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Coagulation Status in Women with Uncomplicated Fetal Death

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ABSTRACT

To determine coagulation tests status in women with uncomplicated fetal death A cross-sectional study conducted in Khartoum, Sudan between January and December 2014. A total of 50 patients with fetal death were matched in maternal and gestational age to 50 normal pregnant women. Standard techniques were used to assess full coagulation tests and red cells indices and hemoglobin in both groups. Both groups were similar in baseline characteristics. Women in the fetal death group had significantly higher D- dimer than in normal pregnant women, (86vs. 30%, p= 0.0004). Of women with fetal death, 8% (n=3) had D-dimer values greater than > 500 ug/ml, 6 % (n=3) and 2 % (n=1) had prolonged PT and aPTT respectively p>0.05. Platelets counts were significantly lower in women with fetal death compared to controls (247.86±73.323 vs. 317.18±73.323, P<0.001), 8 %(n=4) were below the range for normal pregnancy and 2 %(n=1) with Platelets counts <100. There were no significant changes in PT, APTT, Fibrinogens, between both groups p> 0.05. The D-dimer correlated positively and significantly with PT (r=.199, p=0.048) and INR (r=0.201,p=0.044)and negatively with platelets counts (r=-.349,p=<0.001) .There was no correlation between D-dimer, the gestational age, and maternal age. The study demonstrated that 8% of women with IUFD at risk of bleeding supporting the view of termination policy rather than expectant management of fetal death. There was no correlation between D-dimer, the gestational age, and maternal age.

Keywords: fetal death, coagulopathy, coagulation tests

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INTRODUCTION

Pregnancy loss is a common obstetric problem; it complicates over 30% of conceptions. The term fetal death is applied to pregnancy loss after 10 weeks of gestation [1]. Fetal death is preceded by a cessation of previously perceived fetal movements, followed by a decrease in pregnancy-related symptoms. However, the definitive diagnosis is established by real-time ultrasonography documenting the absence of fetal heart pulsations [1].

In the majority of cases (25-60%) of fetal death, the etiological factors are unidentifiable. In clearly identified cases, the cause of fetal death can be attributable to Demographics, maternal age, obesity, medical Disorders and Thrombophilias[3,4].

The management of fetal death is controversial; some authors suggest termination of pregnancy once the diagnosis is established to abort maternal psychological impact of a dead fetus in addition to bleeding diathesis [5,6]. Other workers adopted expectant management since studies have shown that spontaneous labor will start within two weeks of fetal death in 95 % of cases [7], and the danger of coagulopathy will start after 4 weeks from fetal death [8.] Early interference may raise issues associated with induction and waiting too long may also increase the risk of developing DIC and infections[8].

There is no available conclusive laboratory test that can establish or rule out the diagnosis of DIC. The diagnosis of DIC should be based on clinical findings supported by relevant laboratory tests. Despite the Limited utility of the D-dimer in the diagnosis of disseminated intravascular coagulation, the D-Dimer assay has gained significance acceptance over other tests in clinical decisions about the presence of thrombosis [9]. The D-dimer value of 500 ng/mL is widely accepted a cut-off point for diagnosing or ruling out thrombosis in pregnant women [10].

It has been reported that a normal pregnancy is a hypercoagulable state; the risk for thrombosis increased 4.2 folds during pregnancy arising to 14.4 in the postpartum period. The alterations to the haemostatic mechanism in pregnancy increased the risk of hemorrhage, thrombosis, and DIC. In fetal death, tissue thromboplastin is slowly absorbed, depending upon the duration of death, the patients will present with either a compensated or a decompensated state. Most of the literature documented that DIC in fetal death occurs after 4 weeks from death. Based on this concept, we maintained a low threshold for DIC in fetal death, and we adopted the policy of expectant management. Literature on coagulation status in early fetal death is scant.

To our knowledge; no previous study was conducted to determine coagulation status in uncomplicated fetal death. The aimed of this study was to investigate coagulation status in uncomplicated cases of fetal death and to identify those at higher risk of hemorrhage by using

quantitative D-dimer other tests included were Fibrinogen level, prothrombin Time (PT), activated Partial Thromboplastin Time (APTT), platelets count, and fibrinogen degradation products (FDPs). Other tests included were (hemoglobin) Hb%, and red blood cells indices (RBS) indices.

