Original Article

Evaluation of Liver Enzymes in Normal Pregnancies in a University Hospital of Zabol Iran: A Cross-Sectional Study

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Abstract

Objective: Changes in endocrine, nervous, renal, cardiovascular, and respiratory systems during pregnancy have been studied, but changes in liver function have been poorly studied. Therefore, the purpose of this study was to investigate the trend of changes in liver enzymes in normal pregnancy.

Materials and methods: This prospective longitudinal study included 68 pregnant women who were referred to the Obstetrics and Gynecology Clinic of Amiral Momenin Hospital in Zabol in 2021. In terms of the trimester of pregnancy, the presence of underlying diseases, history of previous pregnancies, disorders of the enzymes of recent patients, the patients were evaluated, and the information from the patients' files was analyzed.

Results: The average AST levels in pregnant women in the first, second, and third trimesters were 16.82, 17.47, and 18.00, respectively, which show that garlic consumption is increasing. The average PT in pregnant women decreased in the first, second, and third trimesters. The average direct and total bilirubin levels in pregnant women in the first and second trimesters showed a constant trend. The amount of total protein increased in pregnant women during the first, second, and third trimesters. In the second and third trimesters, the enzyme level was significantly higher in pregnant women than in nonpregnant women. The level of GGT in pregnant women in the first, second, and third trimesters showed a different trend.

Conclusion: Accurate evaluation of patients, especially in the third trimester, is necessary from the point of view of increasing enzyme levels in other countries.

Keywords: Liver Function Tests; Pregnancy; Alanine Aminotransferase (ALT); Aspartate Aminotransferase (AST); Bilirubin

Introduction

During pregnancy, the mother undergoes significant anatomical and physiological changes to nurture and accommodate the developing fetus. According to liver tests, these changes are due to the increase in estrogen and progesterone levels, as well as hemodynamic changes. Abnormal liver tests were observed in 3% of pregnancies. Usually, in normal pregnancies, liver test results are normal or increase slightly within the normal range. An increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), activated gamma glutamyl-transferase (GGT), serum albumin, and total bilirubin levels during pregnancy may be pathological and should be evaluated quickly. Serum fibrinogen levels increase in late pregnancy; however, prothrombin time (PT) and partial thromboplastin time (PTT) do not change during pregnancy. The gestational age at pregnancy is the most important diagnostic clue for diagnosing liver diseases. Liver diseases that occur during pregnancy may be exclusive to pregnancy, become apparent or aggravated during pregnancy, or have nothing to do with pregnancy but occur during pregnancy. Premature delivery is the only choice of treatment for liver diseases associated with pregnancy. Acute fatty liver, preeclampsia, hyperemesis gravidarum syndrome, eclampsia, hemolysis syndrome with increased liver enzymes, decreased platelet count, HELLP, acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy are pregnancy-specific disorders that may cause elevated liver tests and hepatic dysfunction (1, 2). Chronic liver diseases, including cholestatic liver disease, autoimmune hepatitis, Wilson disease, and viral hepatitis, may also occur during pregnancy (3, 4). Several liver diseases are associated with certain periods of pregnancy. Liver diseases exclusive to pregnancy have specific clinical characteristics and times. Frequent vomiting in the first trimester, intrahepatic cholestasis of pregnancy in the second and third trimesters, preeclampsia, HELLP, and acute fatty liver occur in the third trimester (4, 5).

During pregnancy, ALT, AST, GGT 6, and bilirubin remained unchanged, but the range changed with a decrease in the upper part. Serum alkaline phosphatase levels increase in late pregnancy because of both the production of placental isoenzymes and an increase in bone isoenzymes. Consequently, the measurement of serum alkaline phosphatase levels is not a suitable test for the diagnosis of cholestasis. Prolongation of the PT is believed to be a good early marker of hepatic dysfunction. Serum albumin concentration also decreases owing to hemodilution during the first trimester (6).

Serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase, and bilirubin values remain unchanged during pregnancy; however, changes occur in their ranges with a reduction in the upper end, which is a consequence of hemodilution occurring during pregnancy. Alkaline phosphatase is elevated (up to 300%) but is placental in origin. There is an increase in the hepatic synthesis of coagulation factors VII, VIII, and X and fibrinogen; however, the ranges of prothrombin time and activated partial thromboplastin time remain unchanged. It is believed that prolonged prothrombin time is a good early marker of hepatic synthetic dysfunction. Serum albumin concentrations fall due to hemodilution (7, 8).

