Variation in coagulation profile and antiannexinA5 of normal pregnant Iraqi women during three trimesters of pregnancy

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Abstract
The present study is conducted to study the variation in some coagulation parameters and AntiAnnexinA5 of normal pregnant women in Baghdad city. This work was carried out for eight months in Medical City/ Baghdad teaching hospital during January to September 2019. Sixty pregnant women included in this cross-sectional study. Pregnant women were divided into three groups according to the different periods of pregnancy every trimester include 30 pregnant women. Hemostatic parameters which involve Prothrombin time (PT) and activated thromboplastin time (APTT) values showed a significant decrease in (p<0.05) as the pregnancy progresses in comparison with the normal values, while there was (52%) of cases showed a short duration for PT and (32%) of cases showed a short duration for APTT. Fibrinogen levels showing that (55%) of cases were at normal values; (17%) elevated values and (28%) of cases decreased values. Anti-annexinA5 showed non-significant changes among pregnant women.

Key words: coagulation, PT, APTT, Fibrinogen, AntiAnnexinA5

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Introduction
Pregnancy is recognized as a hypercoagulable state that protect women from potentially hemorrhage during placentation and the post-partum period (Hellgren, 2003). The changes in many aspects of hemostasis in normal pregnant women are to maintain placental function during pregnancy and to prevent excessive bleeding in delivery. Most changes in blood coagulation and fibrinolysis create a state of hypercoagulability (Prisco et al., 2005). As most coagulation factors increase in normal pregnancy, the prothrombin time (PT) and activated partial thromboplastin time (APTT) may be shortened (Ehhaboret al., 2013; Haram et al., 2009). Fibrinogen level is increased during normal pregnancy. AnnexinA5, is a multifunctional protein which is expressed from placental trophoblasts and one of its proposed roles is the prevention of thrombosis. The involvement of maternal annexinA5 in the placental system minimizes the likelihood of thrombosis and reduces the risk of fetal loss (Ueki et al., 2012). Anti-annexinA5 is a significant risk factor for thrombosis formation in women with fetal loss (Nojimaet al., 2001).

According to World Health Organization, one woman dies every minute from a pregnancy-related complication. The main causes of mortality are antepartum and postpartum hemorrhage, unsafe abortion, preclampsia, obstructed labor and infection (Chandra et al., 2012). Thus, it is important to know variations in hemostatic changes during pregnancy as well as delivery such that adverse incidents leading to minimized maternal mortality.

Materials and Methods
During the time from January to September 2019, this study was conducted with 60 pregnant women. The pregnant women were collected from Medical City- Baghdad Teaching Hospital, the range of their age was from (18-40 years). Pregnant women were divided into three groups according to different periods of pregnancy every trimester include 30 pregnant women. All blood samples were collected early in the morning from all groups for measurement of PT, APTT, Fibrinogen and AntiAnnexinA5. Coagulation parameters are estimated in plasma of all subjects by using Human instrument for blood coagulation (from Human, Germany). While serum AntiAnnexinA5 IgM and IgG was measured by ELISA using a kit supplied by DRG - Germany.
The Statistical Analysis System-SAS (2012) program was used to detect the effect of difference factors in study parameters. Least significant difference–LSD test (Analysis of Variation-ANOVA) was used to significant compare between means. Chi-square test was used to significant compare between percentage (0.05 and 0.01 probability) in this study.

**Results**

Table (1) shows that the Prothrombin Time (PT), International Normalized Ratio (INR) and fibrinogen values showed a non-significant variation among different trimesters. But Activated Partial Thromboplastin Time (APTT) was significantly decrea sed (p<0.05) showing values of (29.37±0.68); (26.57±0.74) and (27.37± 0.73) seconds in the 1st, 2nd and 3rd trimesters respectively, the 2nd trimester show the shorter time in comparison with 1st and 3rd trimesters.

