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Comparison of Coagulation Status in Women with Intrauterine Fetal Deaths with Controls

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Abstract

Background: The aim of this study was to investigate and compare the coagulation status of patients with Intra uterine fetal death with normal pregnant females; identify those who are at a higher risk of haemorrhage and to predict the complications earlier for better management. **Method:** A prospective comparative study was conducted in NSCB Jabalpur from January 2018 to June 2019. A total of 100 cases of fetal demise >20 weeks gestational age were compared with 100 normal pregnant women who were matched in baseline characters like maternal age and period of gestation. Standard coagulation tests including PT, APTT, D-dimes, and Fibrinogen etc. were applied to all along with a basic complete blood count. **Result**: Most of the coagulation variables in our study had a significant change. In our study women with fetal death had significantly elevated D-dimer (208.54 ± 52.36) as compared to controls (156.84 ± 24.67). We observed that 8% normal pregnant women had an increased D-dimer level (201-500 ng/ml) as compared to 19% of women with fetal loss while 2% of cases had D-dimer values more than 500ng/ml. Platelet count showed a downward trend in cases with 6% of cases having value of <1lakh/cumm. **Conclusion:** There was a strong positive correlation between D dimers and Prothrombin time and a negative correlation with platelet count. It was concluded that D dimer is an important tool in the diagnosis of complications in IUFD along with hypofibrinogenemia and thrombocytopenia. Such high risk women should opt for termination of pregnancy rather than expectant management.

KEYWORDS: Intra uterine fetal death, D dimer, Platelet count, DIC, Coagulation

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INTRODUCTION

The incidence of intrauterine fetal death for the year 2000 in different regions of the world as reported by WHO varied from 4 to 39 per thousand total births.[1] In 2009, the estimated global number of stillbirths was 2.64 million (uncertainty range, 2.14-3.82 million).[2] Antepartum death after the first trimester, more often after mid-pregnancy (20 weeks) or weight <500 gm is termed as intrauterine fetal death (IUFD).[3] Clinically it presents as loss of fetal movements, gradual regression of fundal height, loss or diminished uterine tone and inability to hear fetal heart sound on doppler indicate fetal demise.[4] For definitive diagnosis USG is important.

The etiology of fetal demise is unknown in 25-60% of all cases. In cases where a cause is clearly identified, the cause of fetal death can be attributable to fetal, maternal, or placental pathology.[5] Advanced maternal age (>35 y) and maternal smoking is also significant.

MATERNAL–

- Advance in maternal age (>35 years)
- Obesity
- Race
- Socioeconomic status
- Low educational status
- Smoking

FETAL–

- Congenital malformations
- Male sex

PREGNANCY COMPLICATIONS–

- IUGR
- Pregnancy Induced Hypertension
- Placental Abruption
- Rh isoimmunisation
- Multiple Pregnancy
- Post term pregnancy
- Infections
- Antepartum asphyxia
- Previous history of still birth
- Nuchal cord or knotted cord

MEDICAL DISORDERS–

- Diabetes
- Hypertension
- Chronic Nephritis
- Systemic lupus erythematosus
- Thrombophilias
- Cholestasis of pregnancy

Table 1: Risk Factors associated with fetal death[3]

When IUFD is established we have two options for management – surgically remove

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dead fetus or expectant management up to 2 weeks.

The term "Dead Fetus Syndrome" was coined to describe a pregnancy complicated with an IUFD and a plasma fibrinogen level below 150 mg/dl.[6] However, it was observed that there is increased risk of maternal coagulopathy disorders and DIC with significant fibrinolysis due to release of thromboplastic substances and tissue factors from placenta and dead fetus.[7]

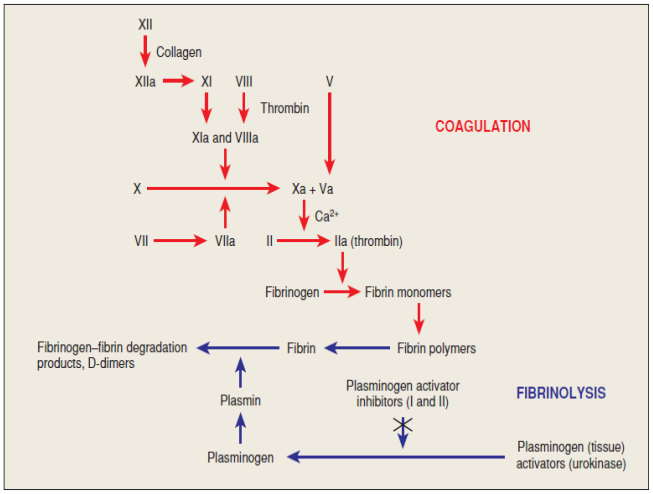

Figure 1: The coagulation and Fibrinolysis Cascades.

