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Frequency of Adverse Maternal and Neonatal Outcomes in Patients with Low Serum Fibrinogen Level and Placental Abruption

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Abstract
Objective: To assess frequency of adverse maternal and neonatal outcomes in patients with low serum fibrinogen level and placental abruption.**Place and duration:** It was held in Gynecology Department Nishtar Hospital Multan from 12 November 2017 to 25 July 2018.**Study Design**: Case control retrospective study.**Methodology:** A total of 100 patients were included in this clinical trial and they were diagnosed with placental abruption. They were categorized on the basis of serum fibrinogen level into three groups; high fibrinogen group (400-600 mg/dL), normal fibrinogen group (300-400 mg/dL) and low fibrinogen group (<200 mg/dL). . The pregnant women with uterine rupture, wound of birth canal, placental accrete, placental praevia, HELLP syndrome, severe preeclampsia, monochorionic multiple pregnancies, major fetal anomalies and sign of intrauterine infection were excluded and all other women with single or more pregnancies were eligible for this clinical study. Computer software SPSS version 23.2 was used for entering and analyzing data. Frequency and percentage was calculated for baseline variables. Frequency and percentage was calculated for laboratory parameters. Frequencies and percentage was calculated for maternal and neonatal outcome variables like mode of delivery, PIH, GDM A, postpartum hemorrhage (PPH), postpartum anemia (PPA), FFP and RCC transfusion, ISTH DIC score, delay discharge from hospital, fetal death, Apgar score at 5 min <7, birth weight, still birth, umbilical artery pH < 7.00, neonatal gestational age and IUFG. ANOVA test was used to find frequency and percentage. P value was < 0.05 was considered to be significant.**Result:** 100 patients were included in this study and they were divided on the basis of serum fibrinogen level into three groups i.e. n=40 high Fibrinogen group (400-600 mg/dL), n=35 normal Fibrinogen group (300-400mg/dL) and n=25 low Fibrinogen group (<200mg/dL). All the data recorded from all three groups regarding PIH, GDM, FFP, RCC transfusion, ISTH DIC score, delayed discharge from hospital was insignificant. The differences were statistically significant of postpartum hemorrhage PPH (p=0.001) and postpartum anemia PPA (p=0.002). The data recorded from three groups regarding, Apgar score at 5 min <7, Birth weight (g), Umbilical artery pH < 7.00 and intrauterine fetal growth was statistically insignificant. The statistical differences observed in three groups were as; fetal death (p=0.047), still birth (p=0.016), and gestational age (weeks) (p= 0.001) respectively.**Conclusion:** It has been concluded that low serum fibrinogen level has higher frequency of adverse maternal and neonatal outcomes including postpartum hemorrhage (PPH), postpartum anemia (PPA), fetal death, small gestation age of neonates and still birth than normal and high serum fibrinogen level.
Keywords: Low serum fibrinogen, Placental Abruption, Maternal, Neonatal outcomes.

Introduction

Fibrinogen is very important component of serum that plays vital role in maintaining homeostatic balance[1]. The process of blood clotting involves the conversion of soluble plasma protein fibrinogen into soluble fibrin. Besides its role in blood clotting, it is also basic component of several pathophysiologic states, such as the proliferation of some sort of tumors, infection, wound healing and the severity of atherosclerosis [2]. Similarly, pregnancy is such a condition which accompanies many changes in haemostatic system, that involves almost every organ of body and blood is no exception. Human body contains coagulation system and during pregnancy this system creates hypercoagulative condition, which means the plasma level of fibrinogen increases than normal level[3]. Normal serum level of fibrinogen is 200-400 mg/dl but during pregnancy its level reaches to 600 mg/dl. It speeds up the intravascular coagulation that maintains the uteroplacental interface[4]. These changes are important to minimize the blood loss by homeostasis after placenta gets separated.

Pregnant women, who have low serum fibrinogen level, often suffer from spontaneous miscarriages and to overcome this problem these patients undergo fibrinogen supplement therapy which helps to sustain pregnancy[5]. Many adverse outcomes of pregnancy like placental abruption, postpartum hemorrhage and spontaneous abortion are seen in patients having very low serum fibrinogen level. It is reported that such pregnancy complications can be treated by using cryoprecipitate[6]. But recent studies show that increasing level of fibrinogen (Fg.) is also very effective to reduce complications of pregnancy. A special case of a woman of six previous abortions has been reported [21], now in seventh pregnancy, she was treated with Fg. supplement therapy to maintain the serum level of fibrinogen higher than normal and it resulted in normal delivery with very low maternal and neonatal complications. It shows that fibrinogen helps to sustain homeostasis because it acts as

substrate for clot formation[7]. It binds to platelets to support blood clotting. Formation insoluble fibrin clot acts as template for both thrombin binding and fibrinolytic system. So, any disturbance in fibrinogen level whether it increases or decreases will disturb all the above mention hemodynamic functions.

