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Postpartum Hemorrhage in Heterozygote Factor XIII Deficient Women Compared With Healthy Women. A Cross-Sectional Experience From Iran

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Abstract

Postpartum hemorrhage (PPH) is a major cause of maternal mortality, which is a common clinical manifestation in women with rare bleeding disorders. In this study, we compare PPH and its complications in heterozygote factor XIII (FXIII) deficient women with healthy women. In this cross sectional case study, 50 women with heterozygote FXIII deficiency and 50 healthy women are evaluated. Data were initially collected by interviewing the women who were receiving FXIII replacement therapy after their childbirths. Data were analysed using SPSS (Version 22) and a *P*-value of less than .05 was considered statistically significant. The mean age in the patient and control groups were 31.2 and 32.5 years respectively. The occurring rate of PPH in the patient group was significantly higher than the control group (34% vs 2%) (*P*-value <.0001). None of the confounding variables such as maternal age, gestational age, numbers, and types of delivery in women with PPH showed any significant differences between the control and patient groups. According to the results of this study, the risk of PPH (early and late), miscarriage, and menorrhagia in women who are heterozygous for FXIII deficiency is significantly higher than healthy women. However, the effect of other factors such as maternal age, gestational age, number, and type of delivery require further studies to delineate any confounding factors.

Keywords

postpartum hemorrhage, heterozygote, factor XIII deficiency, autosomal recessive, rare bleeding disorder, pregnancy, factor XIII

Introduction

Hereditary factor XIII (FXIII) Deficiency was originally reported by Duckert in 1960[1] and the exact prevalence of the disease in different parts of the world has not been fully determined yet. Apparently, as true for other autosomal recessive disorders, FXIII deficiency is more prevalent in regions with higher rates of consanguineous marriages.[1]

Sistan and Baluchestan is a province in the southeast of Iran with a population of more than 2,400,000 people and a massive rate of consanguineous marriages resulting in a very high prevalence of Factor XIII Deficiency (FXIIID).[4,5] A case-report in 2002-2003 discussed a frequency of 30 FXIII deficient patients in every million in the region, the prevalence of which increased to 90 affected individuals in every 1 million in 2012. A prevalence, which, based on the currently available data, is the highest reported prevalence in a single region worldwide.[6] Despite the rarity of FXIIID, a study by Naderi et al showed a prevalence of 120 patients per million in Sistan and Baluchistan, which is comparably more than 100 times higher than the other reported incidence rate of the disease.

Postpartum hemorrhage (PPH) is a predictable complication of rare bleeding disorders.[7] PPH is defined as bleeding after giving birth and is the leading cause of maternal morbidity and mortality worldwide.[8] It is classified into two types: primary or early and secondary or delayed. The primary type is defined as either of the following: 1- loss of more than 500

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mL of blood after vaginal delivery, 2- loss of 700 mL of blood after labor with forceps, or 3- loss of 1000 mL of blood after Cesarean within 24 h after delivery.[8] Secondary bleeding occurs from 24 h to 6 weeks after the delivery with the only difference being that the primary type occurs within 24 h and the secondary one after 24 h.

The most common cause of PPH is an atonic uterus (causing up to 80% of cases).[8] Other causes include infections, cardiovascular complications, hypotonic myometrium, excessive uterine dilatation due to large or twin Fetuses or polyhydramnios, placental abruption, rupture of the uterus or perineum or vagina, etc which are exacerbated by congenital anomalies. PPH alone contributes to 5%-19% of maternal deaths which is a significant proportion within the general population.[10,11] This statistics is better described in a 2018 study which states a worldwide deaths of more than 80,000 women in 2015 alone due to obstetrics hemorrhage.[12,13]

There are a few reports to evaluate the relations between FXIIID and PPH. However, the high prevalence of the disease in our region makes it a more suitable candidate to evaluate this relationship, ie the occurrence rate of PPH in women with FXIIID, its confounding factors, and most importantly, do heterozygote women for FXIIID even experience PPH? If yes, how so? Is it even different from the homozygote variation of FXIIID? To answer these questions, we decided to study the occurrence of PPH in heterozygous FXIII deficiency and compare its rate to healthy women in 1 year (2018-2019), as well as the associated confounding factors that come with it.

