipid concentrations increase in late pregnancy. This hyperlipidemia is a result of the metabolic adaptation to the pregnant state, saving glucose for the fetus. Except when a pregnant woman is suffering from acute pancreatitis, measurement of serum lipid concentrations is rarely useful during pregnancy. Serum concentrations of total globulins are unaffected by pregnancy.

SERUM LIVER FUNCTION TESTS IN NORMAL PREGNANCY

As outside pregnancy, serum liver function tests are essential in the management of liver diseases during pregnancy. Routine liver function

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tests usually include total and conjugated bilirubin, aminotransferases, alkaline phosphatase, and prothrombin time. In addition, gamma-glutamyl transferase (GGT) or 5'-nucleotidase may be used to confirm the hepatobiliary origin of increased levels of alkaline phosphatase. Measurement of serum bile acid concentrations may be useful for the management of cholestasis, especially during pregnancy. However, this test is not easily available and this limits its utilization. Awareness of the physiological changes in liver function tests is indispensable for the interpretation of these test values during pregnancy.

BILIRUBIN CONCENTRATIONS

Total bilirubin concentrations are decreased during all three trimesters of pregnancy. Free bilirubin concentrations have also been found to be lower in pregnant women than in nonpregnant controls during all three trimesters, as are concentrations of conjugated bilirubin during the second and third trimesters. Hemodilution could at least be partly responsible for the decrease in bilirubin concentration because albumin is the protein that transports bilirubin.

AMINOTRANSFERASE ACTIVITY

Measurement of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity levels is the most useful test for the routine diagnosis of liver diseases. The effects of pregnancy in serum ALT and AST activity levels are somewhat controversial. In a few studies, a slight increase in ALT and/or AST activity has been found during the third trimester. However, in the majority of published studies, serum ALT and AST activity levels do not change during pregnancy or remain within the normal limits established in nonpregnant women. In one study, we found a slight increase in ALT during the second trimester of pregnancy compared to nonpregnant women, but all the values remained below the upper normal limit. We did not have any explanation for this slight increase in ALT and only during the second trimester in pregnant women compared to nonpregnant controls. An increase in ALT or AST levels during labor might be due to contractions of the uterine muscle. Thus, it should be emphasized that serum AST or ALT activity values above the upper normal limit before labor should be considered pathologic and should lead to further investigations.

ALKALINE PHOSPHATASE ACTIVITY

Serum alkaline phosphatase activity levels increase in late pregnancy, mainly during the third trimester. By contrast, serum alkaline phosphatase levels are lower in oral contraceptive users. This increase during pregnancy is not due to an increase in the hepatic isoenzyme but rather largely due to the

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production of the placental isoenzyme. During the third trimester, there is also an increase in the production of the bone isoenzyme as documented by an increase in its serum level up to 6 weeks post-delivery. These findings document that the measurement of serum alkaline phosphatase activity is not a suitable test for the diagnosis of cholestasis during late pregnancy and postpartum.

GAMMA-GLUTAMYL TRANSFERASE ACTIVITY

Serum GGT activity has usually been considered to be normal during pregnancy. When we compared serum GGT activity levels between pregnant women and nonpregnant women not taking oral contraception, we did not find a difference in the first trimester. However, we found a slight but significant decrease in GGT activity levels in the second and third trimesters in pregnant women. A significant decrease in serum GGT activity was also found in late pregnancy compared with early pregnancy in women with morning sickness. On the other hand, women suffering from viral hepatitis in early pregnancy have higher levels of serum GGT activity compared to women with viral hepatitis in late pregnancy, and the same has been observed in women taking oral contraceptives. These findings suggest that sex hormones may inhibit the hepatic synthesis of GGT, leading to a decrease in serum GGT activity in late pregnancy.

5'-NUCLEOTIDASE ACTIVITY

In two studies without control groups, no change was found in serum 5'-nucleotidase activity. In one study, serum 5'-nucleotidase activity was slightly higher in the second and third trimesters, compared with controls. A slight increase during the third trimester was also observed in two other studies. This slight physiological increase in serum 5'-nucleotidase during late pregnancy is a limitation for its use in the diagnosis of cholestasis.

BILE ACID CONCENTRATIONS

Increases in serum concentrations of certain bile acids have been reported during pregnancy, and it has been suggested that pregnancy could be associated with subclinical cholestasis. These changes in serum bile acids were minimal and observed mainly in the postprandial state. Moreover, some of these studies did not include a control group. By contrast, in a prospective study, fasting total bile acid concentrations measured during each trimester of pregnancy did not significantly differ from the control group. In clinical practice, when a woman experiences pruritus during pregnancy, the measurement of serum bile acid concentration may be useful for the diagnosis of cholestasis, especially when routine liver function tests are still within normal limits.

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HISTOLOGICAL STUDIES

Standard and ultrastructural examination of the liver during normal pregnancy reveals no or minimal nonspecific abnormalities.

During normal pregnancy, except for alkaline phosphatase and 5'-nucleotidase, most values of serum routine liver function tests remain below the upper normal limits established in nonpregnant women. Thus, when liver disease is clinically suspected in a pregnant woman, any increase in serum ALT and AST activity levels, serum GGT activity, serum bilirubin, or fasting total bile acid concentrations should be considered pathologic and should prompt further evaluation.

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Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road, Daryaganj, New Delhi - 110 002, INDIA
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ISBN 978-93-6616-271-3