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Effects of Antibiotics on Haemostatic Parameters during Pregnancy

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Abstract

An estimated 50,000 Nigerian women die each year from complications of pregnancy and childbirth, accounting for 10% of global estimates of pregnancy maternal death with about 2% resulting from drug induction. This cross-sectional study sets out to evaluate the Prothrombin time test (PT), activated partial thromboplastin time test (aPTT) Erythrocyte sedimentation rate (ESR), and Platelet count (PC) of pregnant women attending antenatal clinics at Oredo Health Centre in Benin City, Edo State. A total number of 130 subjects comprising 100 pregnant women and 30 non-pregnant women were recruited for the study. Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), Platelet count and Erythrocyte Sedimentation Rate (ESR) were studied using standard manual methods. The prothrombin time (sec) of the pregnant women 1st trimester (19.12±0.77b), 2nd trimester (19.90±1.02 b) and 3rd trimester (19.66±0.56 b), activated partial thromboplastin time (sec) 1st trimester (44.02±1.17 b), 2nd trimester (47.72±1.47 b) and 3rd trimester (45.88±1.10b), Erythrocyte sedimentation rate (mm/hr) 1st trimester (24.37±3.04 a), 2nd trimester (37.83±4.53 a) and 3rd trimester (43.25±5.24 a) and platelet count (X109/L) 1st trimester (248.29±23.18a), 2nd trimester (236.33±13.84 b) and 3rd trimester (239.10±16.07 a) were significantly higher than the prothrombin time (sec) 16.48±0.81 a, activated partial thromboplastin time (sec) 36.53±1.42 a, ESR (mm/hr) 29.83±4.14 a and platelet count (X109/L) 201±9.54 an of the non-pregnant women ($p<0.05$). The ESR (mm/hr) of the 3rd trimester (43.25±5.24) was observed to be significantly higher than that of the 1st trimester (24.37±3.04) and 2nd trimester (37.83±4.53) ($p<0.05$). Our investigation showed that antibiotics in pregnancy have a deleterious effect on PT, ESR, APTT and PC studied. We recommend that pregnant women should be given due attention throughout the course and events of pregnancy to prevent or reduce the risk of thrombotic episodes and possible disseminated intravascular coagulation (DIC) with resultant better maternity/child safety and health outcome and educated on the effects of antibiotics to pregnancy.

Keywords: Antibiotics; Pregnancy; Trimester; Coagulation; PT; APTT.

1. Introduction

Antibiotics are medications used to treat, and in some cases prevent, bacterial infections. Antibiotics or antibacterials are a type of antimicrobial used specifically against bacteria, and are often used in medical treatment of bacterial infections. They may either kill or inhibit the growth of bacteria. Several antibiotic agents are also effective against a number of fungi, protozoans and some are toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately [1].

Interestingly, pregnancy is associated with increase concentration of coagulation factors, decrease levels of coagulation inhibitors and decrease fibrinolytic capacity, all of which result in a state of hypercoagulability [2]. The term pregnancy according to Marieb [3] refers to the period from conception to birth. The zygote develops into the placenta and embryo which grows to form the fetus [3]. The normal duration is 265 days from conception to birth, or the more usual calculation of 280 days (40 weeks) from the first day of the last menstrual period [4]. Pregnancy can be classified into three trimesters: first trimester, second trimester and third trimester [5]. During pregnancy, the maternal physiology undergoes many changes [6] and these normal physiological changes assist the fetal survival as well as preparation for labour [7].

Pregnancy is accompanied by major changes in the coagulation and fibrinolytic system [8]. There is also evidence of thrombin activity during normal pregnancy, which sharply increases during placenta separation [9]. The increased level of fibrinogen and other coagulation factors during pregnancy probably represent a compensatory response to local utilization and the resulting hypercoagulability will be advantageous to meet the sudden demands for haemostatic components at placental separation [9]. There are significant alterations in the coagulation and fibrinolytic system during pregnancy and these, together with increase in blood volume and the unique phenomenon of myometrial contraction are thought to help in minimizing the hazard of haemorrhage during and after placental separation. However, these changes also carry the risk of rapid and excessive response to coagulation stimuli [8].

