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Serum Human Tissue Factor Levels in Pregnant Women: Implications for Thrombotic Abortion and Stillbirth Risk

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Abstract:

BACKGROUND: The human tissue factor plays an important role in triggering the coagulation process. It is crucial for normal embryonic growth during pregnancy. However, overexpression of this factor can pose a risk for pregnant women and the fetus, potentially leading to abortion or stillbirth.

OBJECTIVE: The study aims to quantitatively assess the concentration of human tissue factor in pregnant women during various trimesters of pregnancy as well as in non-pregnant women. Additionally, the study aims to include pregnant women with a history of abortion, stillbirth, or both, to compare the results of tissue factor concentrations among these groups.

PATIENTS AND METHODS: Blood samples were collected from 46 pregnant and 40 healthy non-pregnant women in gel activator tubes. Serum was obtained through centrifugation, and serum human tissue factor was measured using an enzyme-linked immunosorbent assay.

RESULTS: The study revealed that there is no significant difference in human tissue factor levels among pregnant women in different age groups (P-value > 0.05). However, there is a significant difference (P-value < 0.05) between pregnant women and non-pregnant healthy females. Additionally, some pregnant women showed elevated levels of this coagulation factor, especially those who had experienced frequent abortions or stillbirths (P-value < 0.05).

CONCLUSIONS: It has been found that tissue factor (TF) levels are significantly higher in pregnant women who have had an abortion or stillbirth compared to those who have not. TF can be considered as a specific and sensitive indicator of the risk of abortion in pregnant women. Therefore, measuring TF levels regularly during pregnancy and taking appropriate interventions for those with high TF levels could be beneficial for early diagnosis and prevention of abortion. Many studies support the idea that TF levels should be monitored during pregnancy to help identify and address potential risks.

Keywords: Abortion; Human tissue factor; Stillbirth.

Introduction:

Tissue factor (TF) assumes a crucial role as a cell-surface glycoprotein, directing the extrinsic coagulation pathway by binding to factor VII/VIIa, activating factors IX and X, ultimately leading to thrombin generation and fibrin formation ^[1]. Throughout pregnancy and delivery, TF, expressed by the placenta and maternal blood vessels, is pivotal for hemostasis to avert excessive bleeding ^[2]. Nonetheless, aberrant TF expression or activation can contribute to pathological thrombosis and inflammation, associated with complications like recurrent miscarriage, preeclampsia, intrauterine growth restriction, and stillbirth^[3–5]. Recurrent abortion is a globally common problem, and many factors play a crucial role in this pathogenesis^[6] such as infections by Toxoplasmosis ^[7].

Noteworthy, placenta-mediated adverse pregnancy outcomes and disorders such as pre-eclampsia and fetal growth restriction are linked to irregular TF activity^[4]. Recurrent miscarriage and stillbirth, affecting 1-5% and 2-5 per 1000 births, respectively, present substantial psychological challenges and necessitate precise etiological comprehension^[8]. Thrombosis, a significant contributor to these outcomes, impedes blood flow and oxygen delivery, resulting in placental insufficiency, fetal growth restriction, and demise ^[9].

In a 2017 investigation of TF pathway inhibitor (TFPI) in high-risk women with placenta-mediated adverse pregnancy outcomes, TFPI activity surfaced as a

potential predictive factor, notably elevated at 24 weeks of gestation^[4,10]. However, no explicit correlation with stillbirth was established, underscoring the imperative for focused research^[4].

While TF and TFPI govern the extrinsic pathway of the coagulation cascade, their intricate roles in pregnancy physiology and pathology remain insufficiently explored^[4]. Genetic variations, hormonal fluctuations, and environmental factors exert an influence on TF expression in pregnancy ^[11,12]. Despite the pivotal role of TF, a scarcity of studies persists on serum human TF (sHTF) levels in pregnant women with diverse obstetric histories. sHTF, representing a soluble form of TF, mirrors overall TF activity and expression ^[13].

