



## Original Article

# Comparison of Liver Function Tests in Normal Pregnancy with Non-pregnant Matched Controls

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### Abstract

**Background:** Change of liver biochemical profiles is normal during pregnancy. It is almost impossible to understand disease processes that can threaten women during pregnancy without understanding normal physiological change. Aim of this study is to evaluate changes in serum liver function tests in normal pregnant women in first, second and third trimester.

**Material and Methods:** The cross-sectional comparative study was carried out in the Department of Obstetrics & Gynaecology of Rajshahi Medical College Hospital, Bangladesh in 2019. This study consists of 90 pregnant women and 90 matched control. Among the 90 pregnant women, 30 were in first trimester, 30 were in second trimester and 30 were in third trimester. Blood samples were taken for routine liver function and protein profiles

**Results:** Serum total and direct bilirubin concentrations were significantly lower in second and third trimester. The mean ALP level was slightly increased in 2nd trimester and drastically increased in 3rd trimesters during pregnancy. Serum ALT and AST activity was significantly increased in third trimester. No significant change in serum total proteins concentration, but serum albumin concentration was significantly lower and serum globulin concentration was significantly higher in all three trimester. Serum albumin/globulin ratio was significantly reduced in second and third trimester.

**Conclusion:** Relative values of various liver function tests during gestational trimesters appear to be the best guide to confirm the diagnosis and treatment strategies. Thus, gynecologists should routinely monitor liver function tests in all gestational trimesters to avoid the future complications to mother and offspring.

**Key words:** pregnancy, liver function test, protein, albumin,

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### Introduction

The anatomical, physiological and biochemical adaptations to pregnancy are profound compared to non-pregnant women.<sup>1</sup> Many of these remarkable changes begin soon after fertilization and continue throughout gestation. Such changes occur in response to physiological stimuli provided by the fetus and hormonal changes that

accompanies pregnancy in mother. During normal pregnancy, virtually every organ and system undergoes anatomical and functional changes that can alter appreciably the criteria for diagnosis and treatment of diseases. So sometimes these physiological adaptations could be perceived as abnormal. Thus physiological adaptations of normal pregnancy can be misinterpreted as

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pathological and also unmask or worsen preexisting disease. The understanding of these adaptations to pregnancy remains a major goal of obstetrics, and without such knowledge, it is almost impossible to understand the disease processes that can threaten women during pregnancy.<sup>2</sup> The serum estrogen and progesterone levels increase progressively and reach a maximum during the third trimester. These sex steroids have effects on metabolic, synthetic, and excretory hepatic functions.<sup>3</sup> The increase in plasma volume that occurs during pregnancy leads to haemodilution and decreases the serum protein concentrations. Serum alkaline phosphatase levels increase in late pregnancy because of both a production of the placental isoenzyme and an increase in the bone isoenzymes.<sup>4</sup> It is therefore not surprising that changes in liver function tests (LFTs) occur during pregnancy. Nevertheless, except for increased alkaline phosphatase levels, which have been clearly demonstrated, the changes in the other LFT values have not been clearly established, and a recent review in this field has shown that there is some discordance in the literature. The identification of these physiological changes is important for the diagnosis of liver diseases during pregnancy.

The physiological changes in liver function in pregnancy are commonly transient and remain only during pregnancy periods only, then it corrects spontaneously.<sup>5</sup> But disorders arising in pregnancy, such as pre-eclampsia and eclampsia, acute fatty liver of pregnancy (AFLP), haemolysis, elevated liver enzyme and low platelets (HELLP) syndrome, cholestasis, hyperemesis gravidarum and isolated cases of raised liver enzymes can have serious implications. Proper interpretation of liver function tests (LFTs) can lead to proper diagnosis and timely management of diseases and may reduce complications in both mother and fetus.

Thus, the aim of this study was to evaluate the changes in serum levels of routine liver function tests, i.e., Total and Direct bilirubin, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Serum total serum proteins, Albumin, Globulins and

Albumin/Globulin ratio (A/G ratio) during normal pregnancy in first, second and third trimester pregnant women compared with a control group of non-pregnant women.

