

## D-Dimer Detection ---- A Potential Screening Method for Abruptio Placentae

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### ABSTRACT

**Introduction:** A number of specific clinical obstetric conditions can lead to coagulation failure with leading problems. One of the most common causes of significant coagulopathy is placental abruption. Placental abruption releases thromboplastin which can lead disseminated intravascular coagulation. D dimmers and FDPs are helpful in diagnosing these complications, D-dimers are the best indicators of disseminated intravascular coagulation.

**Objective:** To assess the significance of D-dimers (epitope DD-3B6) as a diagnostic serological marker in patients of abruptio placentae

**Study Design:** This community based, random, case control study was held from 2002 – 2004.

**Setting:** The subjects were selected from the department of Gynecology and Obstetrics, Services Hospital, Sir Ganga Ram Hospital and Lady Willington Hospital, Lahore.

**Duration of Study:** Study was carried between year 2002 -2004.

**Material and Method:** Two groups were studied including a total of 60 subjects from 20 weeks of gestation onward. Twenty healthy pregnant females as controls and 40 pregnant patients clinically diagnosed with Abruptio placentae were included in this study.

**Results:** Among healthy control (group A) 25% (5) had D-dimer level less than 250 ng/ml while 75% (15) had levels above 250ng/ml. Among patients (group B) of abruptio placentae 5% (02) had D-dimers level less than 250 ng /ml while D-dimer levels above 250 ngs /ml were seen in 95% of patients. High D-dimer levels of more than 2000 ngs/ml were observed only in patients clinically diagnosed by the obstetrician with abruptio placentae 37.5% (15) as shown in Table -1.

**Conclusion:** Plasma levels of D-dimer, were revealed to be reliable diagnostic markers of disseminated intravascular coagulation abruptio placetae. Using these markers, patients with poor outcomes, potentially life threatening condition, could be readily identified on admission

**Key words:** D-dimer plasma levels, abruptio placentae

### INTRODUCTION

The healthy pregnancy is accompanied by changes in the haemostatic system which converts it into a hypercoagulable state vulnerable to a spectrum of disorders ranging from venous thrombo-embolism to DIC [1]. A number of specific clinical obstetric conditions can lead to coagulation failure with bleeding problems. One of the most common causes of significant coagulopathy is placental abruption [2]. Abruptio placentae refer to separation of a normally placed placenta after 20 weeks of gestation and prior to birth [3]. Incidence of abruptio placentae throughout the world is about 0.5% of all pregnancies [3]. The incidence is slightly more among multipara with a preponderance of grand multipara and lower socio economic group. The seriousness and frequency

of obstetric hemorrhage makes it one of the three leading causes of maternal death and a major cause of perinatal morbidity and mortality [2]. Maternal and fetal death may occur because of haemorrhage and coagulopathy.

The prompt and accurate diagnosis of abruption placentae is often a difficult dilemma for the practicing clinician. Early diagnosis of placental abruption can be difficult because the signs and symptoms of abruptio placentae are often late manifestations [4]. Early symptoms can be easily confused with preterm labour. Ultrasonography and standard laboratory tests of coagulations rarely clarify the diagnosis of abruption placentae until the process is well advanced.

As the process of placental abruption progresses, the separation of placenta from the

uterine wall causes escape of thromboplastin, the high concentration of which is found in the placenta. This starts the coagulation and fibrinolysis. During this process, fibrinogen is converted into insoluble fibrin which results in the generation of D-dimers. The investigations of the haemostatic defect in abruptio placentae must use tests which give rapid results to the clinician. FDPs and D-dimers are two of the most helpful tests (Letsky 2000). As D-dimers are not artificially generated in vitro during blood collection its measurement more consistently reflects the in vivo haemostatic activity than do other assays [5,1].

The purpose of this study was to assess the significance of D-dimers as a diagnostic serological marker in abruptio placentae.

**MATERIAL AND METHODS**

This study was undertaken after being reviewed and approved by the Ethical and Research Committee at the Post graduate Medical Institute, Lahore. D-dimer determination was done at the time of labor in patients with clinically diagnosed abruptio placentae.

