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Evaluation of Fibrinolytic Parameters in Pregnant Women Attending Specialist Hospital, Sokoto

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Abstract
Pregnancy has been characterised by raised fibrinolytic markers which is a potent system to protect against excesive clotting and coagulation during pregnancy. However, some complications, such as bleeding and eclampsia can occur before and after delivery. The aim of this study was to evaluate the trimester at which fibrinolytic parameters increase during pregmanacy in order to provide approprates advice on the monitoring of these parmeters. Twenty -one (21) pregnant women in the 1st, 2nd, and 3rd trimesters were recruited for this study while 21 apparently healthy non-pregnant women (controls). The 21 pregnant women were tested at 1st 2nd and 3rd trimester of pregnancy before delivery (prepartum) and after delivery (post-parturm). They were recruited from patients attending the prenatal and postnatal clinics of a Specialist Hospital in Sokoto, North West Nigeria.The result shows no significant difference in D-dimer and plasminogen, when compared with the control ($p < 0.05$) in the 1st and 2nd trimesters. However, a significant increase in Fibrinogen Degradation Products (FDP) and plasminogen when compared to controls ($p < 0.05$) in the 3rd trimester was observed. However, there is no significant difference in pre and post-partum ($p < 0.05$).Our finding shows that there is an increase in FDP and plaminogen at the 3rd trimester, but not in pre-partum and post-partum samples, suggesting that patients should be monitored at the 3rd trimester for FDP and plasminogen level to avoid any possible risk of bleeding after delivery, futher research is needed using more number of participants to justifiy this result.

Keyword: Fibrinolytic System, Pregnant Women, Bleeding.

Introduction

Systemic fibrinolytic activity, as determined by the euglobulin lysis time, is significantly reduced during pregnancy; however, the reduced fibrinolytic activity returns to non-pregnant values shortly after delivery. This condition is known as pregnancy-induced hyper-fibrinolysis, which is an impaired increase in Plasminogen and antiplasmin concentrations during pregnancy (Astedt, 1972). Considering the fact that fibrinolytic reaction is normal when plasminogen activator is administered in excess during the urkinase sensitivity test, it is assumed that the loss of fibrinolytic activity is due to plasminogen activator loss (Bonnar *et al.,* 1969). However, because fibrinolytic breakdown products are somewhat elevated throughout the third trimester of pregnancy, the capacity for localised fibrinolytic action is not lost. Pregnancy is associated with an overall pattern of elevated coagulant and decreased fibrinolytic capacity, which may shield the expectant mother from the haemostatic burden of placental separation (James, 2010). Pre-existing conditions that can cause hypercoagulability during pregnancy include congenital conditions like Factor V Leiden, prothrombin mutation, antithrombin III deficiency, and acquired conditions such as protein C and S deficiency can increase the capacity of this burden (Billon *et al.,* 2001; Dunkey *et al.,* 2009). Fibrinolysis is a physiological process that inhibits the growth of blood clots. It is considered normal to maintain the balance between bleeding and coagulation.

However, during pregnancy, the level of fibrinolytic paramertes increases above normal, which could lead to postpartum bleeding if the patient has an underline condition (Dugdale *et al.,* 2011). The fibrinolytic system's basic components, the locations where it interacts with the coagulation pathway, or the widespread and indiscriminate deposition of fibrinolysis products in the vasculature are typically associated with disorders of the fibrinolytic system (Condie and Ogston, 1976). Nature has consequently altered the fibrinolytic mechanisms during pregnancy to avoid excessive bleeding, which is not surprising. However, especially in the third trimester, placental detachment poses a significant haemostatic difficulty. According to studies, placental detachment during the third trimester causes an increase in fibrinolytic characteristics. Therefore, the aim of this study was to evaluate increase in the fibrinolytic parameters during the 1^{st} 2^{nd} 3^{rd} trimester, incluing pre and post sample during delivery to establish the specific period of rise during pregnancy and to profer appropriate advice to monitor these parameters.

Materials and Methods

Study area

The study was conducted in Specialist Hospital, Sokoto State of Nigeria. Sokoto state occupies an area of short grass savannah vegetation in the north, generally of arid zone.

