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COAGULATION PARAMETERS, PLATELET COUNT AND D-DIMER LEVEL CHANGES IN PREECLAMPSIA AND NORMAL PREGNANCIES IN KHARTOUM STATE

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ABSTRACT

Background: Preeclampsia (P-E) is an obstetric disorder with high morbidity and mortality rates but without clear pathogenic. The dysfunction of the blood coagulation- fibrinolysis system is a silent characteristic of preeclampsia that varies in severity, and necessitates different treatments. A better understanding of the abnormalities of coagulation in the preeclamptic and eclamptic patient may allow the clinician to provide improved management & possibly peripartum therapy. Therefore, it is necessary to find suitable predictors for the onset and severity of preeclampsia. **Aim and objective:** this study designed to compare the coagulation profile, platelet count and D-dimer level in normal pregnancy, severe preeclampsia, and preeclampsia patients to determine the potential indicator of the onset and the severity of preeclampsia. **Materials and methods:** The study was concluded in the Omdurman Maternity hospital and Saudi hospital in Khartoum state during period between May and October 2016.A 50 confirmed cases of preeclamptic/severs preeclamptic patients and 50 normal pregnant women in the third trimester were recruited. Coagulation profile including prothrombin time (PT) activated partial thromboplastin time (APTT), Platelet count and D-dimer test were measured and compared among the study populations. **Results:** Mean value of platelet count was significantly lower in the case group than in control 178. 36 versus 267. 64X10^9, (P= 0.000). Mean vales of APTT (34.60versus 37.07sec) and PT (10.97 versus, 12.54sec) tests, were significantly reduced in control than case group (p= 0.00).D-dimer level (2.21 versus 1.04mg/ml) was significantly greater in case than control group (p=0.00). All coagulation parameters and platelet count did not show any statistical differences between sever preeclamptic and preeclamptic groups .While D.dimer level was markedly greater in sever preeclamptic cases than preeclamptic cases (2.73versus 1.10mg/ml (p= 0.000). **Conclusion:** Raised D-dimer is fairly good indicator of severe preeclampsia and alarming sign for aggressive treatment.

KEYWORDS: PT, APTT, platelet count, D-dimer.

INTRODUCTION

Preeclampsia is one of medical complications of pregnancy. It contributes significantly to maternal and prenatal morbidity and mortality. It is estimated to complicate 2 to 8% of all pregnancies.[1] Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. The number of babies who die from these disorders is thought to be on the order of 500,000 per annum.[2] In Sudan there is high incidence of maternal mortality with preeclampsia, and accounting 4.2% of all obstetric complications and 18.1% of maternal deaths.[3]

Preeclampsia is defined as (P-E), is a syndrome characterized by the onset of hypertension systolic >140mm/Hg or diastolic >90 mm/Hg and either proteinuria (at least 1+ on dipstick or ≥300mg in a 24 hour urine collection) or end-organ dysfunction after 20 weeks of gestation.[4] If left untreated, preeclampsia can progress to convulsion state known as eclampsia. Preeclampsia it is relatively common condition but may become life-threatening for the mother and the fetus.[5]

Preeclampsia can be classified according to the criteria of the American congress of obstetricians and gynecologists (ACOG) Practice Bulletin[6] into two degrees; mild preeclampsia (m P-E)which defined as new onset of blood pressure ≥140/90 mm/Hg after 20

weeks gestation, combined with proteinuria (at least +1, ≥0.3 g/24 h). And severe preeclampsia (s P-E) which defined as blood pressure ≥160/110 mm/Hg, serious proteinuria (at least++, +++, ≥2 g/24 h), and there are different treatments and clinical outcomes for each degree.[7]