If pregnant women are suffering from low serum fibrinogen level, it can leads to placental abruption and a study published in The Journal of obstetrics and Gynecology Research suggests that such patients should be treated with fibrinogen supplement, C-section and prompt maternal blood transfusion and coagulation factors to maintain the serum level otherwise it could result in large amount of blood loss due to placental abruption[8]. This hemorrhagic condition will cause hypovolemic shock and fetal as well as maternal death. Other complications that are related to placental abruption and low serum fibrinogen level are premature birth, still birth, intrauterine restricted growth, mental retardation, DIC, renal failure or failure of any other organ, postpartum hemorrhage, hypovolemic shock maternal and neonatal death.

Due to placental abruption and low fibrinogen level, fetal and maternal mortality rates are 1% in western countries but in our country, maternal mortality rates are 2.5%. It is too high due wide spread pre-existing anemia, restricted medical staff as well as medical facilities and many difficulties with transport of patients[9]. Fetal death is much higher than maternal loss, it is 15% worldwide but in Pakistan it is 50% [10].

There is no study on local level to find the frequency of adverse maternal and neonatal outcome in patients suffering from low serum fibrinogen level as well as placental abruption. So, this clinical trial was designed to find this association.

Methodology:

This study was conducted in Obstetrics and Gynecology department of Nishtar Hospital Multan after taking ethical approval from ethics committee of institution. This study was designed over a period of nine months from 12 November 2017 to 25 July 2018 and 100 pregnant women were enrolled in this trial. All the patients were briefly introduced by the procedure of study and oral informed consent was taken from all participants. The pregnant women with uterine rupture, wound of birth canal, placental accrete, placental praevia, HELLP syndrome, severe preeclampsia, monochorionic multiple pregnancies, major fetal anomalies and sign of intrauterine infection were excluded and all other women with single or more pregnancies were eligible for this clinical study.

100 patients were included in this clinical trial and they were diagnosed with placental abruption. They were categorized on the basis of serum fibrinogen level into three groups; high fibrinogen group (400-600 mg/dL), normal fibrinogen group (300-400 mg/dL) and low fibrinogen group (<200 mg/dL). All these patients were presented to the Emergency Department Obs. and Gyne. Ward Nishtar Hospital Multan. Detailed history, general physical, systemic and abdominal examination was done by senior medical officer (SMO). All the following clinical baseline characteristics were recorded: maternal age, gestational age, parity, presence of genital bleeding, birth weight, and medical complications like thyroid disease, diabetes and hypertension. Placental abruption was differentiated from placental previa by ultrasound. Retroplacental hematoma was also confirmed by pathological diagnosis. All the laboratory investigations such as: platelet count, CBC, clotting time, prothrombin time, fibrin degradation product and activated partial thromboplastin time.

All maternal and neonatal outcomes including mode of delivery, pregnancy induced hypertension (PIH), postpartum hemorrhage, postpartum anemia, FPP and RCC transfusion, ISTH DIC score > 5, delayed discharge from hospital, still birth, fetal death, Apgar score at 5 min < 7, intrauterine fetal growth (IUFG), umbilical artery pH < 7.00, birth weight (g) and gestation age of fetus.

Computer software SPSS version 23.2 was used for entering and analyzing data. Frequency and percentage was calculated for baseline variables like maternal age (years), gestational age (weeks), parity, gravidity and smoking status. Frequency and percentage was calculated for laboratory parameters like hemoglobin level, platelet count, fibrin degradation product, prothrombin time, activated partial thromboplastin time and clotting time. Frequencies and percentage was calculated for maternal and neonatal outcome variables like mode of delivery, PIH, GDM A, postpartum hemorrhage (PPH), postpartum anemia (PPA), FFP and RCC transfusion, ISTH DIC score, delay discharge from hospital, fetal death, Apgar score at 5 min <7, birth weight, still birth, umbilical artery pH < 7.00, neonatal gestational age and IUFG. Standard deviation and mean were used to describe the maternal length of hospital stay (days), Neonatal birth weight (g) and neonatal length of ICU stay (days). ANOVA test was used to find frequency and percentage. P value was < 0.05 was considered to be significant.