The present study included a total of 60 subjects, clinically diagnosed 40 patients of abruptio placentae and twenty healthy controls. These subjects were divided into group A and B

**Group A:** 20 pregnant females between 20-40 years of age with normal pregnancies from 20 weeks of gestation onwards

**Group B:** 40 pregnant females between 20-40 yrs of age with diagnosed abruptio placentae from 20 weeks of gestation onwards

**Exclusion Criteria:**

Women with known coagulation disorders, and a history of drug intake which is known to change the coagulation parameters, diabetics, having hepatic, renal disease were excluded.

**Study Design:**

This is a community based case control study from 2002 to 2004.

**METHODOLOGY**

Sample collection: Dacie and Lewis 2001

Both the slide latex agglutination test and the semi-quantitative determination of fibrin D- dimer was performed with Minutex D-dimer Latex kit provided by Biopool international Sweden kit (cat No: 150707). This D-dimer latex agglutination test uses monoclonal antibodies that are specific for

the cross linked fibrin degradation products. A slide agglutination test was considered positive if agglutination occurred within 180-200 seconds for samples containing 250ng/ml. To assess the concentration of D-dimer fragments of fibrin a semi quantitative test was then performed on the positive cases with plasma dilutions of 1:2, 1:4, and 1:8.

**Statistical Methods (Bland 1988)**

Control and study patients were compared by 't' test with p <0.01 considered highly significant

**RESULTS**

Agglutination occurs within 180-200 seconds for samples containing 250ng/m D- dimer. The mean level of D-dimer in a healthy population is between 8-135 ng/mL and neat plasma from normal healthy individuals should not agglutinate. The incidence of positive and negative D-dimer test results for each group is shown in Table -1

Comparison of the control group with the patients clinically diagnosed with abruptio placentae showed highly significant difference statistically (p value < 0.01). The sensitivity of the D-dimer test in predicting abruptio placentae was 95%, its specificity was 60% and the positive predictive value was 15.4% and the negative predictive value was 0.7%.

**Table 1:** Comparison of D-Dimers In Control Group (A) And Patients With Abruptio Placentae Group (B)

D-dimers (ng/ml)	Group A	Group B
<250	05(25%)	02(5%)
250-500	07(35%)	06(15%)
500-1000	07(35%)	07(17.5%)
1000-2000	04(5%)	10(25%)
>2000	-	15(37.5%)
Total	20(100%)	40(100%)

Statistical analysis:

A vs B p<0.01 HS

Key:

Group A = Control Group

Group B = Subjects with abruptio placentae

D-dimer level in control group A subjects were 25% (05) <250 ng/ml, 35% (07) in 250-500 ng/ml, 35% (07) in 500-1000 ng/ml as compared to 5% (01) in the range of 1000-2000 ng/ml. In patients

with abruptio placentae ( group B ) , 02 out of 40 subjects (5%) had D-dimer levels <250 ng/ml, 06 out of 40 (15%) had levels in the range of 250-500 ng/ml, 07 out of 40 (17.5%) had levels of 500-1000 ng/ml and 10 out of 40 (25%) had levels in the range of 1000-2000 ng/ml and 15 out of 40 (37.5%) had levels in the range of > 2000 ng/ml as shown in Table-1 and Fig 1.1 and Fig 1.2

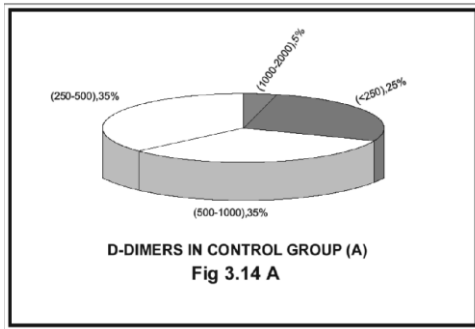


Fig 1.1:

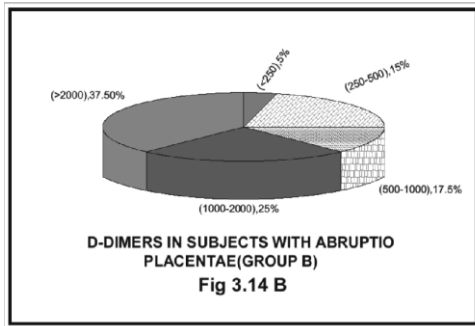


Fig 1.2:

## DISCUSSION

Abruptio placentae is a relatively common complication of pregnancy and not only jeopardize the maternal health but can cause coagulation abnormalities and fibrinolysis in the newborn as well [7,8]. However abruptio placentae have not received the attention it deserves.

