

Association of Fibrinogen Use in Cesarean Delivery with Bleeding and Blood Products in Patients with Placenta Acreata Spectrum: A Retrospective Study

Sezaryen Doğumda Fibrinojen Kullanımının Plasenta Akreata Spektrumlu Hastalarda Kanama ve Kan Ürünü ile İlişkisi: Retrospektif Bir Çalışma

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ABSTRACT Objective: Placenta accreta spectrum (PAS) is a condition with a high risk of perioperative bleeding that can cause maternal morbidity and mortality. Fibrinogen is the first factor of which level decreases in case of perioperative bleeding, although it increases in the last trimester of pregnancy. In this retrospective study, we aimed to evaluate the effect of fibrinogen use on preoperative and postoperative outcomes in PAS patients with high bleeding risk. **Material and Methods:** In this study, the files of 171 patients who were operated on with the diagnosis of antenatal PAS were examined retrospectively. Patients were divided into two groups according to fibrinogen use. Demographic data of both groups, choice of anesthesia, surgical application, amount of fluid, blood and blood product used peroperatively, amount of bleeding and postoperative complications were evaluated. **Results:** A total of 146 patients were included in the study. Patients were divided into two groups: group without fibrinogen concentrate (GNF, n=93) and group with fibrinogen concentrate (GF, n=53). The amount of preoperative bleeding, blood utilization and the total amount of fluid given was higher in GF compared to GNF (p<0.05). Postoperative hospital and intensive care unit (ICU) hospitalization history was higher in GF (p<0.05). **Conclusion:** Fibrinogen concentrate can be used according to the amount of bleeding regardless of the preoperative fibrinogen value in case of bleeding in patients undergoing cesarean section with antenatal PAS. In these patients, anaesthesia management should be determined with a multidisciplinary approach by planning preoperative blood and blood products preparation and ICU according to bleeding and surgical method.

Keywords: Fibrinogen concentrate;
placenta accreta spectrum;
peroperative bleeding

ÖZET Amaç: Plasenta akreata spektrumu (PAS) perioperatif kanama riski yüksek maternal morbidite ve mortaliteye neden olabilen bir durumdur. Fibrinojen ise gebeliğin son trimesterinde yükselmesine rağmen perioperatif kanama durumunda düzeyi ilk azalan faktördür. Bu retrospektif çalışmada amacımız, kanama riski yüksek PAS hastalarında fibrinojen kullanımının perioperatif ve postoperatif sonuçlara etkisini değerlendirmektir. **Gereç ve Yöntemler:** Bu çalışmada antenatal PAS tanısı ile opere olan 171 hastanın dosyaları geriye yönelik incelendi. Hastalar fibrinojen kullanımına göre göre iki gruba ayrıldı. Her iki grubun demografik verileri, anestezi seçimi, Cerrahi uygulama, sıvı miktarı, kan ve kan ürünü, intraoperatif kanama miktarı ve ameliyat sonrası komplikasyonlar değerlendirildi. **Bulgular:** Çalışmaya toplam 146 hasta dâhil edildi. Hastalar fibrinojen konsantrisi kullanılmayan grup (GNF, n=93), fibrinojen konsantrisi kullanılan grup (GF, n=53) olmak üzere 2 gruba ayrıldı. GF'de perioperatif kanama miktarı, kan kullanımı ve verilen toplam sıvı miktarı GNF'ye göre daha fazlaydı (p<0,05). Postoperatif hastane ve yoğun bakım ünitesi (YBÜ) yatış öyküsü GF'de daha fazlaydı (p<0,05). **Sonuç:** Antenatal PAS ile sezaryen yapılan hastalarda kanama olması durumunda perioperatif fibrinojen değerine bakılmaksızın, kanama miktarına göre fibrinojen konsantrisi kullanılabilir. Bu hastalarda kanama ve cerrahi yönetime göre perioperatif kan ve kan ürünleri hazırlığı ve YBÜ planlanarak multidisipliner yaklaşımla anestezi yönetimi belirlenmelidir.

