Case Report ISSN 2639-9342

Gynecology & Reproductive Health

The Outcome of Pregnancy in a Patient with Factor XII Deficiency: A Case Report

Amilia Afzan Mohd Jamil[1,2*], Vairavan Ramesh Valayudham[2] and Noor Shahira Abdullah[3]

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Science, Universiti Putra Malaysia, Selangor, Malaysia.

[2]Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Hospital Serdang, Selangor, Malaysia.

[3]Department of Family Medicine, Faculty of Medicine and Health Science, Universiti Putra Malaysia, Selangor, Malaysia.

[*]Correspondence:
Amilia Afzan binti Mohd Jamil, Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Science, Universiti Putra Malaysia, Selangor, Malaysia.

Received: 20 July 2020; **Accepted:** 13 August 2020

Citation: Amilia Afzan Mohd Jamil, Vairavan Ramesh Valayudham, Noor Shahira Abdullah. The Outcome of Pregnancy in a Patient with Factor XII Deficiency: A Case Report. Gynecol Reprod Health. 2020; 4(4): 1-3.

Keywords
Hageman Factor, Pregnancy, Miscarriage.

Introduction

Factor XII (Hageman Factor) is a plasma serine protease known to be involved in triggering the intrinsic cascade pathway blood coagulation [1]. Factor XII deficiency is a rare genetic blood disorder that causes prolonged clotting of blood in vivo without the presence of protracted clinical bleeding or clotting tendencies. It is passed on by autosomal recessive inheritance [2]. It affects only 1 in 1 million individuals. Factor XII levels are lower in patients of Asian descent than in other ethnic groups [3]. Given the rarity of the disease, there has been no documentation on the incidence and prevalence of Factor XII deficiency in Malaysia

There has been controversy about whether Factor XII deficiency has any significant effects on the course and outcome of pregnancy. Few papers associate the condition with poor pregnancy outcomes, notably recurrent miscarriage, whereas few other articles unable to find any association between Factor XII deficiency and adverse pregnancy outcome.

In this case report, we present a pregnant lady with Factor XII deficiency who had an uncomplicated pregnancy with a good outcome.

Case History

A 34-year-old lady was referred to the antenatal clinic in Serdang for large for gestational age baby. She was in her fourth pregnancy, having had two spontaneous vertex delivery, followed by a miscarriage. Her antenatal history was uneventful. Her glucose tolerance test was normal.

She was diagnosed with Factor XII Deficiency ten months earlier when she presented with a missed miscarriage of triplets. During that admission, her blood investigation showed prolonged activated partial thromboplastin test (APTT). Her thrombophilia profile was reasonable Prothrombin Time, APTT 180, Normal Factor IX and Factor VIII, and 0% Factor XII. Anti Cardiolipin Antibodies and anti-beta 2 glycoprotein 1 IgG was not detectable. Gemeprost was inserted intravaginally, and she had an uncomplicated miscarriage. There was no excessive vaginal bleeding post-miscarriage. However, she defaulted subsequent follow-up.

Her two previous deliveries before the miscarriage were uncomplicated. There was no excessive blood loss or symptoms suggestive of venous thrombosis. She did not require thromboprophylaxis. There was also no known family history of any blood disorders.

Assessment done showed a singleton fetus with estimated fetal weight 3.6 kg via ultrasound scan. The patient was admitted at 39 weeks for delivery. On examination, she was a morbidly obese lady with a body mass index of 42. Other vital signs were within normal limits.

Blood investigation results were normal. Her haemoglobin level = 11.7 gm/dl, platelet count = 240x10/L, liver function test, urea and electrolytes were normal.Her coagulation profile was as shown

in table 1. C3 and C4 are normal. Factor assay showed deficient Factor XII activity (0%, reference value 70-145%) with normal Factor VIII and IX activity.

Laboratory test	Result	Normal Range	Laboratory test	Result	Normal Range
PT	12.7	11.5-16.5	Factor XII activity	0%	70-145%
INR	0.94	0.8-1.1	Factor VIII	57.6%	50-150%
APTT	110	26-39	IX activity	112.9%	50-150%
APTT ratio	3.8	0.8-1.3			
	Full blood picture: Normochromic normocytic picture with anisocytosis. No spherocytes, fragmented cells, or an increase in polychromatic cells seen.				