Available statistic indicates that Nigeria has some of the worst indicators relating to maternal health in the developing world. An estimated 50,000 Nigerian women die each year from complications of pregnancy and childbirth, accounting for 10% of global estimates of maternal deaths [10]. Post-partum haemorrhage has been responsible in most of the cases of maternal death WHO, 2005 [11, 12]. The overwhelming majorities die in resource-poor countries, but an unacceptable number of these women die in resource-rich countries [13, 14]. However, this study is aimed at evaluating the effects of antibiotics in prothrombin time, activated partial thromboplastin time erythrocyte sedimentation rate and platelet count during the three trimester of pregnancy.

Pregnancy and childbirth, two important stages in the life of a woman, pose a special clinical challenge in women with inherent bleeding disorders/coagulation disorders which might result from antibiotics usage. Information about these issues are really scarce and limited to few case reports[15]. However, data are limited and/or somewhat narrow in this area of study.

The aim of the study is to determine the effects of antibiotics in some coagulation profile, which includes, Prothrombin time test (PT), Activated partial thromboplastin time test (APTT), Erythrocyte sedimentation rate (ESR) and Platelet count (PC) during the three trimesters of pregnancy.

2. Materials and Methods

Pregnant women from Oredo Local Government Area of Edo State visiting Oredo Local Government Health Centre were enrolled for this study. A total of one hundred and thirty (130) individuals were recruited for this study which consist one hundred (100) pregnant women and thirty (30) non-pregnant women. Subject data such as name, age and trimester of pregnancy were also obtained. The sample size (N) is calculated from the formula below using prevalence from previous studies.

Samples size (**N**) = $\frac{Z^2 Pq}{d^2}$,

where

N = the desired size

Z = 1.96 (standard score)

P = Prevalence

q. = 1- P

d = sample error tolerated (0.05)

The prevalence used in calculating the sample size for this project was deducted from a similar work done by Isibor *et al.*, 2011 on co-infection of malaria parasite and *S. typhi* in patient in Benin City, Nigeria.

1 – 0.05 = 0.95

$\frac{3.8416 \times 0.05 \times 0.95}{0.0025}$

$\frac{0.182476}{0.0025} = 72.9904$ [16]

Blood samples were obtained from pregnant women who presented at the Oredo health centre who were placed on penicillins antibiotics (for about 3 weeks) which was in line with this study according to their trimesters. Control Subjects (Non-pregnant women), were staff and medical trainees in the health centre.

A total of 9.5ml of blood was collected by clean vein puncture from pregnant women and controls using needle and syringe in which, 6.5ml of blood was delivered into a bottle containing 0.7ml of trisodium citrate and 3ml of blood into another bottle containing 0.06ml of EDTA anticoagulant. The plasma was obtained by centrifugation at 2500g for 15mins using the plasma stoppered tubes and used within 3 to 4 hours of collection.

2.1. Methods of Analysis

Prothrombin Time Test [17]**.** (All test tubes, pipettes and syringes use were plastics). Sample collected and prepared. Reconstitute the control plasmas according to their package inserts. Perform all tests in duplicate Prewarm the PT reagent to 37^0C for at least 10 minutes. Prewarm 100µl of the test plasma or control plasma for 2-3 minutes at 37^0C. Add 200µl Phosphoplastin RL reagent to the plasma, simultaneously starting a stopwatch and record the time required for clot formation in seconds.

Activated Partial Thromboplastin Time [18]**.** (Manual method). Collect blood specimen according to directions in specimen collection and handling section. Centrifuge the anti-coagulated whole blood specimen at 2500xg for 15minutes or equivalent force time. While the blood specimen is centrifuging, reconstitute the control plasma according to the package insert included with each control. Immediately after centrifuging, separate the plasma from the red blood cells and place in a plastic tube at 2 to 8^0C until assayed. The maximum storage time at 2

to 8^0C is 2 hours. Place the 0.025M Calcium Chloride reagent into a test tube and pre-warm to 37^0C (requires approximately 5 minutes). Pipette 100µl of the patient plasma or control plasma into a reaction tube. Gently mix the Phospholin ES Reagent by inversion to re-suspend any sediment. Pipette 100µl of Phospholin ES Reagent into the reaction tube containing patient plasma or control plasma. Incubate the Phospholin ES Reagent and patient plasma at 37^0C for 3-5 minutes. Add 100µl of pre-warmed 0.025M Calcium Chloride, simultaneously starting a timer and record the time (in seconds) required for clot formation. The test results (clot time) are reported directly in seconds as the APTT Time.