Materials and method: We did a prospective comparative study conducted on patients attending the Department of Obstetrics and Gynecology, NSCB Medical College, Jabalpur. Hundred cases and controls each were studied. The cases included patients of intra uterine fetal death proven radiologically with duration not more than 10 days who were admitted in the Department of Obstetrics and Gynecology. The controls comprised of normal pregnant females who visited the OPD of the obstetrics department for routine antenatal checkup. Patients with History of bleeding, any chronic disease, history of liver disease, patients with known coagulopathy, patients on anti-coagulant therapy or who took aspirin in the past week and multiple pregnancy were excluded.

Microvascular thrombus formation can lead to tissue level ischemia and red cell lysis (MAHA). Also, consumptive coagulopathy leads to bleeding. Hence there is significant risk of maternal loss. Normally pregnancy is a hypercoagulable state. During pregnancy, both coagulation and fibrinolysis is augmented but remain balanced to maintain hemostasis. Previous studies showed increased D- Dimers and FDP counts and fall in platelets associated with the IUFD.[8]

Sample size that need to be analyzed was calculated using Right Size (China-Uganda-Zimbabwe) statistical software assuming that (N=5000) i.e. total number of OPD in Obstetrics and Gynecology Department NSCB Medical College Jabalpur during reference period where expected frequency of the IUFD cases was presumed to be at least 20% (i.e. available prevalence of 8-20%) thus considering 95% confidence level with 80% power and confidence interval of 5%, a sample of 93 patients (rounded to 100) will be required. A control group (diseases free or non-high-risk cases) of 100 cases for comparing the various factors will also be taken. Simple random sampling technique was used to recruit the patients

Blood samples were drawn from the patients and tests including routine hematology and coagulation profile were performed on the same. Data recorded in proformas. The data analyzed using the software SPSS 20 for windows. Appropriate univariate and bivariate analysis were carried out using the Student T Test for the continuous variable (age) and chi-square ($\chi 2$) test for categorical variables.

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Observations and results: Age distribution showed that maximum patients in 21 – 30 years being the fact that maximum actively reproducing population lie in this age group. The age of cases and control did not influence the variables to be measured in our study and hence correlation is not derived. The mean gestational age of pregnancy at the time of presentation with IUFD was 23.85±1.28. Care was taken to select controls such that the difference in the gestational age could be removed and make the cases and controls comparable.

COMPARISON OF DEMOGRAPHIC VARIABLES AND BASIC LABORATORY TESTS BETWEEN WOMEN WITH FETAL DEATH (CASES) AND NORMAL PREGNANT WOMEN (CONTROLS)

VARIABLES	CASES	CONTROL	P- value
AGE (Years)	25.57±3.169	25.93±3.893	0.474
GESTATIONAL AGE (Weeks)	23.85±1.282	23.42±1.765	0.05
RBC COUNT (10^{12}/L)	3.64±0.84	4.54±0.54	<0.0001
HB(g/dl)	11.04±2.30	11.35±1.65	0.265
MCV (fL)	93.36±12.75	94.15±9.95	0.174
MCH (pg)	25.69±3.91	25.12±3.20	0.259
MCHC (g/dl)	26.53±0.74	26.62±1.1	0.531

Hematological variables such as hemoglobin, (11.04 ± 2.30 vs 11.35 ± 1.65; P = 0.265), MCV (93.36 ± 12.75 vs 94.15 ± 9.95; P = 0.174), MCH (25.69 ± 3.91 vs 25.12 ± 3.20; P = 0.259) and MCHC, (26.53 ± 0.74 vs 26.62 ± 1.1; P = 0.531) etc. do not vary significantly between cases and controls. However, there was a significant difference in values of RBC count in cases as compared to controls with counts lower in cases (3.64 ± 0.84 vs 4.54 ± 0.54; P <0.0001). This might be due to chance and there should not exist any positive correlation between the RBC counts and coagulation variables under study. Some derangement in WBC counts was present in two thirds of the patients with IUFD but none were septic. Few females with normal pregnancy also had higher WBC values owing to season fever and normal pregnancy physiology. The WBC counts however were not evaluated for any role in IUFD in our study.

