Effects of Vitamins A, C and E on Liver Function in Pregnancy

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Abstract: In a bid to investigate the effect of sub chronic administration of vitamin A, C and E on liver function in early pregnancy, eighty-five female Wistar rats (255-300 g) were employed for the study. They were randomly assigned to three test groups (I, II and III) having 5 treatment subgroups with five rats each, and a control and vehicle group with five rats each. After allowing the female rats to mate with male rats for 6 days, pregnancy was confirmed. The control group was administered 1ml of distilled water, vehicle group 1ml of tween 80, while test groups I, II and III received varying doses of vitamin A, C and E respectively via the intragastric route for 11 days. The results showed a significantly elevated albumin, total protein, AST and ALP levels (p<0.05), following vitamin C and vitamin A administration when compared with control. In the vitamin A treated group there was a dose dependent significant increase (p<0.05) in total protein, AST and ALP levels while vitamin E treated group presented a significantly reduced ALT (p<0.05) with no significant change in total protein levels when compared with control. Conclusively the therapeutic benefit of vitamin A, C and E supplementation in pregnancy is not without an impact on the functional and cellular integrity of the liver.

Key words: Cellular integrity, liver function, pregnancy, vitamin A, vitamin C, vitamin E

INTRODUCTION

Pregnancy is a physiological condition associated with many changes in the internal milieu of the body, in which more and more stress is being laid on the biochemical changes of the body (Kashinakunti et al., 2010). While a number of associations between hepatic dysfunction and pregnancy exist (Hunt and Sharara, 1999), reports show that the physiological changes in liver function during pregnancy are commonly transient and rarely permanent (Jamjute et al., 2009). 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 (Jamjute et al., 2009).

The liver serves multiple functions viz a viz the biotransformation of insoluble compounds (e.g., drugs, toxins, bilirubin), the metabolism and excretion of cholesterol and bilirubin, the production of plasma proteins (e.g., albumin, coagulation factors, alpha- and beta-globulins, transferrin, haptoglobin), the metabolism of amino acids, carbohydrates and lipids (Hunt and Sharara, 1999) and the storage of blood, vitamins and iron (Guyton and Hall, 2006). The diagnostic work-up of abnormal Liver Function Test (LFT) is challenging, as the conditions peculiar to pregnancy have to be considered in addition to the causes affecting the non-pregnant population (Riely, 1994; Knox, 1998). The spectrum of disease is varied and abnormal LFT can be mild with no long-term consequences, or it can be severe, leading to both maternal and fetal mortality (Riely, 1999).

More recently, the observation that women with pre-eclampsia have decreased plasma and a placental concentration of antioxidants (Hubel et al., 1997; Wang and Walsh, 1996) has led to the proposal that placental under perfusion may mediate a state of oxidative stress (Rumbold et al., 2008). It has been suggested that deficiency in antioxidant vitamins would be associated with the development of pregnancy complications like pre-eclampsia, eclampsia (Hubel et al., 1997; Erkkola, 1997). These observations have given rise to increased interest in antioxidants (Kashinakunti et al., 2010). In this context, this study was undertaken to investigate the impact of antioxidant vitamins A, C and E on liver biomarkers in early pregnancy.

MATERIALS AND METHODS

Experimental animals: Eighty-five adult female Wister albino rats weighing (225 - 300 g) were obtained from the
Animal House, College of Medicine, Ambrose Alli University, Ekpoma between August and October 2009. They were housed in a stainless steel cage with plastic bottom grid and a wire screen top in physiology Lab II in the Department of Physiology, Ambrose Alli University, Ekpoma, Edo State, Nigeria. They were assigned into five groups; a control group (n = 5), vehicle group (n = 5) and three test groups (I, II and III) made up of five subgroups (n = 5). They were fed ad libitum with tap water and pelleted feeds purchased from Bendel feeds and flour meal Ewu, Nigeria Limited and allowed to acclimatize for 2 weeks. After which two male Wister albino rats were introduced into each group to allow for mating. The animals were allowed to mate for 6 days after which the male animals were removed from the cage. Pregnancy was confirmed using the palpation method as described by Agematsu et al. (1983) and vaginal smear microscopy method (Long and Evans, 1922; Daly and Kramer, 1998). From the 7th day, administration of the different Vitamins was carried out, the animals began using orogastric tubes and syringes to minimize the loss of test substance (Ejebe et al., 2009). This lasted for a period of 11 days. The administrations were conducted between the hours of 08.00 am and 10.00 am daily.