Table 1: Patient's coagulation profile and full blood picture result.

A multidisciplinary discussion was done involving the hematologist, anesthetist, and blood transfusion specialist. Following that, she underwent lower section Caesarean Section under general anesthesia. The surgical procedure was uncomplicated, and the estimated blood loss was 600ml. She was started on s/c Enoxaparin 40mg OD for six weeks for venous thromboembolism prophylaxis.

Her baby girl, born 3.6kg, was admitted to NICU for poor Apgar score secondary to maternal general anesthesia. There was no bleeding from the cord stump, or bruises mark on her body. The baby's condition improved, but she developed neonatal jaundice. She was put under phototherapy for three days. The patient and her newborn were discharged from the hospital five days after Caesarean Section.

She was seen back at the postnatal clinic after two weeks. She reported no excessive bleeding, and her wound healed well. She had an etonogestrel implant inserted for contraception.

Discussion

Coagulation Factor XII, known as the Hageman factor, circulates in plasma as an inactive zymogen form of a serine protease. It is part of the intrinsic coagulation cascade and activates factor XI and prekallikrein in vitro [4].

Since coagulation factor XII first discovery in 1955, its deficiency is connected with thrombosis instead of bleeding. Some data have shown that Factor XII deficiency has a prothrombotic effect and is associated with recurrent venous thromboembolism and myocardial infarction [5,6]. One proposed explanation is because of impairment of contact activation related fibrinolytic activity in factor XII deficient patients [7].

However, Girolami has challenged this premise, elucidating that in most cases where thrombosis was associated with Factor XII deficiency, other congenital or acquired prothrombotic risk factors are present, for example, pregnancy, postpartum period, surgery and trauma [8]. The fact was supported by a study by Kosler, who established that factor XII is not a determinant in deep vein thrombosis [9]. It has been suggested that factor XII is not necessary for thrombin formation [10].

Lämmle et al. studied 74 subjects aged 8 to 82 years from 14 Swiss families with FXII deficiency. They reported that none of the 18 homozygotes or double heterozygotes for subjects with FXII deficiency and FXII:C of less than 0.01 U/ml had an abnormal bleeding tendency during surgery [11]. This study concurred with findings of Girolami et al., that factor XII deficiency does not only show any bleeding tendency but also can withstand even major surgical procedures without thrombotic complications [12].

An animal study has shown that Factor XII deficiency is a protective factor against pathological fibrin formation involved in thrombosis without interfering with hemostasis. The research further suggests Factor XII inhibition as a safe and selective strategy in the prevention of stroke and thromboembolic disease [13].

The pregnancy outcomes of mothers with factor XII deficiency has been inconsistent. Several studies reported a higher incidence of recurrent pregnancy loss [9,10]. In the research conducted by Gris et al., 9.4% of women with unexplained recurrent primary miscarriages were found out to have isolated Factor XII deficiency [14]. One study also observed that patients with higher levels of Factor XII antibodies, which subsequently decreased the level of Factor XII, is also associated with recurrent pregnancy loss [15]. Ogasawara et al. reported that Factor XII deficiency is a better predictor for subsequent pregnancy loss in women with recurrent miscarriage (but not protein C, protein S, antithrombin III, or Factor XIII) [16].

A few others reported Factor XII has no detrimental effect on pregnancy and that normal gestation and vaginal delivery are possible even in cases with congenital FXII deficiency [11-13].

Factor XII deficiency is not a causative factor for hemorrhagic tendency, with only mild bleeding reported [17,18]. However, a study by Koster et al. have investigated the effect of Factor XII deficiency on premature delivery and found a positive correlation [19].

In our case, the patient had a history of one mid-trimester miscarriage, and the last pregnancy and delivery were uncomplicated with Factor XII activities of 0%. She also underwent a safe cesarean section. However, it is unknown whether her infant has Factor XII deficiency since no investigation was done on her yet.

In conclusion, the case report highlights that Factor XII deficiency is not associated with any adverse effect on the course and outcome of pregnancy.

Acknowledgement

The authors would like to thank the Director General of Health Malaysia for permission to publish this case report.

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