The patient group had 36 females were Para 1, 37 were Para 2, 21 were Para 3 and 6 were Para 4.Control group had 45 females who were Para 1, 33 were Para 2, 14 were Para 3 and 8 were Para 4. Coagulation parameters studied had no correlation with parity status. 10% cases had a history of 1 previous abortion as compared to 2.5 (n=4) controls. Though there were a greater number of previous abortions in cases as compared to controls, there was no significant association between IUFD and history of previous abortions in our study.

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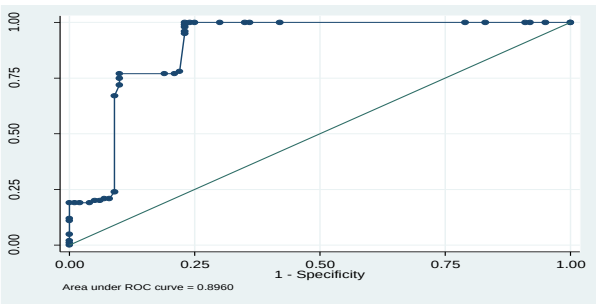
COMPARISON OF COAGULATION PROFILE BETWEEN WOMEN WITH IUFD (CASES) AND NORMAL PREGNANT WOMEN (CONTROLS)

VARIABLES	CASES	CONTROL	P-value
PROTHROMBIN TIME (secs)	15.84±2.03	13.96±0.42	<0.0001
INTERNATIONAL NORMALISED RATIO	1.203±0.16	1.04±0.03	<0.0001
APTT (secs)	34.08±1.92	27.68±2.58	<0.0001
THROMBIN TIME (secs)	16.39±0.97	15.18±0.28	<0.0001
D-DIMER (ng/ml)	208.54±52.36	156.84±24.67	<0.0001
FIBRIN DEGRADATION PRODUCTS (µg/ml)	4.42±0.28	2.54±0.40	<0.0001
FIBRINOGEN (mg/dl)	215.27±34.83	253.78±21.44	<0.0001
PLATELET COUNT (10^9/L)	187.28±45.79	308.95±46.94	<0.0001

There were significant changes in all the coagulation related tests performed in our study. PT was significantly elevated (15.84 ± 2.03 Vs 13.96 ± 0.42; P <0.0001) in prothrombin time in the females with IUFD within 10 days of event. INR values in two groups were within normal range but was on a higher side in the cases (1.203 ± 0.16) as compared to controls (1.04 ± 0.03) suggesting the onset of coagulopathy within few days of IUFD.

Significant prolongation of Thrombin time and higher values of APTT was seen in patients with IUFD. When comparing markers of DIC, D- Dimer, the most important variable in coagulopathy was found to be significantly elevated in cases (208.54 ± 52.36) as compared to controls (156.84 ± 24.67); P <0.001. Fibrinogen levels were lower due to consumption by evolving coagulopathy and hence the values were lower in cases (215.27 ± 34.83) as that compared with normal pregnancy (253.78 ± 21.44); P <0.001. Fibrin degradation was evident by elevation of the fibrin degradation products (4.42±0.28 in cases vs. 2.54±0.40 in controls). Mean platelet count in cases was 187.28 ± 45.7 Vs 308.95 ± 46.94in controls.

It is found that in early post IUFD period (within 10 days) many variables were within normal range but all of them showed a change as compared to controls with normal pregnancy suggesting the evolving pathology of coagulopathy that may lead to fulminant entity of DIC if not promptly intervened.