**Vitamins preparation:** Vitamin A, C and E were purchased from Clarion Medical Pharmaceuticals Nigeria Limited. Tween 80 vehicle was purchased from Sigma Pharmaceuticals Limited. 200 mg of the powdered form of vitamin C was dissolved in 10mls of distilled water and the appropriate dose per kg were prepared for administration. Vitamin A (25,000 IU equivalent to 6 mg retinol and vitamin E, 100 mg) was dissolved in 0.2 mL of tween 80 and water in a ratio of 0.2:0.2:9.6.

**Vitamin administration:** In addition to normal feed, group II received Vitamin C as follows; 200 mg/kg, 250, 300, 350 and 400 mg/kg for treatment sub- groups 1, 2, 3, 4 and 5, respectively. In addition to normal feed, group I and III received Vitamin A and E dissolved in tween 80 respectively as follows; 0.6, 0.7, 0.8, 0.9 and 1.0 mg/kg of vitamin A and 16.4, 18.4, 19.4, 20.4 and 22.4 mg/kg of vitamin E administered to treatment sub- group 1, 2, 3, 4 and 5, respectively.

**Sample collection:** Twenty-four hours after the last administration of vitamins was carried out, the animals were sacrificed after inhalation of chloroform. Cardiac and jugular vein puncture were used to collect blood samples into tubes containing EDTA as anticoagulant and centrifuged plasma preparation was assayed for biomarkers of liver function using standard laboratory procedures.

**Results:**

**Table 1: Effect of vitamin A, C and E in pregnancy on liver functionality**

<table>
<thead>
<tr>
<th>Group</th>
<th>Albumin</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.92±0.16</td>
<td>2.92±0.16</td>
</tr>
<tr>
<td>Tween 80</td>
<td>3.08±0.17</td>
<td>-</td>
</tr>
<tr>
<td>T1</td>
<td>3.00±0.10</td>
<td>4.06±0.15*</td>
</tr>
<tr>
<td>T2</td>
<td>3.14±0.11</td>
<td>6.00±0.23*</td>
</tr>
<tr>
<td>T3</td>
<td>3.80±0.43*</td>
<td>6.70±0.15*</td>
</tr>
<tr>
<td>T4</td>
<td>4.24±0.36*</td>
<td>7.26±0.16*</td>
</tr>
<tr>
<td>T5</td>
<td>4.60±0.46*</td>
<td>7.78±0.17*</td>
</tr>
</tbody>
</table>