MATERIALS AND METHOD

Between January and December 2014, we prospectively studied the blood clotting tests in patients with missed abortion and IUFD referred to the outpatient clinic at Khartoum Teaching Hospital, Sudan. The study was approved by the institutional ethics committees. A prior Informed consent was obtained from each participating woman. The diagnosis of fetal death was based on clinical examination and confirmed by ultrasound examination documenting an absence of fetal cardiac activity. All cases underwent a second scan confirming fetal death. The sonographic examination was performed by the same operator to avoid bias, by using GE logic 200, at a frequency of 3.5 and 6.5 MHZ for trans-abdominal and trans-vaginal scan respectively. Gestational age was calculated from last normal menstrual period and early ultrasound reports .

Study population: fifty women with fetal death were included in this study, and they were matched for age and gestational age to 50 women with normal pregnancy served as controls.

Exclusion criteria were excluded if any of the following abnormality was detected 1) history bleeding; 2) chronic disease; or 3) history chronic liver disease; 4) and patients on anticoagulant therapy.

Data recorded included, demographic characteristics maternal age, parity, gestational age and estimation of the duration of fetal death. Investigations performed for all patients included Fibrinogen level, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Platelets count, and Fibrinogen degradation products (FDPs) and D-dimer for each group. Other basic blood parameters investigated were Hb%, MCH, MCV, MCHC, and hemoglobin.

Blood sampling:

For fibrinogen, FDPs, PT, and APTT test, blood was collected by a clean venipuncture in plastic containers containing 0.109 M Sodium Citrate in a ratio of 9 parts of blood and 1 part anticoagulant. Whenever possible, venous sample was collected without pressure cuff, allowing the blood to enter the syringe by continuous free flow as venous occlusion causes hemoconcentration, increases fibrinolytic activity, platelets release, and may activate some clotting factors.

Sample preparation:

Samples were centrifuged at 4000 rpm for 15 minutes to collect platelet poor plasma (PPP). For platelets count, the sample was collected in clean EDTA venipuncture plastic containers.

Hematological determinations:

Fibrinogen: was assayed by clotting of diluted citrated plasma is obtained by addition of thrombin. The coagulation time is proportional to the fibrinogen concentration. This method determines only the clinically important clotable fibrinogen.

Fibrinogen degradation products, (FDPs), and D-dimer were estimated in the presence of the corresponding antigen; the latex particles coated with monoclonal anti-FDP antibodies agglutinated to form macroscopic clumps.

Prothrombin Time (PT): was obtained by thromboplastin activation to the extrinsic coagulation system in plasma in the presence of calcium ions. The subsequent clotting time is dependent on the concentration of factors II, V, VII, and X. Thus the prolongation indicates a deficiency of one or more of these factors.

Activated Partial Thromboplastin Time :(APTT) was estimated by Cephaloplastin activation of the coagulation factors of the intrinsic system in plasma in the presence of calcium ions. The clotting time depends on the activity of factors VIII, IX, XI and XII as well as of I, II, V, and X. coagulometer and reagents were used to detect above tests were obtained from (Diamed AG, 1785 Cressier sur Morat / Switzerland).

Platelets count: Was counted by using Sysmex blood counter (Sysmex Kx 21N) (system corporation; Mundelein, Illinois, system America, Inc. This machine detects blood cell count by direct current (DC) detection. A blood sample was aspirated, measured to a predetermined volume, diluted at the specified ratio and then fed into each transducer. The transducer chamber has minute hole called the aperture. On both sides of the aperture, there are the electrodes between which flows direct current. Blood cell suspended in the diluted sample pass through the aperture, causing direct current resistance to change between the electrodes. As direct current resistance changes, the blood cell size was detected as electric pulses.