Anahtar Kelimeler: Fibrinojen konsantrisi;
plasenta akreata spektrum;
perioperatif kanama

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Placenta accreta spectrum (PAS) prevents separation of the placenta from the uterus and contraction of the uterus in labour due to the abnormal invasion of the chorionic villi into the myometrium.¹ Therefore, PAS has a high risk of peripartum haemorrhage, which may end with a hysterectomy and has a high maternal morbidity and mortality rate.^{2,3} The amount of bleeding may vary in a wide range, with an average of 2,000-6,000 mL.⁴ As a result of massive bleeding, coagulopathy may develop due to multifactorial causes such as decreased coagulation factors, hemodilution, platelet (Plt) dysfunction, hypothermia and anticoagulants used. As a result of this picture, multiple organ failure, disseminated intravascular coagulopathy, need for intensive care, and even mortality rates may increase.^{5,6} Preoperative antenatal diagnosis of PAS makes it possible to plan the surgical and anaesthetic approach and to prepare blood and blood products.⁷ Perioperative anaesthesia management aims to reduce unnecessary blood transfusion by minimizing blood loss and minimizing complications that may develop.⁸

Fibrinogen is a blood product responsible for primary and secondary hemostasis, reduces acute transfusion reactions and does not require blood group compatibility.⁹ Decreased fibrinogen levels are associated with increased blood loss. Therefore, maintaining adequate fibrinogen levels reduces the amount of bleeding.¹⁰ Fresh frozen plasma (FFP), cryoprecipitate or fibrinogen concentrate can replace fibrinogen. Since fibrinogen content is low in FFP, high volumes should be given. Since there is a risk of infection transmission in cryoprecipitate, fibrinogen concentrate may be preferred more frequently despite its high cost.^{11,12}

We aimed to evaluate the effects of fibrinogen use on perioperative blood product use, intensive care unit (ICU) admission and length of stay, hospital stay and morbidity in patients diagnosed with PAS with high bleeding risk.

MATERIAL AND METHODS

The study was planned after approval of the Clinical Research Ethics Committee (date: January 25, 2023, no: 31). This study was performed with the principles

of the Declaration of Helsinki. Patients who underwent cesarean section and were diagnosed with antenatal PAS between March 2020 and March 2022 were retrospectively analyzed. Our study obtained data from the patient file, our hospital's electronic information centre, and anaesthesia observation files. According to the chi-square test analysis with a significance of $p=0.05$ (α), 90% test power ($1-\beta$), and an effect size of $d=0.5$, the number of samples to be taken in each group was determined as 53. One hundred seventy one patients who underwent cesarean section with antenatal PAS were retrospectively screened and a total of 25 patients were excluded due to missing data. They were divided into 2 groups the group without fibrinogen concentrate (GNF, $n=93$) and the group with fibrinogen concentrate (GF, $n=53$) (Figure 1). Preoperative demographic data of the patients [age, weight, height, body mass index (BMI), comorbidity], American Society of Anesthesiologists (ASA) score, haemoglobin (Hb) and Plt level, type of anaesthesia applied; the amount of perioperative bleeding, the total amount of fluid given, amount of blood used, infant 1. and 5. APGAR score, surgical method (uterine/hypogastric artery ligation, subtotal/total hysterectomy), postoperative Hb and Plt values, blood requirement, ICU admission and length of stay, hospital stay, relaparotomy and complications were evaluated.

ANAESTHESIA MANAGEMENT

In our hospital, electrocardiography, peripheral oxygen saturation and non-invasive or invasive blood pressure monitoring are routinely performed in antenatal PAS patients scheduled for operation. These patients are provided with 16-18 gauge peripheral vascular access. Invasive blood pressure monitoring is performed with radial artery cannulation. In our clinic, 4 units of erythrocyte suspension (ES), 4 units of FFP and 4 g of fibrinogen concentrate are routinely prepared for these cases. In planned elective PAS patients, anaesthesia is selected according to the results of the preoperative evaluation with the surgeon. Although regional anaesthesia (spinal and spinal-epidural anaesthesia) is generally preferred in these cases in our clinic, general anaesthesia is also applied according to the anesthesiologist's preference. For