Platelet Count [18]**.** To 0.38ml (380µl) of 1% ammonium oxalate diluting fluid, 0.02ml (200µl) of a well-mixed blood sample was added. The counting chamber was assembled and charged with the well mixed sample. The counting chamber was left undisturbed in a moist environment for 30minutes. The underside of the counting chamber was cleaned with a cotton wool and the cells examined using first X10 objective to focus and changed to X40 objective to view the small platelets. The platelets were seen as small bright fragments. The platelet seen in 4 small corners squear and 1 small square in the centre was counted (i.e 5 small square in all). The number of platelets in 1 litre of blood was calculated and reported from first principle.

Erythrocyte Sedimentation Rate. Westerngren method [19]. 0.4ml of trisodium citrate anticoagulant was pipetted into a small container. 1.6ml of venous blood or EDTA anticoagulated blood was added to the trisodium citrate and mixed well. Using a safe suction method, blood was drawn to the 0 mark of the Westergren pipette, avoiding air bubbles. The westergren pipette was placed on a Westergren ESR stand ensuring the ESR stand was level, without sunlight and not exposed to vibration. The timer was set for 1hour and after exactly 1 hour, the level at which the plasma meets the red cells was read in millimeter (mm).

Data analysis was performed on the data. Descriptive and inferential Statistics was computed for the PT, aPTT, ESR and PC of the pregnant women at different trimesters to test for the effect of antibiotics on pregnancy, a statistical T distribution analysis test for independent samples was utilized to test and compare pregnant and non-pregnant women for each parameter such as ESR, PT, aPTT and PC. In all, the results were presented in a distribution table. All tests were conducted at 5% significant level and the 95%confidence intervals were also computed where found appropriate. Probability value (p-value) was used to interpret significant factors in the test. P-values that are less than or equal to 0.05 were considered as having significant influence while such values that are found to be more than 0.05 were regarded as not being significant.

3. Results

Table 4.1 shows PT, APTT, ESR, and Platelet count of pregnant women at different trimesters. Table 4.1 below shows the mean ± standard error of mean and the level of significance of PT, APTT, ESR and Platelet count. When the test subjects (all pregnant women) were compared with the control subject (non-pregnant), there was a significant ($p<0.05$) difference in the level of Prothrombin time (PT), activated partial thromboplastin time (APPT), ESR and Platelet count as shown in the table below. All mean values for the test subjects were increased for all test parameters when compared with the control except for APTT and ESR which decreased in the first trimester.

Table 4.2 reveals the means, standard error of mean and the level of significance across the three trimesters. All the values were compared with each other between trimester and none of the parameters were found to be statistically significant except for ESR between first and second and first and the third trimester.

Table-4.1. PT, APTT, ESR, and Platelet count of Pregnant woman at Different Trimesters

Paramerter	Control	1ST Trimester	2ND Trimester	3RD Trimester	F-Value	P-Value	Remark
PT(/Sec)	16.48±0.81 [a]	19.12±0.77 [b]	19.90±1.02 [b]	19.66±0.56 [b]	3.8980	0.0110	S
APTT(/Sec)	36.53±1.42 [a]	44.02±1.17 [b]	47.72±1.47 [b]	45.88±1.10 [b]	13,8700	0.0000	S
ESR(mm/hr)	29.83±4.14 [a]	24.37±3.04 [a]	37.83±4.53 [a]	43.25±5.24 [a]	3.5800	0.0160	S
PLATELET ($x10^9$/L)	201±9.54 [a]	248.29±23.18 [a]	236.33±13.84 [b]	239.10±16.07 [a]	77.7890	0.0000	S

Value in means ± standard error of mean
KEY
S = statistically significantly at P<0.05
NS = Not statistically significantly at P>0.05
NB: Values with superscript ([b])

Table-4.2. PT, APTT, ESR, and Platelet count of pregnant women at different trimester

Parametes	1ST trimester	2ND trimester	3RD trimester	P-value	Remark
PT(Sec)	19.12±0.77	19.90±1.02	19.66±0.56	0.5432	NS
APTT(Sec)	44.02±1.17	47.72±1.47	45.88±1.10	0.0539	NS
ESR(mm/Hr)	24.37±3.04	37.83±4.53	43.25±5.24	0.0166	S
Platelet ($X10^9$/L)	248.29±23.18	236.33±13.84	239.10±16.07	06594	NS