The pathophysiology processes underlying this disorder are described in two stages. The first stage is characterized by reduced placental perfusion possibly related to abnormal placentation with impaired trophoblast cell invasion and inadequate remodeling of the uterine spiral arteries.[8] The second stage refers to the maternal systemic manifestations with inflammatory, metabolic and thrombotic responses converging to alter vascular function which can result in multi-organ damage.[8] The basic pathology of preeclampsia includes reduction in the formation of vasodilators such as prostacyclin and NO (Nitric Oxide), vasospasm and endothelial cell dysfunction which lead to platelet activation and micro aggregates formation, increased the production of vasoconstrictors, impaired synthesis of endogenous anticoagulants, and increased procoagulant production. The changes initiated by endothelial cell injury set in motion a dysfunctional cascade of coagulation, vasoconstriction, and intravascular fluid redistribution that results in the clinical syndrome of preeclampsia.[9]

Along with imbalance between coagulation and anticoagulation factors, thrombocytopenia(platelet count less than 100,000 cumm^3) is the most common hematological abnormality found in preeclampsia and eclampsia (It has been noted that the degree of thrombocytopenia increases with severity of disease (lower the platelet count; greater are maternal and fetal morbidity and mortality).[10] It has been shown that when the platelet count is less than 100,000cumm[3], other haemostatic abnormalities, such as prolonged PT & APTT, and reduced fibrinogen concentration may also be present. From the historical point of view, earlier it was stated that only serial measurements of platelet count was adequate for intrapartum screening Later[11], combination of platelet count and aPTT. Platelet count and liver function tests, platelet count and lactate dehydrogenase[12], platelet count and antithrombin were suggested for early detection and screening of patients with preeclampsia.[13]

At the same time, the coagulation mechanism is still not clear in preeclampsia & severs preeclampsia, which make the coagulation parameter results not certain between these groups & management of these cases may be delayed until the fatal coagulation complications come out. Therefore, finding a reliable, coast effective screening test for preeclampsia, plus to the platelet count and coagulation parameters would play an important role in early prevention and intervention of the disease.

AIMS AND OBJECTIVES

The present study was undertaken to find out variation in coagulation parameters (PT, APTT and D-dimer) and platelet count in normal pregnancy & preeclampsia, sever preeclampsia that can be used as an early indicator for the onset & the severity of the disease.

MATERIALS AND METHODS

This is a case-control study carried out in Omdurman Maternity Hospital and Saudi Hospital in Khartoum state during May-October 2016. A total of 50 normal pregnancies were included as control group, and 50 diagnosed cases of P-E were taken as a case group. The test group was selected and classified to preeclampsia and sever preeclampsia according to the criteria of the ACOG Practice Bulletin[6]. Pregnant women with history of essential hypertension, Diabetes Mellitus , Epilepsy, Renal disorder, sever infection, using anticoagulant drugs, liver disease were excluded.

Written informed consent was received from all participating patients. The whole design, procedure and informed consent of this study were approved by the Research Ethics Committee of Sudan Ministry of health, Omdurman Maternity Hospital and Saudi Hospital.

Blood collection and laboratory methods

A 5mL venous blood were collected and divided into 2.5ml of blood in EDTA-2K container for Platelet count and preserved at 37°C. The blood sample was measured using the Mindray automatic quantitative hematology analyzer (BC-3000plus, made in Germany). The remaining 2.5 ml blood sample was placed into sodium citrate container (32.06 mg/ml final concentration 3.8%) in a 9:1 volume ratio used for coagulation parameters tests. Platelet Poor Plasma (PPP) was prepared by centrifugation at 2500 g for 15 minutes with supernatant separation and divided into two samples, one putted at room temperature for coagulation profile PT and PTT using coagulometer (Thrombotimer I . channel. Auto-star system, Germany, biomed reagent for PT: (10-15 second), APTT: (28- 40 second)). And other part kept in Eppendorf tube and freeze for D-dimer test. D-DIMER test was performed using the Cobas c 111 automatic analyzer (Roch. Germany, cobas reagent <0.5 mg/ml in third trimester 0.13-1.7[14]). All these mentioned parameters of the test group were estimated and compared with those of the control group.

Statistical analysis

Mean & standard deviations and of all variables were calculated using EPI info and SPSS program14.0. The statistical significance was assured using student independ t - test. P values less than 0.05 were considered statistically significant.