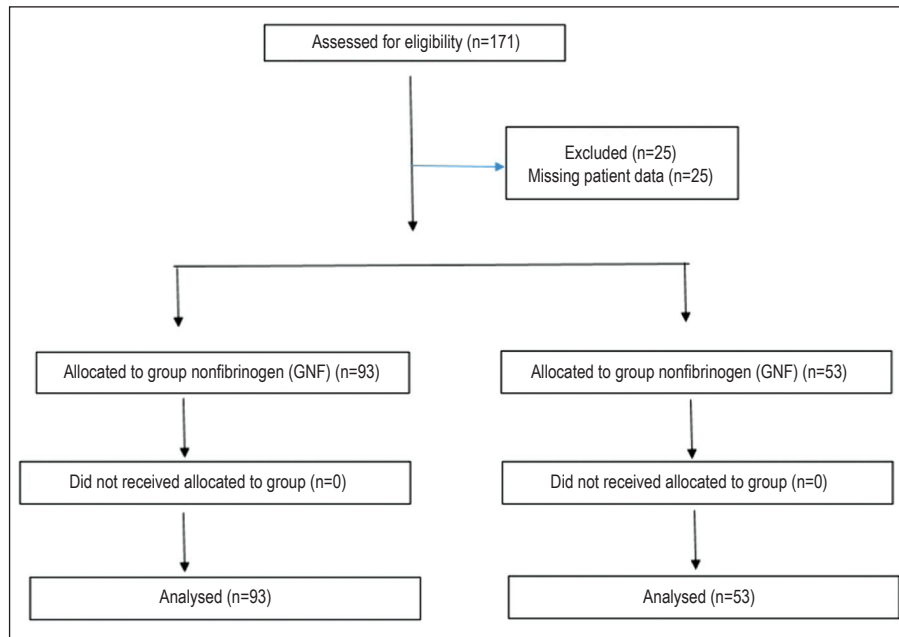


FIGURE 1: Consort of flow diagram of the study.

spinal anaesthesia, 10-12 mg bupivacain and 20 mcg fentanyl are administered according to the patient's height. After spinal anaesthesia, general anaesthesia is initiated in patients who develop perioperative bleeding, surgical midline incision, or hemodynamic instability. Postoperative analgesia of patients undergoing spinal-epidural anaesthesia is provided by patient-controlled epidural analgesia. For general anaesthesia, 1% sevoflurane and 0.05 mcg/kg/min remifentanyl were administered for anaesthesia maintenance, and 100 mcg fentanyl and 1 g paracetamol were administered after the delivery of the baby to patients who were orotracheal intubated after intravenous (iv) propofol and rocuronium induction.

Bilateral transversus abdominis plane block from peripheral trunk blocks is applied for postoperative analgesia in spinal or general anaesthesia patients. Patient controlled epidural analgesia (PCEA) was used for pain relief in regional anaesthesia patients, in addition to PCEA is this block routinely used in our clinic.

Patients with perioperative bleeding over 500 mL are routinely administered 1 g transaminase in 100 mL isotonic as an iv infusion within 10 minutes. Blood and blood product replacement is performed according to hemodynamic data (heart rate, mean ar-

terial pressure) and arterial blood gas values. Those with more than 500 mL of bleeding receive ES: FFP replacement at a ratio of 1:1; fibrinogen concentrate is administered according to the anesthesiologist's preference. The amount of fibrinogen concentrate given changes as the amount of bleeding increases. The fibrinogen concentrate given is started with 2 g and increased in proportion to the amount of bleeding.

The surgeon gives the patient with excessive bleeding an initial uterine massage and iv oxytocin. If bleeding continues, hypogastric and uterine artery ligation or hysterectomy is performed. At the end of the operation, patients who are administered general anaesthesia and who are hemodynamically stable are extubated. The patients with a modified Aldrete score >8 are sent to the ward. Patients with excessive bleeding, hemodynamic instability and the need for vasoconstrictors and inotropes are hospitalized in the postoperative ICU.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. The normally distributed

variables were presented as the mean±standard deviation, while the non-normally distributed variables were presented as the median (interquartile range: 25-75 percentiles). Categorical variables were presented as numbers and percentages. Analysis of variance test (post hoc: Bonferroni correction) was used for the group comparison of the normally distributed variables and the Kruskal-Wallis H test (post hoc: Dunn's correction) was used for the intergroup comparison of the non-normally distributed variables. The chi-square and Fisher exact tests were used for the intergroup comparison of the categorical variables. $p < 0.05$ was accepted as statistically significant.