Study population

The study population included 42 pregnant women attending Specialist Hospital, Sokoto comprising of 21 pregnant subjects whose samples were tested before (pre-partum) and after putting to birth (post-partum), as well as twenty one (21) aged- matched, non-pregnant women who were monitored as controls .The pregnant women were recruited from the Obstetrics and Gynaecology (O&G) clinic as well as the pre and post-natal wards of Specialist Hospital, Sokoto North –Western Nigeria. The controls comprised of students and staff of Specialist Hospital, Sokoto.

Study Design

This was a comparative study designed to evaluate the fibrinolytic parameters in women during the prenatal and post natal period. It was a two componentized study, comprising of pre and post-partum sample analysis. Blood samples were collected (from both subjects and controls) and tested for fibrinolytic parameters. Results of these parameters were generated, and data was analysed using appropriate data analysis instruments.

Sample Size Determination

The sample size for the study was calculated using the standard formula for determination of minimum sample size (Ibrahim *et al.,* 2009)

Sample size n is given by the formula; $n=z^{2pq/d2}$

Where:

n = Minimum sample size

Z = standard normal deviation and probability.

P = prevalence or proportion of value to be estimated from the previous studies.

q = proportion of failure (=1-p)

d = precision, tolerance limit, the minimum is 0.05

Hence n = 42

Therefore, n = $n=z^{2pq/d2}$

Where Z = 95% (1.96)

P = 4.4% (0.044) (NNNS-UNICEF, 2012)

q = 1-0.044(0.956)

d = 5% (0.05)

Therefore, n = $(1.96)2(0.044)(0.956)/(0.05)^2$

n =42

Inclusion Criteria

Healthy pregnant women aged between 15-49 years, attending O&G Clinic as well as patients in pre and post-natal wards, Specialist Hospital, Sokoto, Nigeria. Potential participants were those who have or whom their parents, relatives, husbands or their legal guidance have given written, informed consent, in their first official language. Participants who have filled in the questionnaire or have been interviewed and their clinical and demographic data obtained are noted into a pre structured data collection sheet.

Exclusion Criteria

Pregnant women who have or their parents, relatives, guardians, husbands refused to give written informed consent for them to be included in the study. Potential participants aged below 15 years. Potential participants aged above 49

years. Potential participants who are on anticoagulant therapy especially of vitamin K antagonist.

Ethical Clearance

Ethical approval for this study was obtained from the Specialist Hospital Research Ethical Committee.

Results

This was a two componentalised comparative study of 42 participants comprising of 21 pregnant women (subjects) whose samples were tested at 1st 2nd and 3rd trimester of pregnancy before delivery (prepartum) and after delivery (post-parturm) as well as 21 age- matched, non-pregnant women (controls). The results obtained were also presented as follows. Table 1 shows comparison of Fibrinolytic parameters of test subjects and controls during the first trimester of pregnancy which shows no significant difference (P<0.05). Table 2 shows comparison of Fibrinolytic parameters of test subjects and controls during the second trimester of pregnancy which shows no significant difference (P<0.05).Table 3 shows comparison of fibrinolytic parameters of test subjects and controls during the 3rd trimester of the pregnancy which show a significantly increase in FDP and plasminogen test (P<0.05).Table 4 shows the comparison of fibrinolytic parameters pre and post partum fibrinolytic parameters and control show no significant difference (P<0.05).

Table 1: Comparison of Fibrinolytic parameters of test subjects and controls in first trimester

Fibrinolytic Parameters	First Trimester (n=21)	Control (21)	t-test	P-value
Euglobin test (secs)	170.29±23.34	180.±26.06	1.101	0.293
D-Dimer test	0.28±0.09	0.30±0.05	0.794	0.443
FDP test	0.15±0.09	0.11±0.04	1.000	0.337
Plasminogen test	0.31±0.16	0.33±0.09	0.843	0.416
T-PA test	0.16±0.05	0.17±0.03	0.635	0.537
AT III	0.20±0.24	0.28±0.02	0.959	0.356

* P<0.05 (Significant) There is no significant difference in the level of the fibrinolytic parameters in the subjects during the first trimester of pregnancy (P>0.05).

