

# Impact of Rare Bleeding Disorders during Pregnancy on Maternal and Fetal Outcomes: Review of 29 Pregnancies at a Single Center

## *Impacto de distúrbios hemorrágicos raros durante a gestação na mãe e no feto: revisão de 29 gestações em um único centro*

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### Abstract

**Objective** This study aims to give information about the relationship between different types of factor deficiencies and maternal/obstetric outcomes.

**Methods** We retrospectively reviewed the medical records of eight women with factor deficiency disorders. The demographic and clinical features of the patients after their last pregnancies were registered retrospectively.

**Results** There were 29 pregnancies among the 8 patients. The spontaneous abortion rate was relatively high in two patients with factor XIII deficiency (80% and 57.1%) compared with the other factor deficiency groups. There were 16 births, which included 1 set of twins, and 2 deaths (1 stillbirth and 1 postpartum exitus occurred in the same patient). Intrauterine growth restriction was noted in five cases; four of these occurred in factor X deficiency cases. The mean decrease in hemoglobin level of all patients after birth was 1.7 g/dL (range, 0.2–3.6 g/dL). Red blood cell transfusion was required only in one case of factor XIII deficiency.

**Conclusions** There is currently no consensus on the pregnancy management of women with factor deficiencies because of the limited knowledge due to the rarity of such disorders. Labor should be managed in a dedicated unit with a team consisting of an obstetrician, a hematologist, an anesthesiologist, a midwife, and a pediatrician to minimize the complications.

### Keywords

- ▶ factor VII deficiency
- ▶ factor X deficiency
- ▶ factor XI deficiency
- ▶ factor XIII deficiency
- ▶ hemophilia A
- ▶ pregnancy with hematologic complications

### Resumo

**Objetivo** O presente estudo objetiva fornecer informações sobre a relação entre diferentes tipos de deficiências de fator e resultados obstétricos e maternos.

**Métodos** Análise retrospectiva de registros médicos de oito mulheres com deficiências de fator. Dados demográficos e clínicos das pacientes após sua última gestação foram obtidos.

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**Palavras-chave**

- ▶ deficiência de fator VII
- ▶ deficiência de fator X
- ▶ deficiência de fator XI
- ▶ deficiência de fator XIII
- ▶ hemofilia A
- ▶ gestação com complicações hematológicas

**Resultados** Vinte e nove gestações ocorreram entre as oito pacientes. As taxas de abortos espontâneos foram relativamente altas em duas pacientes com deficiência de fator XIII (80% e 57,1%) se comparadas aos demais grupos de deficiências de fator. Ocorreram dezesseis nascimentos, sendo que um deles foi o de um par de gêmeos, e dois óbitos (um natimorto e um pós-parto na mesma paciente). Restrição de crescimento intrauterino foi identificada em cinco casos, sendo quatro destes com deficiência de fator X. A principal baixa em nível de hemoglobina entre todas as pacientes após o parto foi de 1,7 g/dL (variação, 0,2–3,6 g/dL). Transfusão de hemácias foi necessária apenas em um caso com deficiência de fator XIII.

**Conclusão** Não há consenso atualmente para o manejo de gestantes com deficiências de fator em função do conhecimento limitado, dada a raridade de tais condições. O parto deve ocorrer em uma unidade específica com uma equipe composta de obstetra, hematologista, anestesista, parteira, e pediatra para minimizar as complicações.

**Introduction**

Every pregnancy, labor, and postpartum period can become unexpectedly complicated due to bleeding. Therefore, obstetricians should be aware of the life-threatening complications of hemorrhage, and should always take all the measures to prevent undesired outcomes. Pregnant women diagnosed with factor deficiency disorders must be carefully monitored from parturition through the sixth week postpartum.<sup>1,2</sup> However, there is currently no consensus on the pregnancy management of women with factor deficiencies because of the limited knowledge due to the rarity of such disorders. Therefore, information can only be gleaned from the limited number of cases reported in the literature. A multidisciplinary approach is essential for the pregnancy and labor management of women with factor deficiencies.<sup>1–3</sup> The unpredictable nature of factor deficiencies can complicate all stages of pregnancy; thus, labor should be managed in a dedicated unit, where all necessary predictive measurements (such as blood products, intensive care unit, and laboratory sources) can be taken, and with a team consisting of an obstetrician, a hematologist, an anesthesiologist, a midwife, and a pediatrician to minimalize the complications.<sup>2–4</sup>

In this article, we review our experience with pregnancies complicated by factor deficiencies over the past 10 years. We aimed to report the relationship between different types of factor deficiencies and obstetric outcomes.