Value in means ± standard error of mean
KEY
S = statistically significantly at P>0.05
NS = Not statistically significantly at P>0.05

4. Discussion

In this study, the prothrombin time (PT), activated partial thromboplastin time (aPTT), platelets counts and ESR of the trimesters of pregnant women in Oredo Local Government Edo State were examined. Pregnancy is typically broken into three periods, or trimesters, each of about three months. Each trimester is defined as 14 weeks, for a total duration of 42 weeks, although the average duration of pregnancy is 40 weeks [20]. While there are no hard and fast rules, these distinctions are useful in describing the changes that place over time.

Haemostasis in normal pregnancy involves a complex network of interaction with positive and negative feedback loops, integrating blood vessels; platelets, coagulation factors, coagulation inhibitor and fibrinolysis and has evolved to maintain the integrity of the vasculature. Normal pregnancy is associated with substantial changes in the tissue factor pathway and in the wider haemostatic system. Normal pregnancy is characterized by impressive changes in the activating and inhibitory pathways of coagulation and fibrinolysis resulting in an accelerated, but well balanced, process of thrombin formation and resolution. These changes serve to protect the mother from the bleeding imposed by placentation and delivery, but they also carry the risk of an exaggeration response, localized or generalized, to coagulant stimuli. Hemorrhage occupies an important position in the etiology of maternal mortality and therefore, remains a major problem. There is activation of blood coagulation and a simultaneous increase in fibrinolysis without signs of organ dysfunction during normal pregnancy. These changes increase as pregnancy progresses. During delivery there is consumption of platelets and blood coagulation factors including fibrinogen [21]. In this study, prothrombin time (PT) assesses the extrinsic pathway of coagulation and is sensitive to factors VII, X, V, II and fibrinogen. Also partial active thromboplastin time (aPTT) assesses the intrinsic pathway of coagulation and is sensitive to deficiencies of factors I, II, VII, IX, X, XI, XII. The result of the present study reveals that prothrombin time showed a statistically significant ($p<0.05$) difference when all three trimesters were compared with the control group with increased mean value. This indicates that pregnancy is likely going to have adverse effect on prothrombin time. This result is inconsistent with an earlier report by Cerneca, *et al.* [22] who recorded no change in the mean prothrombin time values among pregnant women. This is however, in line with the earlier report by Buseri, *et al.* [23]. Temal, *et al.* [24], who recorded an increased prothrombin time values among pregnant women. The highest mean value in the second trimester could be as a result of physiolo9gical changes. Activated partial thromboplastin time (aPTT) recorded statistically significant ($p<0.05$) increase in the first, second and third trimesters when compared with the control group with the highest mean value seen in second trimester. This might be attributed to the physiological changes in the maternal haemostatic system arising from the concentration of foetal haemoglobin in the maternal circulation. It is also not clear if antenatal drugs have significant effect on activated partial thromboplastin time.

In this study there was a significant ($p<0.05$) difference in the level of ESR in the test group when compared with control group. This is supported by observation of other studies [25]. This may be as a result of anaemic state of studied group due to plasma volume expansion and decrease in PCV in normal pregnancy; it may also be due to increased level of fibrinogen in pregnancy [26]. However there was an observed decreased in the mean value of ESR of the first trimester and increased value in the second and third trimester when compared with the control. There was an observable increase in the mean value in the test groups with the highest value seen in the first trimester. This is result in inconsistent with Abbassi-Ghanavati, *et al.* [27], who reported that platelet decreases during pregnancy. There was however no significant ($p>0.05$) difference when the first and third trimesters were compared with the control singly but the second trimester showed a significant ($p<0.05$) difference.

5. Conclusion

Hypercoagulability in pregnancy is the propensity of pregnant women to develop thrombosis (blood clots). Pregnancy itself is a factor of hypercoagulability as a physiological adaptive mechanism to prevent postpartum bleeding and this tend to increase the PT and APPT values in this study. However clinicians are encouraged to constantly monitor pregnant women.

Based on the observations in this study and the mixed results of several other studies, I therefore recommended that; Specific research should be carried out to ascertain its actual effect on coagulation mechanism using large sample size also Activated partial thromboplastin time and prothrombin time should be interpreted with caution during pregnancy.

Conflict of Interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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