This study endeavors to quantify sHTF levels throughout trimesters in women with and without a history of thrombotic abortion and/or stillbirth. Envisaging heightened sHTF in women with such a history, particularly escalating with gestational age, the objectives encompass determining sHTF levels in each trimester, contrasting levels between the two groups, and scrutinizing associations with maternal factors. The research's significance lies in unraveling insights into the pathophysiology and prevention of thrombotic abortion and stillbirth, potentially identifying sHTF as a biomarker and therapeutic target for these complications.

Patients and Methods:

Blood samples were drawn from pregnant women from different periods of pregnancy that are distinguished as trimesters, who were enrolled in Akre Pediatric and Maternity Hospital in Akre District of Duhok City- Kurdistan Region-Iraq. Serum samples were collected after blood clotting for 2 hours in a room and after that centrifuged at 2000 g for 20 minutes, then, those samples were Stored at -30°C. Serum human tissue factor (sHTF) levels were quantified and then compared to a variety of pregnant women with or without medical history of abortion and stillbirth risks with control participants. Trimester refers to three-month intervals during pregnancy; a dead fetus indicates fetal demise after 20 gestational weeks; and abortion signified pregnancy termination before 20 gestational weeks.

Serum levels of HTF antigen (HTF-Ag) were analyzed using enzyme-linked immunosorbent assay ELISA (Biotek, USA) and ELISA kit for human tissue factor (ELK biotechnology (Cat: ELK9399), USA). Exclusion criteria encompassed smoking, alcohol consumption, diabetes, renal or liver diseases, and medications affecting coagulation. Statistical analyses were executed via SPSS version 25, presenting descriptive statistics as mean $\pm$ SD for continuous variables and frequency/percentage for categorical variables. Between-group distinctions employed independent t-tests for continuous variables and chi-square tests for categorical variables. Intragroup variations utilized one-way

ANOVA for multiple comparisons, considering $p < 0.05$ as statistically significant.

Results:

In Table 1, the results showed that out of the 46 pregnant women and 40 healthy non-pregnant women who participated in the testing to measure their serum levels of human tissue factor, the pregnant women were aged between 16 and 47 years, with an average age of 27.47 years (± 6.306). Similarly, the healthy control group included individuals aged between 16 and 48 years, with an average age of 32.5 years (± 12.984).

Table 1. General Characteristics of Study Population

Variables	Pregnant Women (N=46)		Control (N=40)	
Age groups (y)	Number	(%)	Number	(%)
16 - 23	16	34.8	16	40.0
24 - 31	17	37.0	4	10.0
32 - 39	11	23.9	4	10.0
40 - 47	2	4.3	12	30.0
48+	0	0	4	10.0
Total	46	100	40	100
Age (Years)	Mean ($\pm$ SD) 27.47(± 6.306)		Mean ($\pm$ SD) 32.5(± 12.984)	

Weather in Table (2) was clear that no significant correlation between age groups and levels of HTF. But, Table (3), showed that the serum human factor values were higher in pregnant women than in non-pregnant healthy females with a significant p-value < 0.05 .

Table 2. TF in pregnant women according to age group

Age Group	No. of Pregnant women	Mean ($\pm$ SD)	P-value
16 - 23	16	158.38($\pm$ 30.18)	>0.05
24 - 31	17	143.55($\pm$ 29.67)	
32 - 39	11	140.09($\pm$ 37.12)	
40 - 47	2	176.51($\pm$ 61.53)	

ANOVA test was Utilized p-value < 0.05 is significant

Table 3 Biochemical characteristics of participants

	Pregnant Women (N=46)	Control (N=40)	
Variables	Mean ($\pm$ SD)	Mean ($\pm$ SD)	P-value
TF (pg/ml)	149.313($\pm$ 33.207)	59.012($\pm$ 20.555)	<0.001

A T-test was performed p-value < 0.05 is significant

TF levels exhibited distinct fluctuations across pregnancy trimesters, reaching their peak during the initial trimester and decreasing thereafter in the second and third trimesters Table (4). A statistically noteworthy disparity was evident between the first and third trimesters ($p = 0.001$). Tables (5) and (6) showed that in pregnant women who experienced stillbirth and abortion during their life, the HTF levels were increased in comparison with no history of stillbirth and abortion cases.