RESULTS

In the present study the coagulation parameters, platelet count and D-dimer test were estimated in 50 healthy pregnant women (controls) and 50 preeclampsia women

(35 sever preeclampsia & 15preeclampsia) in the third trimester of pregnancy. The mean values of coagulation parameters, D-dimer & platelet count in normal pregnant women were within the normal values to the kits used, these finding are represented in Table1, Some abnormalities among control group of coagulation tests are represented in Table 2.

Table-1.Coagulation profile and platelet count in healthy pregnant control group n=50.

Test	MEAN	STD. Deviation
PLT Count	267.64	69.25
PT	10.97	1.24
APTT	34.60	4.04
D-dimer	1.04	0.78

PT: Prothrombin Time. **APTT**: Activated partial thromboplastin time, **P-E**: preeclampsia

Table 2: Distribution among control group the platelet count and coagulation tests abnormalities in healthy pregnant control group n=25

Coagulation abnormality	Total number of cases 25
Thrombocytopenia (<150 X 10^3 mm^3)	1 (2 %)
Prolong PT (>15s)	1 (2%)
Low PT (<10s)	10 (20%)
Prolong APTT (>40s)	6 (12%)
Low APTT (< 28 s)	1 (2%)
Elevated D-dimer (>0.5)	6 (12%)

The mean values of coagulation parameters, and platelet count in preeclampsia were within the normal values to the kits used, while the mean of the D-dimmer was abnormally increased these findings were represented in Table 3. Some abnormalities of coagulation tests are represented in, Table 4.

Table-3: Coagulation profile and platelet count in the patients with preeclampsia n=50.

Test	MEAN	STD. Deviation
PLT Count	178.36	71.57
PT	12.54	1.60
APTT	37.07	7.71
D-dimer	2.21	1.92

Table-4: Distribution of cases depended on the coagulation tests abnormalities in patients.

Coagulation abnormality	Total number of cases%
Thrombocytopenia (<150 X 10^3 mm^3)	18 (36%)
Prolong PT (>15s)	4 (8%)
Low PT(<10s)	3 (6%)
Prolong APTT (>40s)	14 (28%)
Low APTT(<28s)	3 (6%)
Elevated D-dimer (>0.5)	23 (46%)

PT: Prothrombin Time. **APTT**: Activated partial thromboplastin time, **P-E**: preeclampsia

In this study, the comparison of normal pregnant women to the preeclampsia patients for mean platelet count, PT, APPT and D-dimer tests showed that, the mean platelet count was significantly lower in the case group than in control group (178, 36versus 267, 64X10^9). The mean values of APTT & PT were significantly prolonged in case group than in control group (37.07s versus 34.60sec) and (12.54 versus 10.97 sec) respectively (p= 0.00). Elevated- D-dimer level test was significantly greater in case than control group (2.21 versus 1.04 mg/ml) (p=0.00).These finding represented in Table 5

Table-5: Comparison of coagulation tests result between preeclampsia and healthy pregnant women

Test	Sample	Limitation		MEAN	STD. Deviation	P. value
		Minimum	Maximum			
PLT Count	P-E	20.00	365.00	178,36	71.57	**0.00**
	Normal	111.0	436.00	267,64	69.25	
PT	P-E	10.00	16.10	12.54	1.60	**0.00**
	Normal	8.20	17.30	10.97	1.24	
APTT	P-E	25.00	56.00	37.07	7.71	**0.04**
	Normal	28.0	44.80	34.60	4.04	
D-dimer	P-E	0.51	8.57	2.21	1.92	**0.00**
	Normal	0.22	4.9	1.04	0.78	

PT: Prothrombin Time. **APTT**: Activated partial thromboplastin time, **P-E**: preeclampsia

In this study, the comparison made between preeclampsia & sever preeclampsia found that, all coagulation parameters and platelet count did not showed any statistically differences , except D-dimer test which was greater in sever preeclampsia cases compare with preeclampsia cases 2.44 versus 1.10 (p= 0.001). This result presented in Table 6.

Table 6: Comparison in platelet count and coagulation tests between preeclampsia and sever preeclampsia.