Liver function tests: Liver disease during pregnancy is classified into two main cat-egories: those related to pregnancy; and those non-related or coincidental to pregnancy that are present de novo, or are pre- existing chronic liver disease exacerbated by pregnancy (9, 10).

Pregnancy related liver diseases include intrahepatic cholestasis of pregnancy (ICP), acute fatty liver of pregnancy (AFLP) and, hemolysis, elevated liver enzymes and low platelets count (HELLP) syndrome. In addition, pre-eclampsia (PE) and hypereme- sis gravidarum (HG) are frequently associated to liver abnormalities (11, 12).

Changes in endocrine, nervous, renal, cardiovascular, and respiratory systems during pregnancy have been studied, but changes in liver function have been poorly studied. Therefore, the purpose of this study was to investigate the trend of changes in liver enzymes in normal pregnancy.

Materials and methods

This prospective longitudinal cross-sectional study was conducted on 68 pregnant women who were referred to the Obstetrics and Gynecology Clinic of the Amir Al Momenin Hospital in Zbol in 2021. This study was approved by the ethics committee of the Zabol University of Medical Sciences (IR.ZBMU.REC.1400.053). The inclusion criteria for the study were pregnant women aged 18–35 years

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and without a history of underlying disease. Informed consent was obtained from all participants in this research. Patients with high blood pressure, diabetes, liver diseases, and those who used drugs, such as nonsteroidal antiinflammatory drugs (NSAIDs), antiepileptic drugs, antituberculosis drugs, antithyroid drugs, and oral contraceptives, were excluded from the study. Demographic characteristics, including age, gestational age, educational level, and occupation, were recorded. The control group was recruited from patients admitted to the Obstetrics and Gynecology Clinic of Amir Al Momenin Hospital. The control group included women of the same age as the pregnant women (a healthy woman was chosen for each pregnant woman).

Patients were screened according to trimester of pregnancy, underlying diseases, history of previous pregnancies, recent liver enzyme disorders, and information extracted from the patients' files. Liver enzyme levels were recorded at the end of each trimester and entered into a checklist. After the tests, the address and phone numbers were obtained for reference purposes. The liver enzyme levels of the women in the control group were also recorded in the checklist. The measurement of liver enzymes using biochemical methods was performed in the hospital laboratory (Padko kit, Diori BT3500 device) (13). After collecting the data, SPSS 20 software was used to describe the data in frequency format; percentage, mean, and standard deviation were used. An independent t-test was used to compare the mean liver enzymes in the two groups of control participants and pregnant women. A significance level of 0.5 was considered statistically significant.

Results

The study included 140 patients; 50% (70 people) of the study population were pregnant women, and 50% (70 people) were nonpregnant women. The average age of the study population was 28 years, and the average body mass index of the study population was 22.89 kg/m^2.

The mean AST levels in the first, second, and third trimesters were 16.82, 17.47, and 18.00, respectively, indicating an increasing trend. In the first trimester, this enzyme level was significantly lower in pregnant women than in nonpregnant women (p=0.003). This difference was not statistically significant in the second and third trimesters.

The average AST levels in pregnant women in the first, second, and third trimesters were 12.91, 13.80, and 15.25, respectively, indicating an increasing trend. In the third trimester, this enzyme level was significantly lower in pregnant women than in nonpregnant women (p=0.034). This difference was not statistically significant in the first and second trimesters.

The average AST levels in pregnant women during the first, second, and third trimesters were 207.70, 240.58, and 268.15, respectively, indicating an increasing trend. In the third trimester, this enzyme level was significantly lower in pregnant women than in nonpregnant women (p<0.001). This difference was not statistically significant in the second and third trimesters.

The average AST levels in pregnant women in the first, second, and third trimesters were 13.06, 12.98, and 13.13, respectively, indicating a variable trend. This difference was not statistically significant in the first, second, and third trimesters.