Values are mean±SEM (g/dL); Vit. = Vitamin; T = Treatment; *: p<0.05 with control
significant increase in Alb, ALP, APT and TP suggest pregnancy exerts possible hepatotoxic effect as the available data suggest that vitamin A supplementation in pregnancy significantly increases plasma Alb, TP, APT and ALP activities. Comparatively, with the control, this increase was statistically significant in the entire treatment in ALP, APT and TP, in 3rd to 5th treatments in Alb, and conversely non significant different in plasma ALT activity except for the 5th treatment. Thus, this present available data suggest that vitamin A supplementation in pregnancy exerts possible hepatoxic effect as the significant increase in Alb, ALP, APT and TP suggest liver damage. Vitamin A is a known hepatotoxin and multiple cases of hepatotoxicity have been documented with the ingestion of vitamin A in high dosages, usually more than 100,000 IU per day, and rare cases have occurred with dosages of approximately 25,000 IU per day (Riley and Bhatti, 2001). Furthermore, Riley and Bhatti (2001) reported the degree of liver injury associated with vitamin A to depends on the dose. This is true in pregnancy supplementation, as justified by the plasma activity of ALP, APT, TP and Alb in this study. Alcohol potentiates the hepatotoxicity of this vitamin as vitamin A can cause steatosis, perisinusoidal fibrosis, chronic hepatitis and cirrhosis (Bashir and Lewis, 1995). From the result of this study, except for ALT which reduces as dose increases, vitamin C supplementation in pregnancy significantly increases plasma ALB, TP, APT and ALP. This effect was more potent with increase dose of vitamin C; however, at a very low dose, vitamin C (as ALT in 1st treatment and TP in the 1st and 2nd treatments) was not significantly different with the control. Of interest are the findings which reported, vitamin C may partially prevent certain types of hepatic cellular damage (McDowell, 1989; Parola et al., 1992; Sies et al., 1997). From the result of this study, except for ALT which reduces as dose increases, vitamin C supplementation in pregnancy significantly increases plasma ALB, TP, APT and ALP. This effect was more potent with increase dose of vitamin C; however, at a very low dose, vitamin C (as ALT in 1st treatment and TP in the 1st and 2nd treatments) was not significantly different with the control. Of interest are the findings which reported, vitamin C may partially prevent certain types of hepatic cellular damage (McDowell, 1989; Parola et al., 1992; Sies et al., 1997). From the result of this study, except for ALT which reduces as dose increases, vitamin C supplementation in pregnancy significantly increases plasma ALB, TP, APT and ALP. This effect was more potent with increase dose of vitamin C; however, at a very low dose, vitamin C (as ALT in 1st treatment and TP in the 1st and 2nd treatments) was not significantly different with the control. Of interest are the findings which reported, vitamin C may partially prevent certain types of hepatic cellular damage (McDowell, 1989; Parola et al., 1992; Sies et al., 1997).
stated that ‘when the two Vitamins (Vitamin A and E) are combined, a potent liver tonic is achieved and that both vitamins work together to strengthen and rejuvenate a tired liver. This present study presented a non significant change (p>0.05) in protein and a reducing ALP (which is non significant at the 5th treatment) with vitamin E when compared with control. While albumin is favoured at a very low dose (1st treatment) with vitamin E, AST is favoured at high dose (4th and 5th treatment).

Abnormal liver tests occur in 3-5% of pregnancies, with many potential causes, including coincidental liver disease (most commonly viral hepatitis or gallstones) and underlying chronic liver disease (Hay, 2008). Furthermore, there have been numerous publications on the specific causes of abnormal liver function test in pregnancy (Knox and Olans, 1996; Castro et al., 1999; Davidson, 1998; Hunt and Sharara, 1999; Sabai et al., 1993). According to Hay (2008), most liver dysfunction in pregnancy is pregnancy-related and caused by 1 of the 5 liver diseases unique to the pregnant state: these fall into 2 main categories depending on their association with or without preeclampsia. An increased risk of fetal loss has been noted in pregnant patients with chronic liver disease (Lee, 1992). While pregnancy are accompany with elevated liver enzymes, however the cause need to be examined as Smoleniec and James (1993) reported viral hepatitis to be the most common cause of jaundice in pregnancy. The course of most viral hepatitis infections (e.g., hepatitis A, B, C and D) is unaltered by pregnancy (Mishra and Seeff, 1992; Snyderman, 1985). However, a more severe course of viral hepatitis in pregnancy has been noted in patients with hepatitis E (a waterborne virus spread through fecal-oral transmission) and disseminated Herpes Simplex Virus (HSV) infections (Riely, 1994; Mishra and Seeff, 1992; Tsega et al., 1992; Bile et al., 1994; Stagno and Whitley, 1985; Glorioso et al., 1996).

Several procedures have been used to protect the liver from damage by administrations of antioxidants such as β-carotene (Olmez and Karakileik 2004), vitamin C (Mitra et al., 1991; Netke et al., 1997), vitamin E (Parola et al., 1992; Harvey et al., 1994; Durak et al., 1996; Naziroglu, 1999) and selenium-vitamin E combination (Brucato et al., 1986; Sies et al., 1992; Naziroglu, 1999). However, this was not in a pregnant condition and thus, the significant of these vitamins in pregnancy on liver biomarker is not guarantee according to this present study.

Conclusively, rather than ingesting antioxidant vitamin in hyper- hepatic enzymes of pregnancy, the underlying cause need to be examined as this study presented significant increases in liver biomarker even in antioxidant vitamins (A, C, E) supplementation in early pregnancy. However, further research in this respect is required.

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REFERENCES