**Methods**

We retrospectively reviewed the medical records of the pregnancies of eight women with factor deficiency disorders who received treatment from January 2005 to December 2015 in our tertiary university hospital. We used our computerized hospital system to retrieve all of the necessary data. Factor deficiency was diagnosed by an experienced hematologist, and laboratory tests were performed for confirmation.

The demographic and clinical features of the patients after their last pregnancies were registered retrospectively. The

type of factor deficiency, age at last pregnancy, obstetrical history, gestational age at delivery, neonate birth weight and percentile, bleeding complications, hemoglobin levels (at hospitalization prior to delivery, and at the first day postpartum), medical treatments before labor, and blood transfusion after the labor of the last pregnancy were noted (▶ **Tables 1, 2**).

Intrauterine fetal growth restriction (IUGR) was defined as < 10<sup>th</sup> percentile weight for gestational age at birth. Preterm labor was defined as a delivery that occurred before 37 weeks of pregnancy.

All statistical analyses were performed using the Statistical Package for Social Sciences software (IBM-SPSS, Inc., Chicago, IL, USA), version 17. The non-interventional Clinical Research Ethics Board of Hacettepe University approved the conduction of this study.

**Results**

There were 29 pregnancies among the 8 patients. Factor deficiency type and total number of patients were as follows: factor VII (FVII) in one; factor VIII (FVIII) in one; factor X (FX) in two; factor XI (FXI) in two; and factor XIII (FXIII) in two. The median patient age at the last pregnancy was 35 years (range, 23–39 years). The mean total number of pregnancies was 3.6 (range, 1–7). Eleven pregnancies (37.9%) resulted in spontaneous abortion, and factor deficiencies varied among these patients. The spontaneous abortion rate was relatively high in the two patients with FXIII deficiency (80 and 57.1% respectively). There was 1 neonatal death (22-week-old fetus) and 1 intrauterine death (detected in gestational week 24) in 1 patient with FXIII deficiency.

Out of the eight women, vaginal bleeding during the last pregnancy occurred in four. Two of them had FX deficiency, and another two had FXIII deficiency. Three women developed vaginal bleeding in the first trimester, whereas one patient with FX deficiency had vaginal bleeding twice and hematuria once in the second trimester.

There were 16 births included 1 set of twins and 2 deaths (1 stillbirth and 1 postpartum exitus). Intrauterine fetal growth restriction was noted in five cases; four of these occurred in patients with FX deficiency. There was no

**Table 1** Fetal and maternal outcomes in the last pregnancy

	Fd	Gest wk	Newborn gender	Bleeding during Pregnancy	Preop prophylaxis	Postop prophylaxis	Preop hb (gr/dL)	Postop hb (gr/dL)	Bt
Case 1	F7	39w1d	M	–	CoF	CoF	12.9	11.4	–
Case 2	F10	37w3d	F	+	FFP	FFP	11.9	10.5	–
Case 3	F10	36w6d	F	+++	CoF	CoF	12.9	12.1	–
Case 4	F11	36w2d	M	–	FFP	FFP	12.3	9.7	–
Case 5	F11	36w1d	M	–	FFP	FFP	11.6	9	–
Case 6	F13	37w	M	+	–	–	9.4	5.8	+
Case 7	F13	36w	F	+	–	–	10	9.8	–
Case 8	F8	37w5d	M	–	–	–	10.6	9.2	–