Anti-annexinA5 IgM concentration showed non-significant variation among different trimesters and the values were(1.282±0.19); (1.663±0.32) and(1.542 ± 0.24) in 1st, 2nd and 3rd trimesters respectively, the 2nd trimester showed the highest concentration of Anti-annexinA5 IgM in comparison to the normal values. Anti-annexinA5 IgG concentration showed non-significant variation among different trimesters and the values were (1.987±0.32 ); (1.432 ± 0.09) and (1.862 ± 0.16) in 1st, 2nd and 3rd trimesters respectively, the 1st trimester showed the highest concentration of Anti-annexinA5 IgG in comparison to the normal values.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal values</th>
<th>Trimesters</th>
<th>LSD value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (11-13.5 SEC )</td>
<td>10.61 ± 0.17</td>
<td>9.97 ± 0.27</td>
<td>10.28 ± 0.23</td>
</tr>
<tr>
<td>APTT (27-40 SEC)</td>
<td>29.37 ± 0.68 a</td>
<td>26.57 ± 0.74 b</td>
<td>27.37 ± 0.73 ab</td>
</tr>
<tr>
<td>INR (≤1)</td>
<td>0.916 ± 0.01</td>
<td>0.876 ± 0.02</td>
<td>0.907 ± 0.02</td>
</tr>
<tr>
<td>Fibrinogen (1.8-3.5 g/L)</td>
<td>2.29 ± 0.31</td>
<td>2.54 ± 0.22</td>
<td>2.97 ± 0.32</td>
</tr>
<tr>
<td>Anti AnnexinIgM con. (≤5 U/ml )</td>
<td>1.282 ± 0.19</td>
<td>1.663 ± 0.32</td>
<td>1.542 ± 0.24</td>
</tr>
<tr>
<td>Anti AnnexinIgG con. (≤5 U/ml )</td>
<td>1.987 ± 0.32</td>
<td>1.432 ± 0.09</td>
<td>1.862 ± 0.16</td>
</tr>
</tbody>
</table>

Table (2) shows comparison in short prothrombin time and activated thromboplastin time among different trimesters. Table shows that the 1st trimester decreases in PT value in comparison with the normal values. There were 7 from 20 cases(35%) which showed short duration(9.74 ± 0.21) for PT in the 1st trimester. while, the 2nd trimester shows 12 from 20 cases (60%) decrease in PT value(9.11 ± 0.21) in comparison with the normal values. In the 3rd 12 from 20 cases (60%) also showed decrease in PT value (9.63 ± 0.21) in comparison with the normal values. PT value shows a significant decrease in (p<0.05) as the pregnancy progresses.

Table (2): Comparison in Shortprothrombin time and activated thromboplastin time among different trimesters
From other side, Figure (1) shows that 31 from 60 cases of PT (52%) short time less than (10.2 sec) and 29 from 60 cases (48%) were at normal time.

Table (2) also shows that the 1st trimester decrease in APTT value in comparison with the normal values, there was 1 from 20 cases (5%) shows short duration for APTT (22.30 ± 0.00). While the 2nd trimester 11 from 20 cases (55%) shows decrease in APTT value (24.40 ± 0.35) in comparison with the normal values. The 3rd trimester 7 from 20 cases (35%) also shows decrease in APTT value (23.80 ± 0.68) in comparison with the normal values. Table shows APTT was significantly decreased (p<0.05) as the pregnancy progress, from other side, Figure (2) shows that 19 from 60 cases of APTT (32%) short time less than (27 sec) and 41 from 60 cases (68%) were at normal time.

Table (3) shows comparison in Fibrinogen value among different trimesters. Fibrinogen shows a non-significant difference in normal values among different trimesters. The elevated fibrinogen values shows significant differences (p<0.01) among 1st [1 from 20 cases (5%)]; 2nd [3 from 20 cases (15%)] and 3rd [6 from 20 cases (30%)] trimesters with values (7.60±0.00); (4.20±0.26) and (4.82±0.42) in 1st; 2nd and 3rd trimesters respectively. The decreased fibrinogen values shows non-significant differences among 1st [8 from 20 cases (40%)]; 2nd [5 from 20 cases (25%)] and 3rd [4 from 20 cases (20%)] trimesters with values (1.362±0.09); (1.48±0.02) and (1.43±0.05) in 1st; 2nd and 3rd trimesters respectively. In 1st trimester for the comparison in normal (2.48±0.12); elevated (7.60±0.00) and decreased (1.362±0.09) values of fibrinogen was highly significant (p<0.01) differences. In the 2nd trimester for the comparison in normal (2.56±0.16); elevated (4.20±0.26) and decreased (1.48±0.02) values of fibrinogen was highly significant (p<0.01) differences. In 3rd trimester for the comparison in normal (2.48±0.11); elevated (4.82 ±0.42) and decreased (1.43±0.05) values of fibrinogen was highly significant (p<0.01) differences.

Table (3): Comparison in Fibrinogen among different trimesters (normal value = 1.8-3.5 mg/dl)
From other side, Figure (3) shows that 33 from 60 cases (55%) were at normal values; 10 from 60 cases (17%) elevated values more than (3.5 mg/dl) and 17 from 60 cases of fibrinogen (28%) decreased values less than (1.8 mg/dl).