Results

One hundred patients were included in this study and they were divided on the basis of serum fibrinogen level into three groups i.e. n=40 high Fibrinogen group (400-600 mg/dL), n=35 normal Fibrinogen group (300-400mg/dL) and n=25 low Fibrinogen group (<200mg/dL). Demographic and baseline characteristics of all participants had been shown below in **Table No. I** and their differences were statistically insignificant.

Table No. I

Variable	High Fib n=40	Normal Fib n=35	Low Fib n=25	P-value
Maternal age				
<30 years	n=23 (57.5%)	n=26 (74.3%)	n=20 (80%)	0.310
31-35 years	n=10 (25.0%)	n=5 (14.3%)	n=2 (8%)	
36-40 years	n=7 (17.5%)	n=4 (11.4%)	n=3 (12%)	
Parity				
0	n=15 (37.5%)	n=18 (51.4%)	n=10 (40%)	0.622
1-3	n=16 (40%)	n=13 (37.1%)	n=9 (36%)	
≥4	n=9 (22.5%)	n=4 (11.4%)	n=6 (24%)	
Gravidity				
1	n=20 (50%)	n=22 (62.9%)	n=14 (56%)	0.821
2-3	n=11 (27.5%)	n=7 (20%)	n=7 (28%)	
≥4	n=9 (22.5%)	n=6 (17.1%)	n=4 (16%)	
Gestational age				
22-32 weeks	n=32 (80%)	n=28 (80%)	n=15 (60%)	0.135
33-40 weeks	n=8 (20%)	n=7 (20%)	n=10 (40%)	
Smoking status				
Smoker	n=10 (25%)	n=3 (8.6%)	n=2 (8%)	0.073
Non-smoker	n=30 (75%)	n=32 (91.4%)	n=23 (92%)	
p-value ≤0.05 considered as significant				

Table No. II explained the laboratory investigations of all patients. In these parameters; hemoglobin level, platelet count, fibrin degradation products, prothrombin time, activated partial thromboplastin time and clotting time were included. All these parameter were statistically insignificant.

Table No. II

Variable	High Fib n=40	Normal Fib n=35	Low Fib n=25	P-value
Hemoglobin Level				
Normal (12-14 mg/dL)	n=33 (82.5%)	n=30 (85.7%)	n=17 (68%)	0.210
Low (<11gm/dL)	n=7 (17.5%)	n=5 (14.3%)	n=8 (32%)	
Platelets				
Normal (>150,000cumm)	n=35 (87.5%)	n=32 (91.4%)	n=20 (80%)	0.428
Low (<150,000cumm)	n=5 (12.5%)	n=3 (8.6%)	n=5 (20%)	
Fibrin degradation product				
Normal (<10ug/liters)	n=30 (75%)	n=28 (80%)	n=22 (88%)	0.444
Low (>10ug/liters)	n=10 (25%)	n=7 (20%)	n=3 (12%)	
Prothrombin time				
Normal (15 seconds)	n=37 (92.5%)	n=29 (82.9%)	n=18 (72%)	0.088
Low (>15 seconds)	n=3 (7.5%)	n=6 (17.1%)	n=7 (28%)	
Activated partial thromboplastin time				
Normal (35 seconds)	n=38 (95%)	n=34 (97.1%)	n=21 (84%)	0.118
Raised (>35 seconds)	n=2 (5%)	n=1 (2.9%)	n=4 (16%)	
Clotting time				
Normal (6-10 minutes)	n=40 (100%)	n=33 (94.3%)	n=16 (64%)	0.000
Raised (>10 minutes)	n=0 (0%)	n=2 (5.7%)	n=9 (36%)	
p-value ≤0.05 considered as significant				

Table No. III explained the data about mode of delivery and maternal outcomes in three groups. Of the 40 women assigned to the "High Fg group" 36 (90%) went under spontaneous vaginal delivery, but 1 (2.5%) women had C-section, and remaining 3 (7.5%) women had assisted vaginal delivery. Of the 35 women enrolled in the "Normal Fg group", spontaneous vaginal delivery occurred in 30 (85.7%) women, 3(8.6%) women had planned C-section, and remaining 2 (5.7%) women underwent assisted vaginal delivery. Similarly, 25 women were enrolled in "low Fg group" and 8 (32%) women had SVD, 11(44%) C-section and remaining 6(24%)

women had assisted delivery.