Abbreviations: Bt, blood transfusion; CoF, cofactor; d, day; F, Factor; F, female; Fd, factor deficiency; FFP, fresh frozen plasma; Gest wk, gestational week; gr/dL, grams per decilitre; hb, haemoglobin; M, male; Postop, postoperative; Preop, preoperative; w, week.

instance of fetal malformation in our study group. Two patients delivered vaginally (both before the 24th gestational week), while the remaining 16 (88.9%) deliveries were performed by cesarean section (CS). Term labor occurred in 8 (47.1%) pregnancies. In total, there were 10 preterm deliveries, and 2 of them resulted in extremely preterm labors (24 and 22 weeks of gestation), which occurred in the same patient with FXIII deficiency. One case with FX deficiency delivered live twins at gestational week 36 and 3 days.

Five patients were carefully prepared before CS to prevent severe blood loss with the administration of the preoperative prophylaxis, which consisted of cofactors in two cases (FVII and FX), and fresh frozen plasma (FFP) in three (FX, FXI, and FXI). This subgroup received the same medical agents for postoperative prophylaxis. Blood products (red blood cells and FFP) were prepared before surgery in all cases in anticipation of bleeding complications. Two patients with FXIII deficiency were prescribed FFP during their pregnancies, whereas prophylactic administration prior to delivery was not considered due to increased plasma levels.

The pre and postoperative hemoglobin levels of all patients in their last pregnancies were also documented. The mean decrease in the hemoglobin level of the patients was 1.7 g/dL (range, 0.2–3.6 g/dL). Red blood cell transfusion was required only in 1 case with FXIII deficiency (12.5%) due to a decrease in postoperative hemoglobin to 5.8 g/dL, while the other patient with FXIII deficiency had no significant decreased hemoglobin level after surgery.

## Discussion

The plasma levels of the coagulation factors change throughout a normal pregnancy, while the serum concentrations of fibrinogen, FVII, FVIII, FX, and von Willebrand factor increase until reaching their maximum levels in the third trimester. Other factors (that is, FII, FV, FIX, and FXI) decrease or do not change significantly.<sup>4</sup>

Patients with factor deficiency can deliver either vaginally or by CS. An organized delivery plan and an experienced unit with a hemophilia center are necessary to maintain the safety of the mother and the newborn. Elective CS may be an option when the fetal coagulation status is unknown. However, the use of instrumental delivery options, such as fetal scalp electrodes and

**Table 2** Newborn weight and percentile at birth

	Factor	1.Newborn	2.Newborn	3.Newborn
Case1	F7	39w1d/2,960 g/16p		
Case2	F10	34w/1,800 g/6p	37w/2,600 g/13p	37w3d/2,800 g/23p
Case3	F10	36w3d/1,800 g/3p (twin1)		36w6d/2,470 g/8p
Case3	F10	36w3d/2,210 g/6p (twin2)		
Case4	F11	35w/3,680 g/35p	36w2d/2,040 g/4p	
Case5	F11	36w2d/2,570 g/30p	38w5d/3460 g/60p	36w1d/2,570 g/19p
Case6	F13	36w/2,940 g/35p		
Case7	F13	22w/PPex	24w/luex	36w/3,100 g/60p
Case8	F8	38w/3,100 g/45p	37w5d/3,050 g/32p	

Abbreviations: d, day; F, factor; g, gram; luex, Intrauterine exitus; p, percentile; PPex, postpartum exitus; w, week.

fetal blood sampling, is contraindicated if fetal bleeding is expected.<sup>1</sup> We had an extremely high CS rate because of unknown fetal condition and maternal anxiety. Elective CS has an important advantage for hospital staff, because it enables them to prepare for unexpected complications and organize themselves before delivery, easing the pressure on clinicians. These findings are in concordance with data obtained from the current literature, in which the rate of CS is estimated to be 85%.<sup>5</sup>

Regional analgesia remains a concern in patients with factor deficiencies due to the significant risk of spinal or epidural hematomas. Despite the advantages of analgesia, the status of the patient must be carefully monitored by an experienced anesthesiologist.<sup>1,2,6</sup> We usually choose general anesthesia to prevent potential maternal complications, and spinal anesthesia can be applied carefully if the maternal factor levels are in normal plasma ranges.