Statistical analysis:

Statistical package for social sciences (SPSS version 15 for Windows) was used for data recording and statistical analysis. Means were compared between groups by independent t-tests. Chi-square test was used for association between categorical variables. A bivariate regression analysis was used to determine the relationship between the variables. P value was set significant at <0.05.

RESULTS AND DISCUSSION

In the current study, 50 women with fetal death (duration of death was 13±1.6 days) were compared to 50 with normal pregnancy to investigate coagulation status.

women with fetal death did not differ significantly from normal pregnant women in age, gestational age, and Hb%, PCV, RBCS, MCV, MCH and MCHC,(30.84±6.8 vs.

32.58±5.764,=0.17),(21.7±7.9vs. 23.8±8.4,p=0.186), (12.04±1.53vs.12.2±1.22,p=0.518), (36.22±4.2vs.36.5±3.7,p=0.754), (4.2±0.42vs.4.196±0.4,p=0.650), (85.816±6.5 vs. 86.48±6.9,p=0.654), (28.5±3.3 vs.29.2±2.9,p=0.261) and (33.1±1.4vs.33.02±1.3,p=0.889) respectively. Women with fetal death had more previous abortions (1.46±.676vs.0.01±0.042, p<0.001), and of high parity (3.04±2.4vs.4.24±1.135, p=0.002) Table 1.

Table 1: comparison of some demographic and basic laboratory tests between women with fetal death and normal pregnant women

Test	fetal death (n=50)	Normal pregnant (n=50)	p-value
Age in years	30.84±6.8	32.58±5.764	0.170
Number of abortion	1.46±.676	0.01±0.042	0.000
number of delivery	3.04±2.4	4.24±1.135	0.002
gestational age (weeks)	21.7±7.9	23.8±8.4	0.186
Hb g/dl	12.04±1.53	12.2±1.22	0.518
PCV	36.22±4.2	36.5±3.7	0.754
RBCS	4.2±0.42	4.196±0.4	0.650
MCV	85.816±6.5	86.48±6.9	0.654
MCH	28.5±3.3	29.2±2.9	0.261
MCHC	33.1±1.4	33.02±1.3	0.889

Abbreviations: Hemoglobin (Hb);packed cell volume (PCV); red blood cells (RBCs); mean cell volume (MCV); mean cell hemoglobin concentration (MCHC); and confident interval (CI). P value <0.05 was considered significant.

There were no significant changes in PT, APTT, Fibrinogens, between women with fetal death and normal pregnant women p> 0.05. Only 8 %(4) women with fetal death had a normal D-Dimer values for pregnancy (0–0.200 ng/mL), in 84% (n=43) the D-dimer levels was increased (0.201–499 ng/mL), while 8 %(n=3) were found to be at risk of hemorrhage (D-dimer ≥0.500 ng/mL). While in normal pregnancy, 70%9(n=35) had normal D-dimer and 30% had elevated D-dimer and none reported to be greater than ≥0.500 ng/mL. In women with fetal death 6 %(n=3) and 2 % (n=1) had prolonged PT and aPTT respectively p>0.05. Thrombocytopenia was reported in 8 %(n=4) of cases as shown in Table 2.

Table 2: Comparison of abnormal tests values between women with fetal death and normal pregnant women

Test	fetal death (n=50)	Normal pregnant (n=50)	95%CI	p-value
PT	3(6)	0	1.008-.876	0.079
Range	11.0-16.2	12.0-16.0		
APTT	1(2)	0	0.924-1020	0.315
Range	27.9-41.0	29.9-36.2		
INR	43(86)	0	0.602-0.322	P<0.001
range	0.7-1.2	0.8-1.2		

Platelets	4(8)	0	0.848-0.998	0.056
Range	97-448	150-412		
Fibrinogens	Constant	Constant	-	-
Range	150-760	210-620		
Elevated D- dimer	43(86)	15(30)	0.440-0.322	0.0004
Range	0.11-6.53	0.04-0.32		
D- Dimer> 500 ug/m	3 (8)	0	1.008-.876	0.079
FDP	25 (50)	0	0.660-.0379	P<0.001
Range	1.00-2.00	1.00-1.00		

Abbreviations: confident interval (CI); fibrin degradation product(FDP); PT, prothrombin time; aPTT, activated partial thromboplastin time; FDP, fibrin degradation product; INR, international normalization ratio; GA gestational age. P value <0.05 was considered significant.