All the data recorded from all three groups regarding PIH, GDM, FFP, RCC transfusion, ISTH DIC score, delayed discharge from hospital was insignificant. The differences were statistically significant of postpartum hemorrhage PPH (p=0.001) and postpartum anemia PPA (p=0.002)

Table No. III

Variable	High Fib n=40	Normal Fib n=35	Low Fib n=25	P-value
Mode of delivery				
C-section	n=1 (2.5%)	n=3 (8.6%)	n=11 (44%)	0.000
Spontaneous vaginal	n=36 (90%)	n=30 (85.7%)	n=8 (32%)	
Assisted	n=3 (7.5%)	n=2 (5.7%)	n=6 (24%)	
PIH				
Mild	n=3 (7.5%)	n=5 (14.3%)	n=7 (28%)	0.133
Severe	n=2 (5%)	n=2 (5.7%)	n=3 (12%)	
GDM A1	n=1 (2.5%)	n=3 (8.6%)	n=5 (20%)	0.199
GDM A2	n=1 (2.5%)	n=1 (2.9%)	n=1 (4%)	
Postpartum Hemorrhage	n=7 (17.5%)	n=9 (25.7%)	n=15 (60%)	0.001
Postpartum Anemia	n=4 (10%)	n=7 (20%)	n=12 (48%)	0.002
FFP transfusion				
≥10 units	n=8 (20%)	n=20 (57.1%)	n=22 (88%)	0.000
≥20 units	n=6 (15%)	n=15 (42.9%)	n=3 (12%)	
RCC transfusion				
≥6 units	n=11 (27.5%)	n=21 (60%)	n=17 (68%)	0.000
≥10 units	n=10 (25%)	n=14 (40%)	n=8 (32%)	
ISTH DIC score >5	n=4 (10%)	n=7 (20%)	n=7 (28%)	0.172
Delayed discharge from hospital	n=3 (7.5%)	n=6 (17.1%)	n=6 (24%)	0.176
p-value ≤0.05 considered as significant				

Table No. IV described the neonatal outcomes in all three groups. The data recorded from three groups regarding, Apgar score at 5 min <7, Birth weight (g), Umbilical artery pH < 7.00 and intrauterine fetal growth was statistically insignificant. The statistical differences observed in three groups were as; fetal death (p=0.047), still birth (p=0.016), and gestational age (weeks) (p= 0.001) respectively.

Table No. IV

Variable	High Fib n=40	Normal Fib n=35	Low Fib n=25	P-value
Fetal death	n=0 (0%)	n=0 (0%)	n=2 (8%)	0.047
Apgar score at 5 min<7	n=38 (95%)	n=32 (91.4%)	n=15 (60%)	0.000
Birth weight (g)				
<1500	n=1 (2.5%)	n=2 (5.7%)	n=10 (40%)	0.000
1500-2500	n=35 (87.5%)	n=31 (88.6%)	n=13 (52%)	
>2500	n=4 (10%)	n=2 (5.7%)	n=2 (8%)	
Still birth	n=2 (5%)	n=3 (8.6%)	n=7 (28%)	0.016
Umbilical artery pH <7.00	39.60±2.37	31.27±2.50	11.90±2.23	0.000
Gestational age (weeks)				
Small	n=5 (12.5%)	n=7 (20%)	n=12 (48%)	0.001
Large	n=2 (5%)	n=3 (8.6%)	n=5 (20%)	
Intra-uterine fetal growth				
Normal	n=37 (92.5%)	n=28 (80%)	n=10 (40%)	0.000
Restricted	n=3 (7.5%)	n=7 (20%)	n=15 (60%)	
p-value ≤0.05 considered as significant				

Discussion:

The objective of this study was to assess the frequency of adverse maternal and neonatal outcomes in low serum fibrinogen level also associated with placental abruption. This study demonstrated that patients had to suffer

from severe complication of postpartum hemorrhage (PPH) and postpartum anemia (PPA) when serum fibrinogen level decreased to 150 mg/ dL. Similarly, severe neonatal complications like still birth, fetal death and small gestation age were observed when serum fibrinogen level decreased to 250 mg/dL.

In this clinical study, we demonstrated very significant difference in neonatal and maternal outcomes among higher, normal and lower fibrinogen groups. It was observed that all pregnant women included in low fibrinogen group had surprisingly severe maternal and neonatal complications like postpartum hemorrhage (PPH), postpartum anemia (PPA), fetal death, still birth and small gestation age of neonates. There are many studies to explain maternal and fetal outcomes in women having low serum fibrinogen level with placental abruption.