Abruptio placenta is associated with marked changes in normal physiological response of haemostatic mechanism. The separation of placenta from the uterine wall causes escape of thromboplastin, high concentration of which is found in placenta [11, 13, 12, 14, 10]. The hypovolumic shock due to haemorrhage itself is a further stimulus to the process of DIC [15, 16, 17]. Massive blood loss leads to consumptive coagulopathy as all the coagulation factors are exhausted [18]. Pritchard [19] have reported

results from a group of women who had abruptio placenta and identified some of the changes of disseminated intravascular coagulation (DIC). Clark et al [20], found 20% of women with a clinically significant abruptio having a gross clotting defect.

Abruptio placentae is essentially a clinical diagnosis [4]. Importantly, even negative findings with ultra sound examination do not exclude potentially life threatening placental abruptio [2]. Investigations are important tools for making correct diagnosis and use of diagnostic resources is growing steadily [21]. The addition of Doppler color flow studies of the placental bed may be of value but, require special expertise that is usually not available during labor and delivery [4] especially in developing countries like Pakistan.

D-dimer moieties are formed by plasmin degradation of factor X111a cross linked fibrin. D-dimer latex agglutination test utilizes a specific monoclonal antibody reacting with fibrin D-dimer or fragment D of fibrin but not with intact, fibrinogen thus allowing the D-dimer determination in human plasma [22, 23]. No fibrinogen crossover occurs and there is no interference from clotting agents or fibrinogen.

The D-dimer slide test is sensitive and rapid method to improve diagnosis of abruptio placentae at the time of admission. The quality of routine D-dimer testing has improved in recent years [30, 24, 25]. D-dimer is elevated early and high levels persists, reflecting lysis of micro vascular fibrin deposits [26].

This preliminary study is encouraging because the test is quite simple and easy to perform. It appears to offer a potential method to evaluate patients in whom abruptio placentae must be distinguished from other clinical conditions. In this study D-dimers were also found to be significantly increased ( $p < 0.01$ ) in females of abruptio (Group B) as compared to control group (A) as in table 1. This study is consistent with the results of Trofatter et al [27] and Nolan et al [4] who also observed raised values of D-dimers in females of placental abruptio while comparing with control subjects. The most sensitive methods are based on an enzyme-linked immunosorbent assay (ELISA). Working on Elisa to detect the maternal D-dimmer levels Nolan et al [4], Neilson [7] and Sher [11] also had similar findings. In contrast Neiger et al [28] found there was no significant difference between the pregnant women presenting with abruptio placentae in the late second and third

trimester and healthy controls. Elisa is time consuming and not appropriate when a rapid turn round times is required [29]. In contrast supportive tests like D-dimer latex agglutination assays are relatively cheap and their results are quickly available [30]. D-dimer has also been used as a means of screening for thromboembolism [25, 31].

Comparison of the control group with the patients clinically diagnosed with abruptio placentae showed highly significant difference statistically ( $p$  value  $< 0.01$ ). The sensitivity of the D-dimer test in predicting abruptio placentae was 95%, its specificity was 60% and the positive predictive value was 15.4% and the negative predictive value was 0.7%.

Nolan et al reported a sensitivity of 67%, specificity of 93 %, a positive predictive value of 91% and negative predictive value of 48 %. Implying that abruptio placentae group was significantly was more likely to have a positive D-dimer level that those in the non abruptio placentae group. The frequency of the diagnosis varies in different reports because of the difference in the criteria used for diagnosis, and the diverse clinical presentations [28]. Clearly our data need to be confirmed by larger studies over longer period of time. Thus an extended work can be more helpful.

## CONCLUSION

D-dimer levels are indicators of disseminated intravascular coagulation in abruptio placentae. Any early deduction of D-dimer will help and therapeutic measures to be taken should be aimed namely at extracting the thromboplastin material as quickly as possible. We found the fibrin D-dimer to be a valuable, sensitive indicator of secondary fibrinolysis [32] and has a high positive predictive value as an aid for the rapid method to improve the diagnosis of this life threatening condition.

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