## **Materials and Methods**

**Study design:** Cross sectional type of comparative (analytical) study.

**Study Setting:** The present study was conducted at Department of Obstetrics & Gynaecology, Rajshahi Medical College Hospital (RMCH), Bangladesh, from January 2019 to December 2019. It is a tertiary hospital situated in northern part of Bangladesh.

**Study Subjects:** A total of 180 study subjects were enrolled. 90 pregnant women (cases) and 90 non-pregnant healthy women (controls) were selected.

**Inclusion Criteria Cases:** Pregnant women (primigravid) were confirmed by a validated pregnancy test report. All were selected from antenatal care clinics at outpatient department of same hospital.

**Controls:** Total 90 controls (non-pregnant healthy women) were selected from outpatient department of same hospital.

**Exclusion criteria:** Multi gravid, pregnancy with gestational diabetes mellitus, hypertension, and women with other chronic diseases, drug induced abnormal liver function test and women over age 30 were excluded.

**Ethical consideration:** The work approval was taken from the Ethical Review committee of Rajshahi Medical College, Bangladesh. Written informed consent was obtained from the participants to ensure their voluntary participation before preceding the questionnaire and specimen collection.

**Sampling Technique:** Systematic sampling technique was adopted for this study. Every alternate primi pregnant women attended at RMCH outpatient Department for antenatal care were taken as sample (case) and every fifth non pregnant matched women attended for other reasons in the same department were taken as

controls. Matching was done only for the age variable.

**Questionnaire and Data collection:** A structured questionnaire prepared for interview was designated for matching the study need. The questions were also focused on duration of pregnancy and obstetric details. The specific symptoms related to liver dysfunction such as pruritus, persistent vomiting, yellowish discoloration of urine, blurring of vision, diminished urine output, upper abdominal discomfort and anorexia were asked.

**Clinical laboratory Techniques:** Blood samples were analyzed for serum bilirubin, total protein, albumin, globulin, ALT, AST and ALP.

**Statistical Analysis Data:** The data collected during the current study were recorded and analyzed statistically to determine the significance of different parameters by using Graph Pad In Stat statistical software. Results are expressed as mean  $\pm$  SD. The values between non-pregnant women and pregnant women in first, second and third trimesters were compared using ANOVA. P value of  $<0.05$  was considered statistically significant.

## Results

The results of LFT values for pregnant women (case) in first, second and third trimester and non-pregnant women (controls) are compared in Table 1.

Table 1: Serum LFTs in non-pregnant and pregnant women (first, second and third trimester).

Variables	Controls Non pregnant women (N=90)	Case Pregnant women			p value
		First trimester (N=30)	Second trimester (N=30)	Third trimester (N=30)	
Total Bilirubin (mg/dl)	0.79 $\pm$ 0.19	0.64 $\pm$ 0.31	0.69 $\pm$ 0.31	0.55 $\pm$ 0.28	0.0002
Direct Bilirubin (mg/dl)	0.19 $\pm$ 0.08	0.18 $\pm$ 0.12	0.14 $\pm$ 0.08	0.08 $\pm$ 0.06	<0.0001
ALT (U/L)	21.49 $\pm$ 4.21	23.59 $\pm$ 9.23	23.44 $\pm$ 9.58	35.21 $\pm$ 19.54	0.004
AST (U/L)	20.23 $\pm$ 3.91	23.66 $\pm$ 16.18	23.99 $\pm$ 15.13	34.29 $\pm$ 25.68	<0.0001
ALP (U/L)	141.3 $\pm$ 31.4	153.4 $\pm$ 43.5	198.25 $\pm$ 33.4	389.28 $\pm$ 127.3	<0.0001
Total Protein (gm/dl)	6.99 $\pm$ 0.52	7.02 $\pm$ 0.03	6.88 $\pm$ 0.49	6.98 $\pm$ 0.52	Not significant
Albumin (gm/dl)	4.20 $\pm$ 0.41	4.21 $\pm$ 0.43	3.88 $\pm$ 0.51	3.23 $\pm$ 0.48	<0.0001
Globulin (gm/dl)	2.74 $\pm$ 0.45	2.89 $\pm$ 0.51	3.28 $\pm$ 0.58	3.88 $\pm$ 0.68	<0.0001
Albumin/Glob ulin ratio	1.67 $\pm$ 0.53	1.51 $\pm$ 0.42	1.17 $\pm$ 0.38	0.98 $\pm$ 0.33	<0.0001

Note: All data are expressed as mean  $\pm$  SD. p value  $< 0.05$  considered as statistically significant.