RESULTS

In this study, in which 25 patients who underwent cesarean section with the diagnosis of antenatal PAS were excluded from the study, 146 patients were di-

vided into 2 groups as GNF (n=93) and GF (n=53). Demographic data, laboratory results, anaesthesia and surgical procedures are given in Table 1. The mean ages were 32.08 ± 5.4 and 33.9 ± 5.2 years in GNF and GF, respectively. BMI, comorbidities and ASA scores were similar in both groups. The rates of being operated under emergency conditions were 32.3% for GNF and 22.6% for GF ($p > 0.05$). Hysterectomy rates were higher in the group using fibrinogen ($p < 0.05$). Regarding the choice of anaesthesia, spinal, spinal-epidural, spinal-epidural and general anaesthesia were similar between the groups. Preoperative Hb and Plt values were not significantly different between both groups. The preoperative blood fibrinogen levels were 470.5 ± 103.5 and 501.9 ± 84.3 , respectively, and were similar in both groups. Bleeding control was achieved only by cesarean section in 82.8% of the GNF group and 39.6% of the GF group.

TABLE 1: Demographic data and laboratory values between groups before surgery, anesthesia and surgical applications.

	GNF (n=93)	GF (n=53)	p value
Age, year	32.08±5.4	33.9±5.2	0.4
BMI, kg/m ²	37.4±28.1	30.1±3.8	0.3
ASA, n (%)			0.3
II	89 (95.6)	49 (92.4)	
III	4 (4.4)	4 (7.6)	
Co-morbidity, n (%)			0.13
No	78 (83.9)	48 (90.6)	
Cardiac	10 (10.8)	1 (1.9)	
Respiratory	0 (0)	0 (0)	
Endocrin	5 (5.4)	4 (7.5)	
Surgical indication, n (%)			0.1
Urgent	30 (32.3)	12 (22.6)	
Elective	63 (67.7)	41 (77.4)	
Surgical applications, n (%)			<0.001
Artery ligations	1 (1.1)	2 (3.8)	
Subtotal hysterectomy	7 (7.5)	8 (15.1)	
Total hysterectomy	8 (8.6)	22 (41.5)	
Cesarean only	77 (82.8)	21 (39.6)	
Haemoglobin, g/dL	11.4±1.2	10.6±1.3	0.1
Platelet, ×10 ⁴ /μL	232±62.9	226.9±63.5	0.3
Fibrinogen, mg/dL	470.5±103.5	501.9±84.3	0.4
Anesthesia applications, n (%)			0.1
Spinal anesthesia	47 (50.5)	18 (34)	
Spinal and epidural anesthesia	6 (6.5)	8 (15.1)	
Spinal and general anesthesia	1 (1.1)	1 (1.9)	
General anesthesia	39 (41.9)	26 (49.1)	

Categorical variables were shown as numbers (%). Numerical variables with normal distribution were shown as mean±standard deviation. Numerical variables that do not show normal distribution are shown as median (minimum-maximum). $p < 0.05$ shows statistical significance. BMI: Body mass index; ASA: American Society of Anesthesiologists.

Perioperative bleeding amounts were 388±420.4 and 4500±1199 for GNF and GF, respectively. Among the blood products used, ES was 0.3±0.8 and 2.1±2.1; FFP was 0.1±0.6 and 1.5±1.5 and were statistically higher in GF (p<0.05). The amount of crystalloid, colloid, and total fluid given to the patients was statistically significantly higher in GF.

The median value of fibrinogen concentrate used in GF was 2(1-6). Infant APGAR scores were similar in both groups (p>0.05) (Table 2).