Table 4. TF in pregnant women according to Trimesters

Trimester	No. of Pregnant women	Mean ($\pm$ SD)	P-value
first	4	220.29($\pm$ 17.73)	<0.001
Second	4	170.06($\pm$ 9.92)	

Third	38	139.66(±24.92)	
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ANOVA test was Utilized p-value < 0.05 is significant

Table 5. TF in pregnant women according to Dead Newborns History

No. of Dead Newborns during life history	No. of Pregnant women	Mean (±SD)	P-value
No dead	41	147.70(±34.50)	<0.05
1	4	159.32(±16.44)	
2	1	175.50	

ANOVA test was Utilized p-value < 0.05 is significant

Table 6. TF in pregnant women according to No. of Abortion

No. of Abortion	No. of Pregnant women	Mean (±SD)	P-value
0	30	135.27(±25.74)	<0.001
1	12	173.95(±27.76)	
2	3	175.82(±47.36)	
more than 2	1	195.50	

ANOVA test was Utilized p-value < 0.05 is significant

Discussion:

Multiple studies have demonstrated that pregnant women are more prone to hypercoagulation compared to non-pregnant women. This heightened coagulation poses an elevated risk of thrombosis, miscarriage, and recurrent preterm birth ^[14]. spontaneous abortion is the most common complication in pregnant women^[15]. The

elevated risk of venous thromboembolism during pregnancy underscores the importance of vigilance and care during this special time ^[16], and in females with low-birth-weight newborns or stillbirth ^[17].

During this study, researchers discovered that human tissue factor (HTF), which initiates the coagulation process, becomes heightened during pregnancy. And it was discovered that the levels of this particular factor exhibited an increase in the first trimester of pregnancy, followed by a subsequent decrease during the second and third trimesters. This was further validated by other independent studies and this significant result was obtained from other studies ^[1]. Extensive research has provided compelling evidence that excessive expression of HTF may significantly contribute to pregnancy complications, including abortion and stillbirth^[4]. This study also revealed that, there were no significant differences in HTF levels across age groups.

Researchers noted elevated concentrations of sHTF in pregnant women with a history of abortion and stillbirth, compared to normal pregnant women and furthermore, coagulopathies, which are conditions that affect blood clotting, were identified as significant contributors to pregnancy complications. These conditions can impede blood flow and oxygen delivery, leading to issues such as placental insufficiency, fetal growth restriction, and abortion.

It is important to note that when estimating TF (Tissue Factor) concentrations, different commercial ELISA (Enzyme-Linked Immunosorbent Assay) kits can yield varied results. It is noteworthy that the results closely approximated those obtained in

a previous study that determined TF levels in healthy controls. Specifically, the TF levels in healthy controls were found to be 52.4 (with a range of 28.4-72.4) Pg/mL when using the Quantikine ELISA kit. [18].

Conclusion

Currently, there is an ongoing debate and lack of consensus among researchers and medical professionals regarding the identification of a specific biomarker that can effectively and accurately assess tissue factor levels in pregnant women who are categorized as high risk for potential obstetric complications. Recent investigations have uncovered an intriguing potential correlation between tissue factor (TF) levels and the frequency of abortions. These studies have revealed a pattern of increasing TF levels corresponding with a higher number of abortions. Particularly noteworthy is the significant difference in TF values observed in individuals who have undergone two or more abortions compared to those with fewer or no such history. These findings suggest a potential link between TF levels and a history of abortions, warranting further exploration and scrutiny of its implications in maternal health and obstetric care.

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Conflict of interest

The author and co-authors claimed that there is no conflict of interest.

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