A study by Seishi Furukawa, Hiroshi et al, published in Journal of Pregnancy, showed that pregnant patient who had serum fibrinogen level at < 150 mg/ dL then they had higher risk of perinatal outcomes like IUFD, low Apgar score < 7 at 5 min, low Umbilical artery pH < 7.1, IUGR, postpartum hemorrhage and postpartum anemia [11]. Similarly, in our study the percentage of PPH in women of low FG group was 60% but it was low in women of other two groups.

There is clinical study, by Yasmeen Khookharo, Fayaz and K.J.Noorani published in JPMC[12], was designed to assess the maternal and neonatal outcomes in pregnant women suffering from low serum fibrinogen level with placental abruption. It was stated that those patients with lower fibrinogen level of 200 mg/dL, they had high rate of bleeding during pregnancy. It was observed that fetal and maternal mortality, other complications were directly associated with blood loss. Our clinical results demonstrated that PPH was directly related fetal death. It was described in our study that percentage of fetal death was 8% in “low Fg group” because women enrolled in this group were suffering from blood loss.

A clinical study, by B. Charbit, L. Mandelbrot et al published in Journal of Thrombosis and Hemostasis [13], suggested that postpartum hemorrhage (PPH) was major source of maternal and neonatal mortality and morbidity related to childbirth. Its results demonstrated that patients with lower fibrinogen level than < 155 mg/dL had severe PPH. Our results were similar to that study.

Another study; designed by Cande.V. Ananth, G.S.Berkowitz et al [14] published in JAMA, this clinical trial showed that placental abruption with low serum fibrinogen level had very profounding maternal and neonatal complications including preterm delivery, still birth, low birth weight, increased IUFGR, increased IUFD and higher rates of C-section. Our result explained that low fibrinogen level is directly associated to PPH and it was strongly related to still birth.

M.Cortest, C.Denewx et al designed a clinical study published in British JOA [15]; its results show that fibrinogen level has very strong relationship with course of hemorrhage and low serum fibrinogen at < 200 mg/dL increased PPH. It demonstrates that when fibrinogen level decreases to < 200 mg/ dL, it increases 12 times PPH. This also shows that fibrinogen level between 200- 300 mg/dL has less severe PPH, maternal and neonatal mortality and morbidity.

It was observed in our study that percentage of PPA and PPH was 60% and 48% respectively in “low serum Fg group” having serum fibrinogen level less 200 mg/dL. Liangcheng Wang, Shigetaka et al [16]; organized a clinical study published in Journal of OBS and Gynecology, this study suggests that patients have higher rates of PPH and postpartum anemia (PPA) when patients have fibrinogen level at < 155mg/dL but when fibrinogen level reaches down at< 255mg/dL then neonatal outcomes including, still birth, low Apgar score, fetal death, IUFD and IUFGR are observed.

In our study, it was observed that bleed led to spontaneous abortion and C-section. The percentage of C-section was 44% in “low Fg group” and it was much than other two groups. S. Evron, S.O.Anteby et al; designed a case report [17], in which they explained that low serum level fibrinogen led to greater bleeding tendency or venous thrombosis. This resulted to spontaneous abortion, maternal and neonatal mortality.

Kanchanna A, Girijavana DSS, compared 100 pregnant patients having low serum level fibrinogen to normal pregnant women, in this study out of 100 cases, 40 were pregnancy induced hypertension (PIH), 25 were IUFD, 25 were aborted and 10 were with placental abruption at the end of clinical trial [18]. Similarly, in our study percentage of fetal death was 8% in “low Fg group” and that was higher that other two groups because fetal death was zero in other groups.

Ernest W. Page, Lee D. Fulton, Mary B, in their study they explain, low serum level fibrinogen during pregnancy lead to hemorrhage syndrome that is directly associated to placental abruption. It increases risk of maternal and neonatal complications as well as fetal death [19].

Wolfgang. M, Dennis G and Inge.S conducted a retrospective study of four cases of hypofibrinogenemic patients. Three out of four patients underwent three consecutive abortions due to lack of serum fibrinogen in 6th, 7th and 11th weeks of pregnancy. It was also concluded that lack or decrease level of serum fibrinogen during pregnancy leads to placental abruption, PPH, PPA, thrombosis, fetal death and preterm delivery [20]. All above mentioned studies are in favor of our clinical trial.