Material and Methods

This descriptive-analytical cross sectional study was performed in 2018-2019 in Ali Asghar Hospital in Zahedan. Our patient group included 50 women whose children were homozygote for FXIII deficiency and 50 normal, healthy women of the same age-groups of the patients. Our patient group routinely visited the hospital to receive FXIII replacement therapy for their FXIIID. Every patient in this study filled a written form declaring their consent to participate in the study. Unfortunately though, in some cases, patients were deprived of any education, so the consent form was written and signed by their spouses, in the presence of a mediator from Zahedan University of Medical Sciences Ethics Committee. To collect our data, we gave the patients in both groups a questionnaire in which they filled the following: Age, gestational age, type of deliveries, number of births (and the type of deliveries in each). All the PPHs and the time of bleedings we have of our patients, we not only asked in the questionnaire but verified with all the documents we had on the patients, to avoid any errors. To further explain, we work at the only rare bleeding disorders in the Sistan and Baluchistan province which is at Ali Asghar Hospital in Zahedan, and we keep fully updated and detailed documents from each one of our patients. With this extra verification step, we ensured a smaller chance of error in our data and statistical analysis.

To distinguish between the heterozygous and the homozygous in our selection process, we first called up the mothers of our FXIIID patients. The age and time of diagnosis were not factors of exclusions here as FXIIID is a lifelong condition and the majority of the homozygous FXIIID patients were diagnosed years ago, with checking for Tryptophan 187—Arginine mutation—[14,15] with no affiliations to any particular centers, we sent our samples to the centers which gave back the results the quickest at the time-. Given that FXIIID is an autosomal recessive condition, thus at least one parent must be a carrier even if the other one has FXIIID -which we would have known since we had the records, and again, we were selecting only the mothers-. However, to be further sure of the heterozygous state of the mothers, we checked for FXIIID symptoms and their bleeding histories, as well as referring to the documents and information we had on their pregnancies and prenatal conditions. We then selected the patients who met all the 3 conditions (ie 1- having at least one child with FXIIID. 2- Has symptoms, though not as severe as FXIIID, but enough to not be counted entirely healthy. 3- Had prenatal complications or information related to FXIIID).[16]

Statistical analysis was done using SPSS software version 22 (SPSS Inc., Chicago, IL). Descriptive results were presented as mean, standard deviation, frequency, and percentage. The $\chi 2$ test was used to compare the qualitative variable between the 2 groups. The quantitative variable was compared by the Student *t*-test between the 2 groups. A P-value $<.05$ was considered to be statistically significant.

Results

The mean age of the patients in the patient group and the control group was 31.2 ± 8.95 (18-57) and 32.5 ± 8.67 (18-51) years respectively and the mean number of deliveries in the patient and the control group was 3.9 ± 2.46 and 3.1 ± 1.79, respectively.

The history of pregnancies and related clinical data are shown in Table 1.

The history of PPH, abortion, bruising, and menorrhagia are shown in Table 2. The occurrence of PPH in the patient group is significantly higher (17/50) compared to the control group (1/50) ($P < .0001$). In addition, history of abortion, bruising and menorrhagia presented at a significantly higher rate in women in the patients group compared to the control group. None of the patients had experienced hemarthroses or cerebral hemorrhage which are considered significant complications of FXIIID.

Discussion

Our results show that the occurrence of PPH in patients with FXIIID is statistically and clinically significant. In this study, other bleeding symptoms in the patient group included; menorrhagia (22%), bruising (16%), gingival bleeding (8%), hematuria (4%), fecal bleeding (2%), and epistaxis (2%); which were

Table 1. The History of Pregnancies and Related Clinical Data in the 2 Groups.

Category	Control	Patients	*P*-value
Hx of delayed PPH			
Yes	–	3	.24
No	50	47	
Age of labor			
30 or less	1	16	1
Above 30	–	1	
Weeks of pregnancy			
Less than 37 weeks	1	16	.25
Above 37 weeks	–	1	
Type of delivery			
Natural	–	10	.25
With forceps	1	5	
C-section	–	2	
Total number of pregnancies			
1-2	–	8	.58
3-5	1	8	
More than 5	–	1	
Epistaxis			
Yes	–	1	1
No	50	49	
Gingival bleeding			
Yes	4	8	.11
No	–	–	
Hematuria			
Yes	–	1	.49
No	50	49	
Fecal blood			
Yes	–	1	1
No	–	49	

Abbreviation: PPH, postpartum hemorrhage.

higher than the control group who experienced only abortion (8%), bruising (2%) and menorrhagia (2%).