Total and direct bilirubin concentrations in serum were significantly lower in second and third trimester compared to non-pregnant and first trimester pregnant women. Serum ALT and AST activity was slightly increased in 1<sup>st</sup> and 2<sup>nd</sup> trimester but significantly increased in third trimester compared to non-pregnant

women. No significant increase in serum ALT and AST activity during first and second trimester compared to non-pregnant women. Nevertheless, all serum ALT and AST values remained below the upper normal limit. Serum ALP activity was significantly higher in third trimester compared with non-pregnant, first and second trimester pregnant women. Serum ALP activity was also significantly higher in second trimester compared to non-pregnant women.

There is no significant change in serum total proteins concentration. But serum albumin level was significantly lower and serum globulin concentration was significantly higher in all three trimester compared to non-pregnant women. Serum A/G ratio was significantly reduced in second and third trimester compared to non-pregnant and first trimester pregnant women.

## Discussion

Histological evaluation of liver biopsies, including examination with electron microscope, has shown no distinct changes in liver morphology in normal pregnant women.<sup>2</sup> But some of the laboratory tests used to evaluate hepatic function yield appreciably different results during normal pregnancy. Moreover, some of the changes are similar to those in non-pregnant patients with liver disease. In this cross-sectional comparative study, we measured liver function tests in healthy pregnant women which are in first, second and third trimester and in controls not receiving oral contraception.

Total and direct bilirubin concentration in our study was significantly lower in second and third trimester than control and first trimester pregnant women. A decrease in serum total bilirubin concentration has already been observed during pregnancy in various studies.<sup>6</sup> Haemodilution could at least partly be responsible for the decrease in bilirubin concentration because albumin is the protein that transports bilirubin.<sup>7</sup>

Liver cells contain several enzymes which may be released into circulation in liver damage. Measurement of aminotransferases group of enzymes in serum namely serum glutamate pyruvate transaminase (SGPT; recently called as Alanine transaminase-ALT) and serum glutamate oxaloacetate transaminase (SGOT; recently known as Aspartate transaminase-AST) are widely used to assess the liver function. In our study we found significantly higher serum ALT and AST activity in third trimester compared to non-pregnant, first and second trimester pregnant women. No significant increase in ALT and AST activity

during first and second trimester compared to non-pregnant women. All values were within normal limits. There no obvious explanation for this slightly increased serum ALT and AST activity during the second trimester. In two studies serum ALT and AST activity was higher in late pregnancy than in early pregnancy.<sup>8</sup> Two another studies also shown serum AST values significantly higher in late pregnancy.<sup>8,9</sup> An increase in AST and ALT levels was found during labour, which might be caused by contraction of uterine muscle.<sup>10</sup> Larrain and Girling, in a study highlight that healthy pregnant women typically do not have elevated aminotransferases and, in fact, levels may decrease in pregnancy.<sup>11,12</sup> The results are not in accord with present study. However, in normal pregnancy aminotransferases can rise in the puerperium. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of abnormal aminotransferases and also seen in pregnancy.<sup>13</sup> But, in contrast, Bacq et al concluded that serum ALT activity was significantly higher during second trimester of pregnancy compared with non-pregnant women.<sup>14</sup> Pradumna et al., Joshi et al., and Bacq et al demonstrated ALT activity levels do not change during pregnancy or remain within the normal limits established in non-pregnant women.<sup>14,15,16</sup> which diverges with current study. So AST and ALT activity remain controversial during pregnancy and before labor and should lead to further investigations.

