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Exploring the Postpartum Pyrexia Related to Inherited Coagulopathies in a Cohort of Iranian Women

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Abstract

Background: Postpartum pyrexia results from various causes with bacterial infection heading the list. However, there are many other possible causes such as bleeding. Congenital deficiency of the coagulation factors causes inherited coagulopathies most of which are rare. Following delivery, the reduction in coagulation factors puts these mothers at greater risk of postpartum excessive bleeding.
Objectives: We aimed to assess postpartum pyrexia in bleeding disorder mothers.
Methods: This study was conducted on 98 bleeding disorder patients and 199 controls. Using a standardized questionnaire, the data were collected by consulting a specialist. The subject's medical records during pregnancy and labor were also reviewed. Postpartum fever was defined as temperature > 38°C in the first 10 days after delivery excluding the first day. The data were analyzed using Chi-square statistical analysis and $P < 0.05$ was considered statistically significant.
Results: Postpartum pyrexia was detected in 11.2% of the patients compared to 4% of the controls. The statistical analysis revealed a significantly higher incidence of postpartum fever among the coagulation disorder patients ($P = 0.019$). Considering the infection, our data showed that in the patient group, fever was mostly due to (unknown) reasons other than infection.
Conclusions: Our results revealed that besides hemorrhagic complications in inherited bleeding disorders, postpartum fever could also be a sign of threat. Early identification and diagnosis of these threats greatly improve the childbirth outcomes in high-risk mothers.

Keywords: Coagulation Disorders, Childbirth, Postpartum Pyrexia, Postpartum Haemorrhage

1. Background

Postpartum pyrexia is defined as a temperature of 38°C or more (1). It happens in any day of the first 10 days following childbirth, excluding the initial 24 hours (2). A common etiology for postpartum pyrexia is infection with the local spread of colonized bacteria (1). Endometritis and wound infections are among the leading causes of postpartum sepsis (3). The infection incidence also increases subsequent to membrane rupture (4). In addition, postpartum haemorrhage (PPH) is a risk factor for puerperal pyrexia that occurs following a variety of complications such as trauma or coagulation defect (5). During cesarean section, the internal organs are traumatized that can cause mild internal hemorrhage and could be sever in bleeding disorder patients (6). Episiotomy could also lead to bleeding because the area surrounding the perineum has extensive vasculature (7).

One of the most common causes of PPH is poor blood clotting. When a vessel is injured, a number of mechanisms are conducted to stop bleeding. To induce clot formation, coagulation factors, which naturally are found in tiny amounts in the blood stream, need to be activated (8). Congenital deficiency of the factors causes inherited bleeding disorders most of which are rare. These disorders, including hemophilia A and B, von Willebrand disease, factor VII, X, XIII, XI, XII, and V deficiencies are mostly transmitted as autosomal recessive conditions. Frequency of coagulation disorders is different within populations, being elevated where consanguineous marriages are common (9). Following delivery, the reduction in coagulation factors puts these mothers at greater risk of PPH (6). The management of PPH associated with coagulopathies consists of either blood products (e.g. fresh frozen plasma, cryoprecipitate) or uterotonics (e.g. oxytocin, misoprostol) (10, 11). Developing fever following blood product replacement has been reported in publications (12, 13). Uterotonics such as misoprostol also trigger fever in some women with an unclear reason (14).

In the present study, we aimed to elucidate the contribution of postpartum pyrexia as an additional complication in women with inherited coagulation disorders.

2. Methods

This study was designed to include 98 inherited bleeding disorder women in comparison with 199 women with normal pregnancies. The study was done in Tehran haemophilia centers and general hospitals.

The patients were selected to be interviewed based on international criteria guidelines under the supervision of experienced haematologists. Carriers of Haemophilia A or B and von Willebrand disease patients comprised 45% and 29% of all cases, respectively. A few cases of other types of coagulopathies were also incorporated in the survey including factor VII, X, XIII, XI, XII, and V deficiencies. Women suffering from hypofibrinogenemia, Glanzmann's thrombasthenia, and Bernard-Soulier syndrome also participated in our study.

A questionnaire was designed for assessment of complications including fever. The questions were framed by consultation with medical statistics experts and validated to avoid any bias. The postpartum fever was defined as a body temperature > 38°C within the first 10 days of delivery except for the first day. It has been shown that not all fevers are due to infections and there are many other possible causes such as bleeding. In this study, we looked for fever generally as the sign of any inflammation, infection, and blood product or medications side effects.