Test	Sample	Limitation		MEAN	STD. Deviation	P-value
		Minimum	Maximum			
PLT Count (c/cumm3)	P-E	66,00	296,00	185	58	**0.27**
	Sever P-E	20.00	365,00	162	76	
PT (Sec)	P-E	10,00	16,00	12.8	1.8	**0.57**
	Sever P-E	10,10	16,00	12.37	1.6	
APTT (Sec)	P-E	28	56	38	7.99	**0.70**
	Sever P-E	25	50	37.14	7.47	
D. Dimer	P-E	0,51	4,10	1.10	0,88	**0.001**
	Sever P-E	0,53	8,57	2.44	1.8	

PT: Prothrombin Time. **APTT**: Activated partial thromboplastin time, **P-E**: preeclampsia

DISCUSSION

Pregnancy is a condition associated with hypercoagulability, including an increase in the majority of clotting factors, decrease in the quantity of natural anticoagulants, a reduction in fibrinolytic activity and reduction in the platelet count.[15] Obstetrician & gynecologist considered reduction in the platelet count < 100,00 cumm^3 as a beginning of all coagulation disorders like preeclampsia & DIC.[16] The more reduces in platelet count, the more in e severity of the case. These facts guide the physician to use the platelet count only as a baseline test for coagulation disorders. On the other hand, not all coagulation disorders involved reduction in the platelet count. These management lead to delay in the diagnosis of the cases till fatal complication come out.[17]

The present study found that most of healthy pregnant women tend to have normal coagulation parameters except for some cases which showed thrombocytopenia, shortage in PT which reflect hypercoagulability in the third trimester of pregnancy. In the present study we documented increased prolongation in APPT in some cases in normal pregnancy despite they had normal platelet count, which indicate coagulation abnormalities like DIC. So, we concluded that platelet count >150,000/cumm3 cannot assure the physician that no other significant clotting abnormalities are present. However, the measurement of aPTT seens to be important for early detection of coagulation abnormalities in pregnant women who have normal platelet counts in the third trimester.

Similar findings were documented by several studies. Chaware S A et al (2015)[18], Asiya Naaz et al (2015)[19], Lei Han et al (2014)[20], Awad Elkareem Abass et al (2016)[21] in their studies they documented that during late pregnancy, the platelet count, PT were significantly decreased while APTT was normal.

In the present study, the comparison of normal pregnant women to the preeclamptic patients for platelet count, mean PT, APTT & D-dimer showed that preeclamptic group had a significant reduced in the platelet count, and elevated in PT, APTT D-dimer test.

Our results are agreed with Lei Han *et al*. (2014)[20], Asiya Naaz *et al*. (2015)[19] Chaware S A *et al* (2015)[18], founded a significant decrease in platelet count in preeclampsia patients in a comparison to the healthy pregnancy ,increased APTT and D-dimer (DD) during late pregnancy. These findings suggest consumption of platelets in intravascular coagulation with fibrinolytic system activating causing raised fibrin degradation product.

Till today there is no certain differences between preeclampsia & sever preeclampsia regarding to the coagulation pathway.[12] The result obtained by the present study was completely agreed with this fact, for exception in the significant raised in the D-dimer level which is documented by our study. The above pattern of D-dimer values can be explained by activation of coagulation and fibrinolytic system. Our result correlate well with Melina de Barros *et al* (2012)[22], their studies documented significant increased in D-dimer test in sever preeclampsia in comparison to preeclampsia.

Preeclampsia is characterized by thrombocytopenia and coagulation abnormalities indicating intravascular coagulation. Platelet counts and activated partial thromboplastin time have predictive value in severe cases of pregnancy. With this routine screening tests, coagulation disorders of normal pregnancy, preeclampsia can be detected.

CONCLUSION

The coagulation test should be introduce in the routine examination of the pregnant women in the third trimester. Raised D-dimer, more than low platelet count, are fairly good warning indicator of deterioration of the condition to preeclampsia and it can alert the clinician to opt to seriously address the case and to consider further investigations and confirmation. The investigations have

to be correlated with other investigations and the clinical picture of the patients.

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