Alkaline phosphatases are membrane-bound glycoproteins found in many tissues. ALP originates mainly from two sources: liver and bone. There are four main alkaline phosphatase variants, intestinal, placental, placental-like and a

non-tissue specific isoform. The enzymes may be present in other tissue like intestine, kidney, placenta, leukocytes. The serum ALP values rises in third trimester.<sup>15</sup> In our study also serum ALP activity was significantly higher in third trimester compared with non-pregnant, first and second trimester pregnant women. Serum ALP activity was also significantly higher in second trimester compared to non-pregnant women. Another cross sectional study carried over a period of one year on 150 pregnant women and 50 age matched control depicted ALP level was higher in 1st, 2nd and 3rd trimesters and in control respectively.<sup>5</sup> The increased ALP level is in correspondence to current study. The similar results were also reported in earlier studies carried out by Joshi et al., Loganathan et al and Jamjute et al<sup>7,18,19</sup> which is compatible to present study. The raise in ALP is mainly attributed to the added placental secretion or due to increase in the production of the bone isoenzymes.<sup>17,20</sup> Because of the lack of specificity, the measurement of serum ALP activity is a poor test for the diagnosis of cholestasis during the third trimester of pregnancy.<sup>21</sup> Alkaline phosphatase may be elevated up to 10 times normal; however, alkaline phosphatase can also be increased during the third trimester normally.<sup>22</sup> Bacq et al also confirmed serum ALP activity significantly higher during the third trimester compared to non-pregnant women and during second trimester compared to first trimester<sup>14</sup> is quite similar with current study. Same type of findings was also experienced by Salman for ALP activity during his research.<sup>23</sup> Most studies showed increase in ALP activity in second and third trimester.<sup>24,25</sup> Alkaline phosphatase activity in the placenta is associated with preterm delivery and trophoblast alkaline phosphatase activity is altered in pre-eclampsia.<sup>26</sup> The regulation of human placental alkaline phosphatase is not well described, but is transcriptionally regulated by steroid hormones, peroxisome proliferator-activated receptor (PPAR- $\gamma$ )<sup>27</sup> and the short chain fatty acid butyrate.

Albumin is synthesized in the liver. The rate of synthesis is constant in normal individuals at 150 to 250 mg/kg/day, resulting in the production of 10 to 18 g of albumin daily in a 70-kg man. The

liver produces albumin at less than half of its capacity. The primary factors affecting albumin synthesis include protein and amino acid nutrition, colloidal osmotic pressure, the action of certain hormones, and disease states. A considerable amount of albumin passes through the glomerular filtrate daily during pregnancy and most of this is reabsorbed in the renal tubules, being broken down in the process and therefore lost to the body. Moreover, albumin is the major protein frequently found in normal urine.<sup>30,31</sup> The present study reports the mean albumin level (gm/dl) with standard deviation in pregnant women in their 1st, 2nd and 3rd trimester were  $4.21 \pm 0.43$ ,  $3.88 \pm 0.51$ ,  $3.22 \pm 0.48$  respectively and the albumin level in non-pregnant healthy women was  $4.20 \pm 0.41$ . This finding demonstrates the mean albumin level was decreased in the 2nd and 3rd trimester as compared to 1st as well as non-pregnant healthy women ( $p < 0.0001$ ). A study carried by Noor et al at Dhaka Central International Medical College, Dhaka estimated serum albumin (g/dl) as  $3.97 \pm 0.64$ ;  $3.53 \pm 0.53$  and  $3.53 \pm 0.54$  in 1st, 2nd and 3rd trimesters respectively and in non-pregnant healthy women as  $4.30 \pm 0.71$ .<sup>32</sup> The results are quite similar to current study. Similarly, the study carried by Zannat et al determined serum albumin of control group of non-pregnant women in reproductive age and women in first and third trimester of pregnancy were  $3.83 \pm 0.027$ ,  $3.57 \pm 0.044$  and  $3.31 \pm 0.05$  respectively. Serum albumin was decreased in first and third trimester of pregnancy than in non-pregnant women and maximum decrease seen in third trimester.<sup>33</sup> The results obtained confirms with present study. Maryam et al showed serum albumin level decreased from the first trimester and became progressively more accentuated with the advancement of pregnancy.<sup>34</sup> The results of present study also bears similarity with the studies of Bacq et al conducted on pregnant women in France.<sup>14</sup> Similar results parallel to current study were also obtained by Gohelet al.<sup>6</sup> Honger claimed that the synthesis of albumin is inhibited by progesterone and or estrogen.<sup>35</sup> This lower concentration of serum albumin is claimed to be result of proteinuria and hyper catabolism of albumin with no detectable loss of albumin in

interstitial fluid or gut. Nutritional deficiencies may be implicated for this phenomenon.<sup>36</sup> On the other hand, Olufemi et al found that the amount of albumin synthesized in the intravascular compartment was significantly greater at 9.5 g/day in pregnant subjects compared with 6.3 g/day in non-pregnant control subjects which is contradictory to the existing results.<sup>38</sup>