In general, there was a significant prolongation of PT in women with fetal death compared to controls (14.478±5.764vs.13.762±.9024 seconds=0.003). The overall concentrations FDP, D-Dimer, INR were significantly elevated in women with fetal death compared to controls, (1.70±.789vs. 1.00±.000, p= P<0.001), (1.4±1.6vs. 0.17±0.065, p= P<0.001), (1.051±.1411 vs. 0.977±0.0902, p=0.002) respectively. Platelets counts were significantly lower in women with fetal death compared to controls (247.86±73.323 vs. 317.18±73.323, P<0.001) with No significant differences were observed in the fibrinogen level and APTT as shown in Table 3.

Table 4 shows Pearson correlation between the different tests used for evaluation of clotting tests among women with fetal death. The APTT was correlated positively with PT (r=.304, p=0.032). The INR was strongly correlated positively with both PT and APTT(r=1, p<0.001), (r=0.303, p=0.031). The D-dimer correlated positively and significantly with PT (r=.199, p=0.048) and INR (r=0.201,p=0.044)and negatively with platelets counts (r=-.349,p=<0.001) .There was no correlation between D-dimer, the gestational age, and maternal age.

Table 3: Comparison of quantitative tests values between women with fetal death and normal pregnant women

Test	fetal death (n=50)	Normal pregnant (n=50)	p-value
PT	14.478±5.764	13.762±0.9024	0.003
APTT in sec.	33.966±3.2145	34.110±1.8082	0.783
INR	1.051±.1411	0.977±0.0902	0.002
Platelets	247.86±73.323	317.18±73.323	P<0.001
Platelets<100	1(2)	0	1.00
Fibrinogen mg/dl	470.20±134.612	476.20±92.9	0.796
FDP	1.70±.789	1.00±.000	P<0.001
D dimer ug/ml	1.4±1.6	0.17±0.065	P<0.001

Abbreviations: Hemoglobin (Hb); packed cell volume (PCV); red blood cells (RBCs); mean cell volume (MCV); mean cell hemoglobin concentration (MCHC); and confident interval

(CI); fibrin degradation product(FDP); PT, prothrombin time; aPTT, activated partial thromboplastin time; FDP, fibrin degradation product; INR, international normalization ratio; GA gestational age. P value <0.05 was considered significant.

Table 4: Pearson correlation of the coagulation tests estimated in women with fetal death

	Age	GA	PT	APTT	INR	Platelets	Fibrinogen	D dimer
Age in years	1							
GA	-.141							
	.163							
PT	.049	-.123	1					
	.630	.222						
APTT	.019	.095	.224*	1				
	.850	.347	.025					
INR	.049	-.124	1.**	.223*	1			
	.627	.218	.000	.026				
Platelets	.086	-.133	-.088	-.049	-.092	1		
	.394	.187	.385	.631	.362			
Fibrinogen	-.055	-.018	-.074	-.123	-.072	.097		
	.588	.857	.463	.223	.476	.335		
D dimer	.048	.106	.199*	.120	.201*	-.349**	-.171	1
	.633	.292	.048	.235	.044	.000	.089	

Notes that: *Correlation is significant at the 0.05 level (*P*, 0.05); **Correlation is significant at the 0.01 level (*P*, 0.01). Signs in front of the number determine the direction of the relationship

Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; PCV, packed cell volume; FDP, fibrin degradation product; GA gestational age.

DISCUSSION

In this study, 8% of women with had a D-dimer value > 500 ug/ml. Moreover, 8% of them had thrombocytopenia and 6 % and 2 % had prolonged PT and APTT. There was no correlation between D-dimer, the gestational age, and maternal age.

Normal pregnancy is associated with marked changes in hemostasis that favor thrombosis [11]. There is an elevation in procoagulant levels, but antagonists of coagulation remain unchanged. This hypercoagulable state indicates thrombin/fibrinolysis activity, is increased during normal pregnancy while platelets counts decrease prevents hemorrhage during delivery and the postpartum period. The D-dimer, which for unknown reasons[12].