Postoperative parameters are given in Table 3. The duration of hospitalization, ICU admission and ICU hospitalization days was statistically significantly

longer in GF. When the blood requirement in the first 24 hours postoperatively was analyzed, no significant difference was observed between the 2 groups. Blood product amounts were 0.2±1.2, 0.4±1.1, respectively (p>0.05). When complications were evaluated, relaparotomy, renal, infectious complications and bleeding were similar (p>0.05). In laboratory results, Hb and Plt values were (10.4±1.4, 9.8±1.2) and (208.7±56.9, 179.1±57.6) for GNF and GF, respectively (p>0.05).

DISCUSSION

Our study showed a direct relationship between the amount of bleeding and fibrinogen utilization in pa-

TABLE 2: Peroperative amount of fluid, blood and bleeding, baby APGAR scores.

	GNF (n=93)	GF (n=53)	p value
Amount of bleeding, mL	388±420.4	4500±1199	<0.01
Amount of crystalloid fluid, mL	2191±1003	3288.6±1712.3	0.02
Amount of colloid fluid, mL	83.3±203	287.8±303.6	<0.01
Total amount of fluid given, mL	2312.3±1043.5	3675.4±1760.8	0.02
Total amount of blood given, unite	0.5±1.4	3.7±3.5	<0.01
ES amount, unite	0.3±0.8	2.1±2.1	<0.01
FFP amount, unite	0.1±0.6	1.5±1.5	<0.01
Used fibrinogen concentrate, g/L Median (minimum-maximum)		2 (1-6)	
1 st minute APGAR	7 (2-9)	7 (1-9)	0.2
5 st minute APGAR	9 (5-10)	8 (5-10)	0.3

Categorical variables were shown as numbers (%). Numerical variables with normal distribution were shown as mean±standard deviation. Numerical variables that do not show normal distribution are shown as median (minimum-maximum). p<0.05 shows statistical significance. ES: Erythrocyte suspension; FFP: Fresh frozen plasma.

TABLE 3: Evaluation of postoperative parameters between groups.

	GNF (n=93)	GF (n=53)	p value
Duration of stay in hospital, days	3.5±1.5	6.4±5.7	0.003
ICU admission			0.01
Yes	3 (3.2)	11 (20.8)	
No	9 (96.8)	42 (79.2)	
Hospitalization in ICU, n (%)	0.04±0.2	0.6±1.9	0.01
Presence of need for blood	9 (9.7)	9 (17)	0.2
Amount of blood used, unite	0.2±1.2	0.4±1.1	0.5
Surgical complications			
Relaparotomy	1 (1.1)	0 (100)	0.6
Other complications			0.5
Renal	2 (2.2)	0	
Infections	1 (1.1)	1 (1.9)	
Bleeding	1 (1.1)	0	
Haemoglobin, g/L	10.4±1.4	9.8±1.2	0.4
Platelet, ×10 ⁴ /µL	208.7±56.9	179.1±57.6	0.1

Categorical variables were shown as numbers (%). Numerical variables with normal distribution were shown as mean±standard deviation. Numerical variables that do not show normal distribution are shown as median (minimum-maximum). p<0.05 shows statistical significance. ICU: Intensive care unit.

tients who underwent cesarean section with a diagnosis of antenatal PAS. Hospital stay, ICU admission and length of stay were significantly more extended in the fibrinogen group. The choice of anaesthesia was similar in both groups. Surgical interventions were more invasive in the fibrinogen group. The total amount of blood (ES, FFP) and fluid used perioperatively was higher in this group ($p < 0.05$). There was no significant difference between preoperative and postoperative laboratory results.