The mean albumin levels in the first, second, and third trimesters were 4.26, 4.35, and 4.49, respectively, indicating an increasing trend. In the third trimester, this protein level was significantly lower in pregnant women than in nonpregnant women (p=0.001). In the second and third trimesters, this protein level was significantly higher in pregnant women than in nonpregnant women (p<0.001).

The average total protein levels in pregnant women in the first, second, and third trimesters were 6.35, 6.45, and 6.50, respectively, indicating an increasing trend. In the second trimester, this enzyme level was significantly higher in pregnant women than in nonpregnant women (p<0.001). This difference was also statistically significant in the first trimester (p=0.004).

The mean total bilirubin levels in the first, second, and third trimesters were 0.87, 0.75, and 0.73, respectively, indicating a decreasing trend. In the first trimester, this enzyme level was significantly higher in pregnant women than in nonpregnant women (p<0.001). However, in the second and third trimesters, this difference was not statistically significant.

The average direct bilirubin levels in the first, second, and third trimesters were 0.20, 0.20, and 0.20, respectively, indicating a consistent trend. There were no statistically significant differences in the first, second, and third trimesters.

The average PT in pregnant women in the first, second, and third trimesters were 13.16, 13.04, and 13.05, respectively, indicating a decreasing trend. There were no statistically significant differences in

the first, second, and third trimesters.

Because of the frequency of liver disorders and diseases during pregnancy, this study was conducted to determine the frequency of liver enzyme disorders and the outcome of pregnancy in Zabol.

Discussion

In our study, most overweight patients were 40 years old.

The results of the studies conducted by Tessema et al. and Jasovic–Siveska et al. show that maternal age is a possible risk factor for preeclampsia. Advanced maternal age is associated with the development of preeclampsia (14, 15). Takafumi and his colleagues in 2021 (Japan), by examining liver transaminase levels during pregnancy, showed that the ALT level began to decrease in the first half of the third trimester and was lowest in the second half of the third trimester and on postpartum day 1 (median [interquartile range]:8 [6–11] U/L, 8 [6–10] U/L, respectively). The decline reversed and returned to the nonpregnant state by postpartum days 2–7. The AST level remained unchanged, regardless of pregnancy. The prevalence of abnormal liver transaminases (AST >40 U/L and ALT >40 U/L) was <1% in the third trimester; however, it increased to 3–5% on postpartum days 2–7 (16), which is consistent with the results of our study.

The study conducted by Hassan et al. in 2022 in Ethiopia with aim to evaluate serum uric acid and liver function tests among pregnant women with and without preeclampsia showed that there were statistically significant differences in the mean serum uric acid, ALT, and AST levels between preeclamptic pregnant women and normotensive pregnant women ($p<0.05$). There were no statistically significant differences in mean total and direct bilirubin levels (17). There was also a significant difference in the mean serum uric acid, alanine transaminase, and aspartate transaminase levels across the different gestational age categories.

However, in our study, the mean ALT and AST levels in pregnant women in the first, second, and third trimesters showed an increasing trend.

In the study conducted by Salman MI under the entitled "Changes in liver function tests during pregnancy in 2009", 90 pregnant women with an average age of 29.14 ± 0.062 years and 30 nonpregnant women with an age group of 28.0 ± 041 were evaluated. The results of this study indicated that the levels of serum albumin and T.S.B were significantly lower in all three trimesters than in the control group ($P<0.001$). S.ALP activity in the third and second trimesters was significantly higher in the control group ($p<0.001$). ALT activity in the third trimester was significantly higher in the control group ($P\leq0.05$). Serum AST activity and PT did not differ significantly between pregnant and nonpregnant women (18).

In the study conducted by Younas A and colleagues, entitled "Determining of the reference interval of liver function tests during pregnancy in the urban area of district Rawalpindi, Pakistan" (2018), 754 pregnant women with an average age of 24 and 25 years were evaluated. The results of the study indicated that the reference intervals for bilirubin, albumin, ALP, and ALT in the first trimester included: bilirubin 3–9 μmol/L, albumin 31–45, ALT 3–35 and ALP 122–224 U/L. In the second trimester, bilirubin, 2–7 μmol/L, albumin, 28-45 g/L, and ALT 1–33U/L, and 131–300U/L (19).