**Figure (3): Percentage of Fibrinogen among different trimesters of pregnancy.**

**Discussion**

Pregnancy characterized by profound changes in the haemostatic system, these changes constitute a physiologic safety valve which are aimed at enhancing haemostasis, thereby preventing excessive maternal blood loss during parturition (Urasoko et al., 2009). PT measures the extrinsic and common coagulation pathways, and is sensitive to levels of vitamin K coagulation factors (II, V, VII, and X), while APTT assesses coagulation via the intrinsic and common pathways and is sensitive to all coagulation factors except FVII and FXIII. Both PT and APTT seem to be of value for monitoring hemostasis during obstetric hemorrhage (Erhabor et al., 2013). Szecsi et al., (2010) approved that throughout pregnancy, labor and postpartum, PT remained largely unchanged, as they were within non-pregnant comparison ranges. The finding of shortened a PTT in pregnant women can in part be explained by increase in levels of FV, FVIII, FIX and FXII (Hammerova et al., 2014). Jeremiah et al., (2012) observed non-significant differences found during pregnancy but Saha et al., (2009) reported that APTT reduced in pregnancy as opposed to puerperium time, while Awwioro et al., (2013) reported that APTT increased when pregnant occurring. Plasma fibrinogen assessment is important not only in the early diagnosis of hemostatic failure but also in directing replacement therapy during the fibrinopenic condition (Nachtigall, 2009).

Anti-annexinA5 antibodies are directed at annexinA5 a phospholipid-binding protein belonging to the ubiquitous family of annexins, antibodies to annexinA5 have a procoagulant influence, inducing apoptosis of endothelial cells (Balevaet al., 2010). Infusion of anti–annexinA5 antibodies decreased the availability of annexinA5 to bind to the trophoblast surfaces and caused placental thrombosis, necrosis, and fetal loss (Wang et al., 1999). Nojima et al., (2001) study suggests that anti-annexinA5 is a significant risk factor for thrombosis formation in women with fetal loss, in addition, the authors studied several known thrombogenic risk factors and demonstrated anti-annexinA5 was the only significant risk factor for fetal loss in these patients. EL-Gharib et al., (2010) reported that there was a positive relationship between anti-annexinA5 and recurrent miscarriage.

The significantly decreased PT value reflects the tendency of the high coagulation state of the blood (Haleet et al., 2013). Hui et al., (2012) and Oluronshola et al., (2011) reported a decrease in the PT during
normal pregnancy, particularly in the third trimester. The activation of coagulation with shortening of the PT in normal pregnancy appears to be the dominant argument. Buseri et al., (2008) reported an increase in PT in normal Nigerian pregnant women, probably associated with an inhibition of coagulation and exaggerated fibrinolysis.

Nancy et al., (2015) had noted that the APTT was significantly shorter in normal pregnancy, compared to controls; this was attributed to the rapid activation of coagulation factors which are active in the intrinsic pathway (particularly factors 8 and 10). Similarly, Thornton et al., (2010) observed that the APTT significantly decreased from the first through the third trimester of normal pregnancy. Interestingly, these changes were more marked in the third trimester. Indeed the third trimester could represent a point of remarkable activation of coagulation and inhibition of fibrinolysis.

The amount of fibrinogen rises gradually through pregnancy, this shift is part of pregnancy hypercoagulability. It is established that pregnancy is a procoagulable state; thus, it is not shocking that this research and other studies have found a rise in fibrinogen as the precursor to fibrin starting in early pregnancy (O'Riordan and Higgins, 2003). Choe, (2002) observed that the amount of fibrinogen increased gradually throughout gestation, which in the late 3rd trimester was 1.6 fold higher than in the 1st trimester.

Reducing the amount of fibrinogen suggests hemostatic disease (Miami et al., 2013). Brenner, (2004) approved that in normal pregnancy there is a rise in the plasmin activity responsible for fibrinogenolysis and fibrinolysis which may induce a decline in the amount of fibrinogen. Diminished production of the fibrinogen may be attributed to 1) diminished or unstable fibrinogen. 2) Reduced production of the fibrinogen and levels of antigen can inhibit the ability of the body to form a stable blood clot. 3) Chronically low rates may be associated with decreased performance due to hereditary disorders such as a fibrinogenemia or hypofibrinogenemia, or acquired conditions such as end-stage liver disease or extreme malnutrition. 4) Acutely low levels are often correlated with fibrinogen intake such as can be seen with severe fibrinolysis. 5) Rapid, large-volume blood transfusions (dilutional coagulopathy) may also result in reduced fibrinogen rates (Okwesili et al., 2017).

Conclusions
Prothrombin time (PT) and activated partial thromboplastin time (APPT) was significantly decreased as the pregnancy progress, whereas fibrinogen concentration was significantly elevated in the three trimesters compared to normal values. Anti-annexinA5 shows non-significant changes among pregnant women.

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References