Massive postpartum hemorrhage (PPH) is a major cause of maternal morbidity. Prompt diagnosis and appropriate management are keys for preventing unintended consequences.<sup>4</sup> Patients with factor deficiencies require more careful monitoring because of their tendency to bleed. Preventive measures, such as the normalization of hemostatic factor levels, early detection of uterine atony, and careful delivery to prevent trauma are absolutely necessary for patients with inherited bleeding disorders.<sup>1,5</sup>

Factor X, which is the first enzyme in the coagulation cascade, participates in the common thrombus formation pathway. Factor X is synthesized in the liver and is maintained in the blood at a concentration of  $\sim 10\mu\text{g/mL}$ .<sup>7,8</sup> It is also known by the eponym Stuart–Prower factor, and it is a vitamin K-dependent plasma glycoprotein associated with coagulation.<sup>9,10</sup>

Factor X deficiency (FXD) is a rare, autosomal recessive, inherited disorder that occurs at a rate of about one case per million, and is an important complication that can result in severe bleeding beginning at birth. Patients with FXD can experience some life-threatening issues, such as epistaxis, gastrointestinal bleeding, hematuria, hemarthrosis, hematoma, umbilical cord bleeding, and central nervous system bleeding.<sup>7</sup>

It is difficult to predict the pregnancy outcomes of women with FXD because of the limited number of cases. Factor X deficiency seems to be a cause of premature labor, neonatal death, and pregnancy complications such as vaginal bleeding and placental hematoma. One of our FXD patients suffered from hematuria once and vaginal bleeding twice during her pregnancy that were controlled with cofactor (CoF) administration. Hematuria during pregnancy has not been underlined in the literature, but it seems to be a benign phenomenon with effective treatment. Because of the risk of PPH, clinicians should always be aware of this complication and prepare an emergency plan.<sup>10</sup> Previous studies showed that preterm labor is a potential risk for these patients, and our study group supported these findings: out of all 5 deliveries, 3 were before the 37th week. We observed only one abortion in the FXD group, a finding similar to those of the literature, in which miscarriage rates were not expressive. Additionally, we found increased IUGR rates, and clinicians should consider this obstetric outcome.<sup>7,10</sup>

Factor XI is also important in the coagulation cascade. As with FX, FXI is also synthesized in the liver, and it circulates in the plasma as an inactive precursor.<sup>11</sup> Factor XI deficiency (FXID), also known as ‘hemophilia C’, ‘plasma thromboplastin antecedent deficiency’, and ‘Rosenthal syndrome’, is an uncommon autosomal inherited disorder that occurs at a frequency of about one case per million persons.<sup>12</sup> Factor XI deficiency is not associated with an increase in miscarriage rates, and most pregnancies end without major complications. However, women with FXID are at a greater risk of uncontrolled bleeding during labor or invasive procedures, such as curettage. The CS ratio is not significantly increased by FXID, thus vaginal delivery should be considered as the first option if all conditions are suitable.<sup>13</sup> One patient in the study cohort had two early pregnancy losses, which is not an expected complication in this group. These abortions do not seem to be associated with bleeding disorders, but rather other factors that were not described clearly, such as chromosomal abnormalities or infections.

Factor XI levels are not predictive for bleeding complications, as plasma levels seem to be stable during pregnancy. The most advantageous predictor of a major complication is a remarkable bleeding history of the patient.<sup>4,12</sup>

The guidelines suggest a prophylactic treatment with FXI concentrate during and after delivery for patients with FXID. However, FFP can be considered as an option.<sup>11,12</sup> Each of our patients received FFP prophylaxis, as recommended in the literature, which resulted in no bleeding complication.