ROC OF D - DIMER

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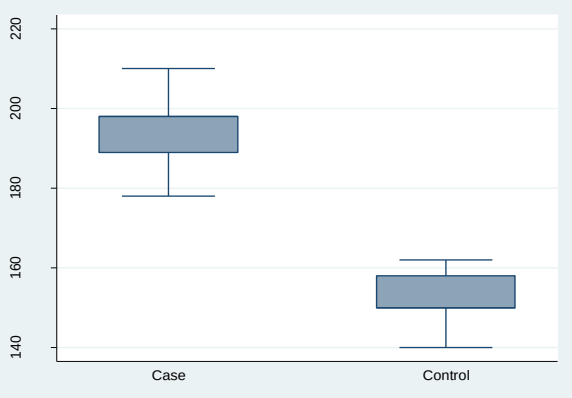
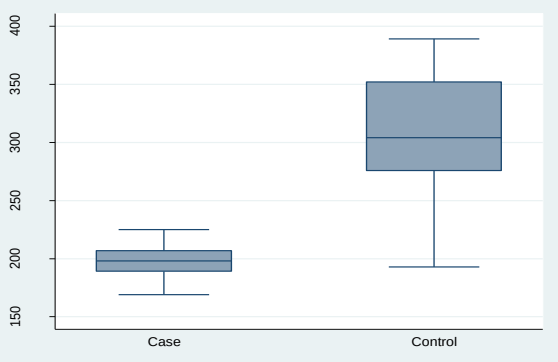


Box and Whisker Plot showing changes in D-dimer between cases and controls.

Receiver operating characteristic (ROC) analysis to quantify the accuracy of diagnostic test (D-DIMER) showed that at cut-off ≥ 168 D-DIMER the sensitivity, specificity, Positive predictive value and Negative predictive value for prediction of IUFD was 100% (95% CI: 96.4-100), 77% (95% CI: 67.5-84.8), 81.3% (95% CI: 73.3-87.8) and 100% (95% CI: 95.3-100) respectively. The area under curve was 0.90 (95% CI: 0.85-0.94).



Box and Whisker Plot showing changes in D-dimer between cases and controls.

For cases the Pearson's correlation coefficient (r) between D Dimer and platelet was -0.71 with P <0.0001 and -0.27 for controls; P= 0.007. This suggests a platelet count decreases and the values of D Dimer increases as the coagulopathy advances and this change is more significantly evident in patients with IUFD. Correlation coefficient between Prothrombin Time (PT) and D dimers for cases was r = 0.80 (P < 0.0001) and for controls r= 0.73 (P<0.0001) suggesting strong positive correlation between PT and D Dimers. As the days after fetal demise increases the prothrombin time increases and also the values of D Dimers suggesting the ongoing coagulopathy process.

Discussion: Normal pregnancy is associated with marked changes in homeostasis that favor thrombosis. 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.[9]

Psychological stress either at work or at home raises the risk of myocardial infarction across

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all ethnic groups in geographic regions in both genders. Plausible pathophysiological mechanisms involve direct neuroendocrine effect. The autonomic imbalance is associated with stress. Vagal inhibitory influence decreases and sympathetic activity increases.[10]

Intra hepatic cholestasis of pregnancy is associated with an increased incidence of perinatal complications, including an increased fetal mortality rate. The incidence of intra hepatic cholestasis of pregnancy in a Swedish population during 1971–74 and 1980–82 was reported to be 1.5% and 1%, respectively. There is no clear correlation between any aspect of maternal disease severity and adverse pregnancy outcome.[11]

CONCLUSION

Though there was a change in almost all of the coagulation variables for pregnant females i.e. PT, APTT, TT, FDP, Fibrinogen, D-dimer and Platelet count, but all were within the normal range. This explains the fact that pregnancy is a hypercoagulable state. The derangements were significant in uncomplicated IUFD. Examining role of platelets in IUFD, we conclude that it needs close follow up and monitoring and hence is an important tool for deciding the management protocol for patients with IUFD. However, hypofibrinogenemia finds no role in deciding the management. We can make it a guide that if the patient has D-dimer values in normal range along with adequate platelets and fibrinogen level above 150 mg/dl expectant management can be done if the woman consents. This can be done while monitoring the trend in the coagulation profile. However, D-dimer values more than 500 ng/ml along with thrombocytopenia <1 lac/cumm and hypofibrinogenemia < 150mg/dl is strong indicator for immediate danger of DIC and immediate intervention is required to avoid development of further complications in these females.

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