The controls were selected randomly from healthy Iranian women who referred to state health care services. They were interviewed by the same person who asked the patients applying the same questionnaire. Exclusion criteria included medical disorders complicating pregnancy as well as complications of delivery procedures such as uterine perforation.

This study was approved by the ethics committee of Tarbait Modares University and all participants provided written informed consent to take part in the study.

To reject the null hypothesis of no fever effect, the significance level was chosen at 5% to ensure a power of 80%. The sample size was calculated by EpI Info 7.0.9.34 software. Published literature was used to support the analysis assuming that the fever occurs in 5 - 10% of childbirths. A case-control study is preferred when the disease is rare because the cases can be intentionally searched for the disease. As a result, the study was defined as unmatched case-control study with 95% confidence interval. The data were analyzed using Chi-square statistical analysis in SPSS (V.16.) software. T-test was used to compare differences between two independent variables with normal distribution and the Mann-Whitney U test was applied to non-normally distributed data. P-values less than 0.05 were considered statistically significant.

3. Results

Main demographic and obstetric characteristics of the study subjects are summarized in Table 1. The mean age of each group was approximately 32 years. Although cases and controls were from the same social communities (with equal access to medical care), the mean number of miscarriage was different between the groups ($P < 0.001$). It was the issue for newborn death frequency that was significantly higher in the patient group ($P = 0.01$).

The detailed pregnancy medical histories of the cases and controls are indicated in Table 2. The data confirm the homogeneity of the groups with respect to various parameters. There was no significant difference between the two groups except for the mode of delivery. Overall, 58% of the cases versus 29% of the controls delivered their children by caesarean section. The difference between the two groups was statistically significant ($P < 0.001$).

We analyzed the detailed data obtained by questionnaires. Since the mother's body temperature often increases immediately after delivery, the first day fever was not indicated as a positive sign. The patient's medical notes taken during pregnancy or labor were reviewed focusing on the management and treatment of each patient or control subject.

Our results demonstrated that only 4% of the healthy women experienced fever. In contrast, 11.2% of the mothers with inherited bleeding disorders showed this complication. The statistical analysis revealed that there was a significant association between inherited coagulopathies and postpartum fever. The Pearson Chi-Square was calculated as 5.692 with $P = 0.019$. As some parameters influence postpartum fever, we adjusted the analyses for these factors. Table 3 represents multivariate logistic regression using the enter method that predicts age, any kind of chronic diseases, placental abruption, premature rupture of membranes, and preterm birth. The significance of correlation between coagulation disorders and postpartum pyrexia remained unchanged, suggesting that our analysis was not markedly affected by confounding factors (OR 2.76, 95% CI: 1.015 - 7.546).

Furthermore, we assessed the infection rate between the two groups. Patients demonstrated 2% of any kind of infection versus 3.5% observed in controls (Pearson Chi-Square 0.515, $P = 0.347$). Although the difference was not statistically significant, our results showed that most of the reported fevers in the patient group are due to (unknown) reasons other than infection (9%). Our data also discovered a link between postpartum bleeding and pyrexia. 18.4% of individuals who experienced postpartum bleeding also demonstrated fever compared to 4% without bleeding episodes ($P < 0.001$).

Table 1. Baseline Demographic and Obstetric Characteristics of the Study Subjects

	Mean	Standard Deviation	P-Value
Age			0.78
Controls (n = 199)	32.4	7.3	
Cases (n = 98)	32.5	7.4	
Weight			0.07
Controls (n = 199)	61.6	9.1	
Cases (n = 98)	64.06	10.6	
Age at last pregnancy			0.27
Controls (n = 199)	25.9	4.3	
Cases (n = 98)	25.2	4.3	
Pregnancies			0.68
Controls (n = 199)	2.01	1.1	
Cases (n = 98)	2.1	1.2	
Deliveries			0.16
Controls (n = 199)	1.9	1.14	
Cases (n = 98)	1.74	0.94	
Miscarriage			< 0.001
Controls (n = 199)	0.11	0.58	
Cases (n = 98)	0.28	0.69	
Live birth			0.04
Controls (n = 199)	1.8	0.96	
Cases (n = 98)	1.6	0.93	
Still birth			0.06
Controls (n = 199)	0.02	0.14	
Cases (n = 98)	0.06	0.23	
Newborn death			0.01
Controls (n = 199)	0.01	0.09	
Cases (n = 98)	0.06	0.23	