Table 2: Comparison of Fibrinolytic parameters of test subjects and controlsin Second Trimester

Fibrinolytic Parameters	Second Trimester (n=21)	Control (21)	t-test	P-value
Euglobin time (secs)	198.71±25.66	180.±26.06	1.104	0.078
D-Dimer	0.57±0.38	0.30±0.05	1.135	0.092
FDP	0.19±0.07	0.11±0.04	1.663	0.122
Plasminogen	0.52±0.35	0.33±0.09	1.368	0.196
T-PA	0.19±0.03	0.17±0.03	1.587	0.138
AT III	0.27±0.08	0.28±0.02	2.084	0.059

*P<0.05 (Significant) There is no significant difference in the level of the fibrinolytic parameters in the subjects during the second trimester of pregnancy (P>0.05).

Table 3 : Comparison of Fibrinolytic parameters of test subjects and controls in third trimester

Fibrinolytic Parameters	Third Trimester (n=21)	Control (21)	t-test	P-value
Euglobin time (secs)	211.14±29.48	180.±26.06	4.839	0.066
D-Dimer	0.79±0.09	0.30±0.05	3.458	0.081
FDP	0.25±0.03	0.11±0.04	2.139	0.011*
Plasminogen	0.89±0.05	0.33±0.09	2.699	0.019*
T-PA	0.21±0.04	0.17±0.03	2.513	0.270
AT III	0.31±0.06	0.28±0.02	2.062	0.490

* P<0.05 (Significant) There is significant difference in the level of the fibrinolytic parameters in the subjects during the third trimester of pregnancy (P<0.05).

Table 4 : Comparison offibrinolytic parameters in test subjects and control at point before and after delivery

Test	Pre-Partum (n=21)	Post-Partum (n=21)	Control (n=21)	F-ratio	P-value
Euglobin test (secs)	194.71±28.11	203.14±48.93	180.±26.06	2.713	0.074
D-Dimer test	0.32±0.34	0.33±0.43	0.30±0.05	0.217	0.065
FDp test	0.25±0.04	0.19±0.05	0.11±0.04	22.516	0.081
Plasminogen test	0.59±0.61	0.51±0.49	0.33±0.09	1.320	0.097
T-PA test	0.16±0.04	0.15±0.07	0.17±0.03	0.401	0.672
AT III	0.35±0.17	0.33±0.24	0.28±0.02	3.435	0.079

*P<0.05 (Significant) The comparison of pr e-partum and post-partumfibrinolytic parameters with controls shows no significant difference in the Euglob ulin test, D-Dimer test, Plasminogen test and T-PA test as compared to control groups (P>0.05).

Discussion

During pregnanacy multiple concentrations of clotting factors and fibrinalytic paramters rise and predispose the potential pregnant, women to generate abnormal fibrin, promote thrombosis and thromboembolic disorders. On the other hand, clotting deficiency or bleeding disorders of any kind in pregnant women subjects them to risk of pre-partum or postpartum haemorrhage (PPH). There is further evidence that deficiency in plasminogen activator activity is responsible for the decreased fibrinolytic systemic activity in pregnancy Bonnar *et al.* (1970). The comparison of prepartum fibrinolytic parameters and postpartum fibrinolytic parameters with controls shows that Euglobulin lyse time, D-dimer, plasminogen and T-PA of pre- partum fibrinolytic parameters, postpartum fibrinolytic parameters and control show no significant difference (P<0.05). However, FDP test of prepartum and postpartum fibrinolytic parameters were significantly higher than that of the control group (P<0.05).

Also, antithrombin 111 (AT111) of pre partum and postpartum fibrinolytic parameters were significantly higher than that of the control group (P<0.05). The result shows that FDP level was highest during the third trimester and lowest in the first and second trimesters. The third trimester is also the time during which anti-thrombin levels are highest. This may be a reflection of the activities preparatory towards parturition wherein which thrombotic tendencies start to go up (Ren *et al.,* 2020) .Our finding is in agreement with the previous report of Wang et al.

(2021) who states that fibrinolytic parameters show no significant difference during the first and second trimesters of pregnancy but show significant rise during the third trimester of pregnancy.

It is clear that localized fibrinolytic activity is not completely abolished because the capacity of the pregnant women to form FDP is maintained and the levels in the late pregnancy may be slightly raised over the non-pregnant range (Woodfield et al., 1968). Our finding of elevated FDP in the pre-partum women is in line with the report of Lee *et al.* (2006) who observed an elevated level of FDP during some obstetric and gynaecological management of women with inherited bleeding disorders. Their report however disagrees with the finding in this study of elevated AT-III levels in the pregnant women. They stated that plasminogen and antiplasmin concentration rise during pregnancy but systemic fibrinolytic activity, as measured by euglobulin lyse time is markedly depressed during pregnancy; the reduced fibrinolytic activity returns to non-pregnant values very soon after delivery.