Conclusion: It has been concluded that low serum fibrinogen level has higher frequency of adverse maternal and neonatal outcomes including postpartum hemorrhage (PPH), postpartum anemia (PPA), fetal death, small gestation age of neonates and still birth than normal and high serum fibrinogen level.
Finding Source: Nil
Conflict of Interest: Nil

References

1) Ness PM, Budzynski A.Z, Olexa S.A and R.R; ***Congenital hypofibrinogenemia and recurrent placental abruption.***JOOG.2016;61(4):519-23
2) Weiner .A.E, Reid D.E and Roby C.C; ***Coagulation defects associated with premature separation of the normally implanted placenta:*** American JOG.2016;60(2):379-86.
3) Roque .H, Stephenson .C, Lee M.J, Funai .E.F, Popiolek .D, et al; ***Pregnancy‐related thrombosis in a woman with congenital afibrinogenemia: a report of two successful pregnancies.*** American JOH. 2015;76(3):267-70.
4) Bonnar. J, McNicol .G.P and Douglas A.S; ***Coagulation and fibrinolytic mechanisms during and after normal childbirth***. Br JOM. 2017;2(5703):200-3.
5) Brenner. B; ***Haemostatic changes in pregnancy***. JTH. 2015;114(5-6):409-14.
6) Edwards R.Z and Rijhsinghani. A; ***Dysfibrinogenemia and placental abruption***. JOG. 2018;95(6):1043.
7) McNamara .H, Mallaiah .S, Barclay .P, Chevannes .C and Bhalla .A; ***Coagulopathy and placental abruption: changing management with ROTEM-guided fibrinogen concentrate therapy.*** International JOA. 2015;24(2):174-9.
8) Parasnis .H, Raje .B and Hinduja .I.N; ***Relevance of plasma fibrinogen estimation in obstetric complications***. JPGM. 2017;38(4):183.
9) Moloney. W.C, Egan. W.J and Gorman .A.J; ***Acquired afibrinogenemia in pregnancy***. New England JOM. 2018;240(15):596-8.
10) Eskes .T.K; ***Abruptio placentae***. European JOG and Reproductive biology. 2016 Dec;75(1):63-70.
11) Furukawa.S, Sameshima. H, Ikenoue .T, Ohashi .M and Nagai.Y. ***Is the perinatal outcome of placental abruption modified by clinical presentation?*** JOP. 2017;2(5);234-253.
12) Khooharo .Y, Memon .F.A and Noorani .K.J; ***Disseminated intravascular coagulation in Abruptio Placentae***. PJMS 2016;25(4):660-4.
13) Charbit.B, Mandelbrot. L, Samain .E, Baron G and Haddaoui. B, et al; ***the decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage***. Jth. 2017;5(2):266-73.
14) Ananth C.V, Berkowitz. G.S, Savitz .D.A and Lapinski .R.H; ***Placental abruption and adverse perinatal outcomes***. JAMA. 2015;282(17):1646-51.
15) Cortet M, Deneux.T.C, Dupont. C, Colin.C, Rudigoz. R.C, Bouvier.C. M.H et al; ***Association between fibrinogen level and severity of postpartum hemorrhage: secondary analysis of a prospective trial***. BJA. 2017;108(6):984-9.
16) Wang .L, Matsunaga. S, Mikami .Y, Takai .Y, Terui K,et al; ***Pre‐delivery fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption***. JOOG Research. 2016;42(7):796-802.
17) Evron .S, Anteby .S.O, Brzezinsky .A, Samueloff. A and Eldor. A; ***Congenital afibrinogenemia and recurrent early abortion: a case report***.EuropeanJOG.2018;19(5):307-11.
18) Kanchanna .A and Girijavana .D.S; ***Fibrinogen levels helps in early detection of abnormal pregnancies.*** International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2016;6(1):232-9.
19) Page E.W, Fulton L.D and Glendenning M.B; ***The cause of the blood coagulation defect following abruption placentae***. American JOOG. 2017;61(5):1116-22.
20) Miesbach .W, Galanakis .D and Scherer. I; ***Treatment of patients with Dysfibrinogenemia and a history of abortions during pregnancy***. Blood Coagulation & Fibrinolysis. 2017;20(5):366-70.
21) Frenkel .E, Duksin .C, Herman. A, Sherman .D.J; ***congenital hypofibrinogenemia in pregnancy: report of two cases and review of the literature***. JOG. 2015;59(11):775-9.