In the study conducted by Girling and colleagues entitled "Liver function tests in pre-eclampsia: importance of comparison with a reference range derived for normal pregnancy", the results indicated that the reference AST, ALT, bilirubin and GGT were each lower in uncomplicated pregnancy than the nonpregnant laboratory reference ranges. Among cases with elevated liver function tests in the pre-eclampsia group, 37% were abnormal only by the new reference ranges. Using the new ranges, the prevalence of elevated liver function tests was significantly higher in the pre-eclampsia group (54%) than in those with pregnancy induced hypertension (14%) ($P < 0.01$). In pre-eclampsia cases, abnormal liver function tests were associated with greater proteinuria ($P < 0.05$), lower platelet count ($P < 0.001$) and more maternal complications ($P < 0.01$) compared to normal liver function tests; there was no difference between the groups in the severity of hypertension (20).

In the study of Naz et al., 80.6% of pregnant women were aware with the idea of PIH. The friends and family members, followed by medical specialists were the first individuals that pregnant women consulted in order to get knowledge. As a result of their performance, 47.1% of the participants obtained a score that indicated they had a low level of comprehension. The participants' ages, type of family, history of PIH or gestational diabetes, performing sports, and attending frequent antenatal care appointments were all important factors in their

knowledge score (21).

The study of García-Romero and colleagues entitled "Liver disease in pregnancy: Medical aspects and their implications for mother and child" showed that liver disease was present in 11.24 % of all pregnancies. Associated liver disease was found in 10.8% of all pregnancies, mainly those related to pre-eclampsia (9.9% of pregnancies). Only 0.56% was due to liver disease that was co-incidental or preexisting; the acute or chronic hepatitis C virus was the most frequent in this group (0.12%) (22).

When managing pregnancy in referral hospitals in Latin America, it is important to discard liver alterations early for adequate follow up of the disease and to prevent adverse consequences for the mother and child.

They also determined the reference values of the first and second trimesters of liver function tests during pregnancy. This case not only helps to monitor the normal biochemical changes in pregnancy but also leads to the rapid diagnosis of fatal complications of pregnancy (10). In a study conducted by Al-Hamdani et al. (2011), entitled "Evaluation of some Liver Function Tests during the Different Gestational Period, 150 pregnant women aged 16–41 and 50 nonpregnant women aged 17-40" were evaluated. The results of the study showed no significant difference in AST activity in all trimesters compared to the control group. ALT serum activity showed a significant decrease in the pregnancy trimesters compared to that in the control group. Serum ALP activity significantly increased with the progression of pregnancy. However, the AST/ALT ratio did not show a significant difference with pregnancy progression. There was no significant difference in serum bilirubin levels (direct and indirect) compared with the control group in all trimesters (23).

In a study conducted by Prakash (2019), biochemical analysis of liver function tests in different trimesters of pregnancy, 224 pregnant women (cases) and 112 healthy nonpregnant women (controls) were evaluated (24).

The results of the study showed that the average level of ALP increased slightly in the second trimester but increased strongly in the third trimester of pregnancy. However, the average levels of ALT protein and albumin decreased in the second and third trimesters compared to those in the first and non-pregnant or primiparous healthy women. For all the parameters, the differences were significant.

Among the limitations of the study were the non-cooperation of pregnant women, the non-referral of some patients at the end of each trimester, and the Corona limitations.

Conclusion

The mean PT in pregnant women in the first, second, and third trimesters showed a decreasing trend. The average direct and total bilirubin levels in pregnant women in the first and second trimesters showed a constant trend. This enzyme level was significantly higher in pregnant women than in non-pregnant women. The average total protein level in pregnant women in the first, second, and third trimesters showed an increasing trend. In the second and third trimesters, the enzyme level was significantly higher in pregnant women than in non-pregnant women. The average GGT levels in pregnant women in the first, second, and third trimesters showed variable trends. The average AST level in pregnant women in the first, second, and third trimesters showed an increasing trend. Liver disease and pregnancy complications that affect liver transaminases include preeclampsia and HELLP, hemolysis, elevated liver enzymes, and low platelet counts. Therefore, the accurate evaluation of patients, especially in the third trimester of pregnancy, is necessary in terms of increased liver enzyme levels.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

None.

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