Factor VII is a vitamin K-dependent coagulation factor that is synthesized in the liver.<sup>3</sup> Factor VII deficiency (FVIIID) is the most common of these rare autosomal inherited disorders. The prevalence of mild FVIIID is up to 1 in 500,000 in the general population, and, 1 in 350 among heterozygous patients.<sup>14</sup> The plasma levels of FVII increase by  $\sim 4$  times during pregnancy, which seems to be a protective strategy to prevent PPH. However, bleeding diathesis is not correlated with clinical manifestations. A heterozygous patient can present with a massive hemorrhage, while a patient with severe factor deficiency may have no complications, even after delivery.<sup>1,15</sup>

Life-threatening bleeding can occur in women with FVIIID due to perineal trauma during vaginal delivery or CS. For this reason, patients may require the administration of FFP, prothrombin complex concentrate, or recombinant FVII.<sup>16</sup> Careful management of such patients is necessary because of the potential of maternal morbidity due to bleeding, and the newborn can also have a bleeding disorder. This group of patients, especially those with a history of bleeding, must be evaluated even more carefully in order to prevent massive PPH.<sup>14</sup> We encountered no significant obstetrical complications among our patients. One patient with FVIIID received prophylaxis to prevent PPH before and after the CS, which seemed to be successful.

Factor XIII deficiency (FXIIID) is also an important coagulation factor disorder detected in our series. Congenital deficiency of blood coagulation factor XIII is a rare autosomal recessive inherited disorder that occurs at a rate of 1 case in 1–2 million persons, most often in countries where consanguineous marriages are more common, like our country.<sup>17,18</sup> Factor XIII

is a plasma transglutaminase enzyme that stabilizes fibrin and amino acids during the coagulation cascade.<sup>19</sup> Factor XIII deficiency (FXIID) is associated with hemorrhagic diathesis, recurrent spontaneous abortion, defective wound healing, prolonged bleeding after trauma, and especially prolonged umbilical bleeding after birth.<sup>17</sup>

The importance of FXIID to the obstetrician is the increased incidence of complications, such as miscarriage, placental abruption, recurrent pregnancy loss, preterm labor, and PPH. Fresh frozen plasma, cryoprecipitate, or factor concentrate must be administered to increase the plasma factor level up to 10% to prevent pregnancy losses. Patients with FXIID need to be evaluated carefully, and prophylactic FFP can prevent undesirable pregnancy losses; as suggested in the literature. Successful pregnancy outcomes are possible with the proper treatment, including factor XIII sources.<sup>20</sup> We also found an increase in poor obstetric outcomes in this patient group, which is in accordance with the literature.

Factor XIII deficiency complicated with PPH is rare, as compared with the other factor deficiencies, and it occurs in ~ 25% of all women with the disorder. Although the underlying mechanism remains unknown, it is probably associated with the use of prophylactic therapy during pregnancy and labor. The most important complication of FXIID seems to be early pregnancy loss among untreated patients.<sup>21</sup> Our findings show a high prevalence of abortion, which is consistent with data provided by a previous study, which reported that the miscarriage rate increases to more than 90% without treatment. Additionally, there was only one instance of severe bleeding after delivery between two patients (four deliveries) in our study group. The PPH risk reported in the literature is ~ 25%, our findings support this.<sup>20</sup>

Factor VIII is a plasma protein with an important function in the coagulation cascade. Factor VIII deficiency (FVIID), which is also known as hemophilia A, is mostly common in males.<sup>22</sup>

Factor VIII levels increase during pregnancy, especially during the third trimester, which may be a protective mechanism against maternal blood loss. The severity of the disease is dependent on FVIII plasma levels, although all affected patients are at risk of bleeding during pregnancy.<sup>23</sup> The successful management of such patients without any complications has been reported in a limited number of case reports.<sup>24</sup>

Patients with hemophilia A are at a greater risk of PPH. For these patients, all preventive measures must be initiated to avoid bleeding complications. In patients with hemophilia A, CS offers only a minimal advantage over vaginal delivery to the neonates, so the mode of delivery must be decided based on the obstetric and maternal conditions.<sup>23,24</sup> Our patient developed PPH in her first delivery, while her second delivery was performed by CS without any complication. Although hemophilia A is not associated with undesired obstetric outcomes, PPH remains a potential risk among these patients.

#### Conflict of Interest

The authors have no conflict of interest to declare.

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