To compare the different aspects of our study with others, we divide our study into two sections; prevalence of PPH, and its complications, respectively. The prevalence of PPH in patient with FXIIID in this study (34%) is much higher compared to the study done by Mahmoudi et al which was 7.1%.[14] and other studies including the homozygote FXIII deficiency.[17] This inconsistency can be explained by the difference in the study population, genetic variations, and mutations in the patients -which can cause higher rates of PPH in the heterozygotes in our population compared to the homozygotes of the other studies-. The smaller population studied by Mahmoudi et al could also act as a culprit causing this discrepancy. Despite the available evidence, the mutation hypothesis requires a further, more lab focused research.

Table 2. The History of PPH, Abortion, Bruising, and Menorrhagia in the 2 Groups.

Category	Control	Patients	*P*-value
Hx of PPH			
Yes	1	17	<.0001
No	49	33	
Hx of abortion			
Yes	4	19	<.0001
No	46	31	
Bruising			
Yes	1	8	.03
No	49	42	
Menorrhagia			
Yes	11	1	.004
No	39	49	

Abbreviation: PPH, postpartum hemorrhage.

An important sequela we consider here is late PPH which occur in 6% of the women our patient group, while none of the women in the control group show any. Another interesting result in our study is the 38% prevalence of abortion in our patient group compared to the 8% in our control group which is statistically significant. This event has biologic plausibility as stated by Inbal et al in 2003. They declared FXIIID and Fibrinogen deficiency as the only two coagulation factor deficiencies associated with pregnancy loss. Pregnancy loss in these patients is most likely due to abnormal placental implantation, causing an increased antepartum hemorrhage due to placental abruptions.[18] Hence, with the studies added, pregnancy loss is a mutual symptom in both homozygous and heterozygous FXIII deficiencies. However, it seems that the prevalence of abortion is even higher than the rate we found in this study, which shows the importance of emphasizing on the risks of abortion in heterozygote women with factor XIII deficiency. We make this assumption based on our exclusion of nonpregnant women at the start of this study. This confirms the increased incidence of PPH in FXIII deficiency found in other studies.[19]

Mahmoudi et al. In 2011 reported the prevalence of subcutaneous bleeding (10.7%), nasal bleeding (7.1%), gingival bleeding (7.1%), PPH (7.1%), and severe or long-term bleeding after minor trauma (7.1%). Though the occurrence of these symptoms are statistically different from our study, they are in direct correlation with our findings, implying an increase in bleedings in heterozygote women compared with the healthy ones.[17]

This paragraph focuses on the findings of two studies by James et al and Naderi et al; commenting on the high prevalence of menorrhagia in women with Factor XIII deficiency. The prevalence of menorrhagia in heterozygote women is seemingly similar to that of the homozygote women, and in this regard heterozygote women suffering from this disorder need prophylactic interventions just like the homozygote women.[20,21] The prevalence of other bleeding symptoms does not seem to be as important as PPH and menorrhagia in heterozygous women with Factor XIII deficiency.

Conclusion

In conclusion, this study proves that PPH is a highly probable and a predictable complication of FXIII deficiency in women, even if they are heterozygous for the disease. Though statistical differences between the heterozygous and homozygous populations of FXIII deficiency necessitates further studies to find the exact prevalence of the symptoms, PPH, as a definite one, remains an exception, requiring insight and cautious to correctly predict, manage and treat.

Limitation

- A lack of patient cooperation that, despite the thorough explanations of the benefits that this study brings and its possible impacts on solving their issues, persisted throughout the study.
- Language barriers due to the existing regional dialects. To mitigate this issue to the possible extent, we asked our linguistically capable colleagues to help us with communications.
- A lack of genetic testing; our diagnoses of FXIII deficiency were solely based on clinical and inheritance presentation as no genetics testing is available to reassure the diagnoses. However, given the straightforward autosomal recessive inheritance pattern, children born homozygote for FXIII deficiency are definitely born to both parents of heterozygote status.

Declaration of Conflicting Interests

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