The pregnant woman is prepared for possible bleeding with increased procoagulant factors in the third trimester.¹³ One of these is fibrinogen, known as factor I, which is involved in clotting. However, it is the first factor of which blood level drops in case of bleeding. Hypofibrinogenemia occurs due to direct loss due to bleeding, hemodilution due to fluid replacement, decreased synthesis due to hypothermia and increased destruction due to acidosis.¹⁴ Fibrinogen levels for critical hemostasis are controversial. The European Society of Anaesthesiology guideline recommends a blood fibrinogen level above 1.5-2 g/L in patients with haemorrhage.¹⁵ However, a study by Lang et al. showed that fibrinogen concentrate in perioperative bleeding increased clot strength even at low Plt counts independent of fibrinogen level.¹⁶ In the study by Stotler et al., no relationship was shown between fibrinogen use and preoperative fibrinogen level, and it was thought that replacement should be performed independently of fibrinogen level.¹⁷ Since the average amount of bleeding in PAS patients is 2,000-6,000 mL and fibrinogen level is the first coagulation factor to decrease in case of bleeding, we think it is important to perform fibrinogen replacement without waiting for fibrinogen level when massive bleeding starts.

Preoperative antenatal diagnosis of PAS makes it possible to plan a multidisciplinary approach, including surgical approach, choice of anaesthesia, and perioperative blood and blood products preparation.⁶ In these patients, the risk of perioperative bleeding decreases with the hysterectomy decision.¹⁸ In our study, the fact that the postoperative blood and blood product needs were similar in both groups is due to the fact that hysterectomy was performed as a surgical approach and bleeding control was achieved in the fibrinogen group.

In abnormal placenta placement, anaesthesia can be selected according to appropriate physical examination, surgical invasion and bleeding expectations. Although general anaesthesia is generally preferred for airway safety in peripartum haemorrhage, regional anaesthesia can also be used.¹⁹ A retrospective study of 350 placenta previa by Parekh et al. showed that regional anaesthesia provided hemodynamic stability and reduced blood loss and the need for blood transfusion even in severe bleeding.²⁰ Despite this, anesthesiologists often prefer general anaesthesia in patients with massive bleeding and transfusion.²¹ Since anesthesia management becomes difficult in PAS patients, the choice of anesthesia in our patients should be decided with a multidisciplinary approach together with surgery.^{22,23}

The study by Stinger et al., showed that mortality rates due to bleeding decreased when ≥ 0.2 g fibrinogen concentrate was given per unit of ES transfused. In this study, since FFP was used more in the group given fibrinogen, it was thought that FFP may also contribute to low mortality.²⁴ In our study, fibrinogen support was provided from both fibrinogen concentrate and FFP since ES: FFP was administered in a 1:1 ratio in blood replacement.

One of the limitations of our study is that it was a retrospective study. The second limitation is that the use and amount of fibrinogen are according to anesthesiologist preference and cannot be standardized. Another limitation of our study is that fibrinogen support was provided from both fibrinogen concentrate and FFP since FFP replacement was applied in a 1:1 ratio in patients who underwent ES replacement. Studies using Plts, cryoprecipitate or plasma as fibrinogen sources may contribute to this distinction. Another shortcoming is the lack of bedside methods such as thromboelastography or thromboelastometry for fibrinogen replacement.

CONCLUSION

PAS; anesthesia management requires a multidisciplinary approach that includes providing surgical conditions, delivering the baby under optimum conditions, preparing for massive bleeding and transfusion, and providing postoperative analgesia.

In these patients, fibrinogen concentrate can be used for perioperative bleeding regardless of preoperative blood fibrinogen level. In patients diagnosed with PAS, it is very important to have immediate access to adequate volumes and types of blood and blood products during labour. Therefore, every institution should have a standardized bleeding protocol for bleeding management.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Duygu Akyol, Necmiye Ay, Funda Gümüş Özcan; **Design:** Duygu Akyol, Funda Gümüş Özcan; **Control/Supervision:** Duygu Akyol, Ali Kahvecioğlu; **Data Collection and/or Processing:** Duygu Akyol, Ali Kahvecioğlu; **Analysis and/or Interpretation:** Duygu Akyol, Ali Kahvecioğlu; **Literature Review:** Duygu Akyol, Necmiye Ay; **Writing the Article:** Duygu Akyol, Necmiye Ay; **Critical Review:** Duygu Akyol; **References and Findings:** Duygu Akyol; **Materials:** Duygu Akyol, Necmiye Ay, Ali Kahvecioğlu, Funda Gümüş Ay.

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