This study shows no correlation between D-dimer maternal age and gestational age therefore, the rise in the D-dimer cannot be explained by age or gestation. Some authors reported that during pregnancy in healthy women D-Dimer levels increase with gestational age[13] while some studies failed to demonstrate this relationship[13]. Lack of this correlation in the current study is an expected finding for non-growing babies.

The correlation between D-dimer and maternal age is under-studies. In a study by Shehata et. [14] Demonstrated a positive significant correlation. Studies on normal pregnancies showed no relation between D-dimer and maternal age [13]. We reported no correlation between the levels of the D-dimer and maternal in this study, no previous was performed on the relation between D-dimer and maternal age in pregnancies complicated with fetal death.

Our study demonstrates that 86 % of women with fetal death have an elevated D-dimer compared to 30% (p=0.0004). Also, it shows 8% of women with fetal death had D-dimer levels >500 ug/ml which put them at a higher risk of hemorrhage. Despite controversy about the value of D- dimer in diagnosing thrombosis and hemorrhages, there is consensus that a level of 500 ug /mL or greater is used to diagnose or exclude thrombosis in pregnant women and smokers'(10). Strikingly, a high percentage (10%) of D-dimer greater than >500 ug/ml was reported among normal pregnancy population using the same quantitative method for D-dimer estimation[13]. Our findings are consistent with previous work by Parasni et al. who reported 10.5% prevalence of abnormal coagulation among women with fetal death within 24 hours following delivery.

Further, such high level of D-dimer was found to be associated with a 2.9-fold increased risk of overall mortality [15]. This study shows high proportion of women is liable to hemorrhage, this finding contradicts with a low prevalence rate of DIC. The possible explanation is that DIC complicating fetal death is classified as chronic in which blood is exposed to tissue thromboplastin continuously or intermittently giving enough time for Pathogenic balance between consumption of platelets and coagulation factors and its production. The risk of DIC increases progressively after the fourth weeks from fetal death [15]. High values of D-dimer should be combined with ultrasonography and radiography when suspecting embolism [17].

In the current study, thrombocytopenia complicated 8 % of cases. In one study evaluating the prevalence of coagulation in fetal death after delivery, authors found that 10.4% of patients had abnormal tests values [6]. Later authors found that PT and a platelet count had high predictive positive values, 100%and 91% respectively. In the current study prolonged PT and APTT were reported in6% (3 cases) and 2% (1 case) cases respectively. If the cut-off points for thrombocytopenia is taken as counts 100x109 we would have 2 %(1 case) prevalence of thrombocytopenia. Despite these abnormal parameters, none of our patients had bleeding during the antenatal period. In pregnancy, the prevalence of thrombocytopenia was reported to be 7.6%[18].However, thrombocytopenia is the most common hematologic abnormality seen during pregnancy.

In a study examining predictors of bleeding, authors found that only a prolonged PT was the predictor of bleeding [19] while other parameters were not significantly associated with

bleeding. Another recent clinical data reported that at fibrinogen level of <150–200 mg dl−1, there is already a tendency for bleeding [20]. this indicates that studies failed to identify the triggering event in DIC; it might be the net effect of all parameters or there might be genetic factors or biosocial differences responsible for the initiation of active bleeding. In this study, there was a negative correlation between the D-dimer and platelets count, unlike normal pregnancy authors reported that no relationship existed[13], this may indicate an ongoing process of consumptive coagulopathy in fetal death .

The current study, demonstrates no changes in the prothrombin time and activated partial thromboplastin time, Fibrinogen level, and basic laboratory tests.Studies have shown that fibrinogen concentration is the least sensitive test for diagnosing DIC, and low fibrinogen is the last finding in these cases [21].

CONCLUSION

Eight percent of women with fetal death have D-dimer level >500 ug/ml that put them at higher risk of bleeding. Performing selected tests to screening for DIC might be misleading as no single test is perfect. This study supports adopting intervention policy rather than expectant management of fetal death.

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