Table 2. Pregnancy Medical History of the Study Subjects

	Cases (n = 98)	Controls (n = 199)	P-Value
Morning sickness	12 (12.24)	18 (9.04)	0.42
High blood pressure	5 (5.10)	4 (2.01)	0.51
Preeclampsia	2 (2.04)	9 (2.51)	0.42
Gestational diabetes	2 (2.04)	6 (3.01)	0.99
Premature rupture of membranes	8 (8.16)	11 (5.52)	0.45
Preterm birth	1 (1.02)	1 (0.50)	0.44
Cesarean Section	57 (58.16)	58 (29.14)	< 0.001

Data are presented as No(%).

4. Discussion

Postpartum fever occurs mostly following infection or bleeding, within or around the uterus or other organs such as bladder (15, 16). In a large case-control study published in 2007, fever was reported as the most common postpartum complication. However, it had happened after a mean of 31.1 h following delivery. Among other complications examined, bleeding was reported as the earliest. Only 15.5% of women developed bleeding later than 6 h subsequent to childbirth. The authors emphasized that bleeding was the most dangerous complication studied (17).

Boni and colleagues showed that multiple necrotic uterine leiomyomas could lead to severe puerperal fever. They suggested that extensive necrotic degeneration of the fibroids caused this complication (18). The fever may also be related to lactation suppression (19). Christian et al have reported that folic acid–iron therapy during pregnancy reduced the risk of postpartum hemorrhage with a relative risk of 0.59. In addition, puerperal sepsis was less common in those receiving folic acid-iron, folic acid–iron–zinc, and multiple micronutrients than in controls (20).

It has been shown that bleeding disorder patients have more hemorrhagic risks during and after pregnancy. Following delivery, the reduction in coagulation factors puts the mothers at greater risk of postpartum excessive bleeding (21, 22). In a comprehensive survey in the United States, 37.6% of 109 females with inherited bleeding disorders showed postpartum hemorrhage (23). A significant higher PPH rate has also been observed in both primary and secondary postpartum hemorrhage in Iranian patients (6). To improve outcome of PPH, particularly when coagulopathy is present, blood products are used for the correction of blood clotting abnormalities (11). It has been shown that coagulopathy leads to increased risk for blood product transfusion as well as for hysterectomy and maternal morbidity (24). It should be noted that developing fever is a common symptom of blood or blood components replacement (12). In addition, misoprostol, a synthetic prostaglandin, is widely used for the management of PPH. Fever is a recognized side effect of misoprostol, which is also difficult to discriminate from an intra-uterine infection (25).

We performed this study to understand the relationship between bleeding disorders and the chance of developing postpartum pyrexia. We found a rather high significant association between coagulopathies and postpartum fever. Our data showed that in coagulation disorder patients, fever is mostly due to (unknown) reasons other than infection. It could be interesting to further explore the correlation between fever and PPH managements. Prospec-

Table 3. Multivariate Logistic Regression Model

Variables	B	S.E.	Wald	P-Value	Odds Ratio	95.0 % C.I. for EXP(B)	
						Lower	Upper
Coagulation disorders	1.01	0.51	3.95	0.04	2.76	1.01	7.54
Age	0.03	0.03	1.04	0.30	1.03	0.96	1.11
Preterm birth	1.15	0.73	2.51	0.11	3.18	0.76	13.30
Chronic diseases	1.49	1.04	2.04	0.15	4.46	0.57	34.72
Placental abruption	1.02	1.33	0.59	0.44	2.79	0.20	37.98
Premature rupture of membranes	0.10	0.05	3.39	0.06	1.11	0.99	1.24
Constant	-4.75	1.32	12.92	< 0.001	< 0.001		

tive investigation needs to be done to distinguish between fever due to infection and fever due to other complications.

Based on our knowledge, fever in coagulation disorder patients has never been addressed in literature.

4.1. Conclusion

As a conclusion, women at risk of severe bleeding should be examined precisely to minimize the risks. In addition to hemorrhage, fever should also be taken seriously as an alert in women with bleeding disorders by their birth attendants. The appropriate assessment and monitoring of the patients can improve the pregnancy outcomes and their quality of life.

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Footnotes

Authors'Contributions: Shirin Shahbazi designed the research, analyzed and interpreted data, and wrote the manuscript; Lida Moghaddam-Banaem contributed to study design, analyzed, and interpreted data and wrote the manuscript.

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