The loss of fibrinolytic activity is presumed to be loss of plasminogen activity, because when this is added in excess in the urokinase sensitivity test, the fibrinolytic response is normal and the capacity for localized fibrinolytic activity is not lost. However, because fibrin degradation products are slightly raised during pregnancy, when activator activity is produced in excess as in the urokinase sensitivity test, the fibrinogen response is normal (Ren *et al.,* 2020). This is further evidence that deficient activator activity is responsible for decreased systematic fibrinolytic activity in pregnancy. Plasminogen level are raised in pregnancy (Bonnar *et al.,* 1969) but these are counter balanced by a similar rise in antiplasmin activity activator. It is clear that localized fibrinolytic activity is not completely abolished because the capacity of the pregnant woman to form fibrin is maintained and levels in the late pregnancy may be slightly raised over the-none pregnant range (Woodfield *et al.,* 1968). Since fibrinogen and plasminogen are present abundantly in pregnancy the longed lysis time in pregnancy is presumed to be due to diminished activator activity. The work of Woodfield *et al.* (1968) is in agreement with the finding as noted in this study. Also the postpartum fibrinolytic parameters in group 11 shows that FDP test and antithrombin111 test of pre partum and postpartum fibrinolytic parameters were both significantly higher than the control group ($P<0.05$), while other postpartum fibrinolytic parameters were not significantly different with the controls ($P<0.05$).This may be a reflection of a boosted fibrinolytic activity in the post-partum women, to counter any peripartum hypercoagulability in the women. There was no significant difference in fibrinolytic parameters between the pre-partum and post-partum pregnant women ($P>0.05$) except in FDP and AT-III ($P<0.05$). This shows that FDP test and AT-III are significantly higher in pre partum and post-partum women than the control. This implies that among the fibrinolytic parameters of prepartum and postpartum women, FDP test and AT-III test are significantly higher in pre-partum women and post-partum women. Increase in the level of these two pro-fibrinolytic parameters shows that there is sustained fibrinolytic activities in women soon after childbirth. This is in agreement with the work of Howie *et al.* (1975) who reported that despite the increase potentials to form thrombin in pregnancy, there is no compensatory rise in antithrombin III (Wang *et al.* (2021). Following delivery, antithrombin III levels rise during the first week of puerperium which may reduce the rise of thromboembolism after delivery. There is also evidence of increased thrombin activity during normal pregnancy which sharply increases during placental separation. Antithrombin III, the main inhibitor of thrombin and activated factor X shows no compensatory rise during pregnancy but increases during the puerperium (Lee *et al.,* 2006). There was no significant difference in the Euglobulin lyse time ($P<0.05$) in postpartum women.This finding is in contrast with the report of Shaper *et al.* (1966). who stated that that one of the most dramatic observations in pregnancy is the profound depression of the fibrinolytic parameters as measured by the Euglobulin lyse time which returns to normal 30 minutes of delivery (Shaper *et al.,* 1966).

Fibrin plays an essential role in haemostasis as both the primary product of the coagulation cascade and the ultimate substrate for fibrinolysis. A higher antithrombin111 relates to the ability of the pre-partum pregnant women to prevent excessive tendency to bleeding and clotting which may portend danger to the developing foetus. Fibrinolysis efficiency balances that of the coagulation system and is greatly influenced by clot structure, the rate of thrombin generation, the reactivity of thrombus-associated cells such as platelets, and the overall biochemical environment. The coagulation and fibrinolytic enzyme systems play an essential role in maintaining the integrity of the vascular tree (Bonnar *et al.,* 1969). When a blood vessel is damaged, the coagulation system arrests the haemorrhage and the vessel blockage is subsequently cleared by fibrinolysis. Placental separation represents a profound haemostatic challenge. It is therefore not surprising that evolution has modified the coagulation and fibrinolytic systems during pregnancy to prevent undue bleeding. These might have a strong connection to our findings in the present study.

Conclusion

In conclusion, pregnant women attending anti-natal clinic should be monitored for FDP and Plasminogen in the third trimester of the pregnancy to avoid possible pre-eclampsia, postpartum bleeding and thrombosis.

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