Globulins are a heterogeneous group of large serum proteins other than albumin which includes hundreds of serum proteins including carrier proteins, enzymes, complement, acute phase proteins, lipoproteins and immunoglobulins. Most of these are synthesized in the liver, although the immunoglobulins are synthesized by plasma cells. The current study reports that the mean globulin level with standard deviation was  $2.89 \pm 0.51$ ,  $3.28 \pm 0.58$  and  $3.88 \pm 0.68$  in their 1st, 2nd and 3rd trimesters respectively and  $2.74 \pm 0.45$  in healthy controls. The result depicts minor variation in different trimesters as compared to controls ( $p < 0.000$ ). Similarly, in another study serum globulin (g/dl) in pregnant females was  $2.64 \pm 0.75$ ;  $2.78 \pm 0.77$ ;  $2.49 \pm 0.70$  in 1st, 2nd and 3rd trimesters respectively and in non-pregnant women as  $2.61 \pm 0.88$ .<sup>32</sup> The results are in accord with present study. The almost stable serum globulin in the face of haemodilution suggests an increased serum globulin content of blood during pregnancy. Increases in the globulin fraction usually result from an increase in immunoglobulins, but there can be an increase in other proteins in pathologic states that have characteristic electrophoretic patterns. Malnutrition and congenital immune deficiency can cause a decrease in total globulins due to decreased synthesis, and nephrotic syndrome can cause a decrease due to protein loss through the kidney. Delivery has been associated with increased dietary protein requirements in humans. During their period of rapid growth, the fetus and placenta accrue proteins very rapidly. Protein status is usually assessed by measuring levels of total serum proteins, albumin, or plasma non-essential and essential amino acid ratio.<sup>35</sup> It is universally known that serum protein anabolism occurs in the liver and plasma cells and catabolism

of low molecular weight in the kidneys. Alterations in function of any of these sites will affect the appropriate serum protein fractions.<sup>36</sup> Likewise, a study carried at Dhaka, Bangladesh noted total protein (gm/dl) as  $6.61 \pm 1.00$ ;  $6.31 \pm 1.02$  and  $6.01 \pm 0.94$  in 1st, 2nd and 3rd trimesters respectively and in non-pregnant healthy women as  $6.92 \pm 0.98$ .<sup>32</sup> The results are in accordance with present study. Another study carried by Adedeji et al highlights progressive fall in total protein was at 33-36 weeks of gestation.<sup>37</sup> The total serum protein concentration is known to be of limited value on its own. An important factor in the etiology of protein changes is the effect of hormones, especially estrogen, on the synthesis and degradation of proteins such as alpha-fetoprotein, salivary amylase, prolactin and the proteins of the "pregnancy zone".<sup>38</sup> The explanatory clarification towards decreased serum protein level is that the increase in plasma volume that occurs during pregnancy leads to haemodilution. Hence, it decreases the serum protein concentrations without altering the albumin: globulin ratio. The changes in total serum protein concentration may result from dehydration and over loading with fluid. The principles of serum protein changes are lowering of the concentration of albumin fraction probably resulting from renal serum albumin loss, which may have exceeded the reported increase in serum albumin synthesis. A direct relationship of quality and quantity of dietary proteins with decrease in plasma proteins in cases of protein malnutrition has been reported and maternal malnutrition may be aggravated by pregnancy.<sup>39</sup> It has been suggested that pregnant women in developing countries consume diets with a lower quantity of protein, minerals and vitamins.<sup>40</sup> This inadequate dietary intake may be responsible for hypoproteinemia and hypoalbuminemia during pregnancy.<sup>41</sup>

## Conclusion

Identification and understanding of above changes in liver function tests in first, second and third trimester of normal pregnant women is important for the diagnosis of liver diseases during pregnancy, otherwise it can be misinterpreted as

pathological and can also unmask or worsen preexisting disease.

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