Original Article

# Hematological indices in prolonged menstruation: New roles for blood groups and coagulation factors

**Shirin Shahbazi[1]*, Azam Baheiraei [2], Fatemeh Oskouie [3, 4]**

*[1*]Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University Tehran, Iran*
*[2] Community Based Participatory Research Center, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran.*
*[3] School of Nursing and Midwifery, Iran University of Medical Sciences, Tehran, Iran*
*[4] Nursing Care Research Center, Iran University of Medical Sciences, Tehran, Iran*
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## Abstract

**Background:** Menorrhagia is the most common type of abnormal uterine bleeding, caused by disruption of hormonal regulation, uterine function or blood clotting. Developing an effective diagnostic strategy for menorrhagia will improve patient's quality of life and the disease management. Here we investigated the links between hematological characteristics and prolonged menstruation to determine the importance of the first line coagulation screening tests in young women .**Materials and Methods:** In a case-control design supervised by a specialist, 43 menorrhagia cases and 104 age-matched controls were selected. Menstrual characteristics were evaluated by a standardized questionnaire distributed to high school and university young students. First line coagulation screening tests were performed for both groups and hematological indices were statistically assessed. **Results:** Statistical analysis showed that prolonged menstrual bleeding was significantly correlated to prolonged bleeding time (p value, 0.01) as well as red blood cell count (p value, 0.04). The O blood group showed the greatest contribution to the bleeding periods longer than 7 days (53.4 %(. Additional coagulation tests revealed a patient with coagulation factor VII deficiency. **Conclusion**: The results of the present study revealed the importance of menorrhagia management in young women and showed a significant correlation between prolonged menstrual bleeding and blood types . Our study findings also suggest a significant association between prolonged menstruation and bleeding time test, emphasizing on the role of blood coagulation traits in susceptibility to menorrhagia.

**Keywords:** Menorrhagia, Coagulation, Blood groups, Hematological traits

***Corresponding Author:** Shirin Shahbazi. Tel: (+98) 21-82884556; Email: sh.shahbazi@modares.ac.ir

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## Introduction

Endometrial tissue undergoes rapid and serial changes during menstrual phases. This functional layer proliferates and differentiates in a steroid hormone-dependent manner(1). Shedding of the endometrium results in menstrual flow consisting of blood, mucus and cellular debris (2).

Menorrhagia also known as heavy menstrual bleeding (HMB) is defined as hemorrhage more than 80 milliliters and/or longer than seven days per menstrual cycle. HMB is one of the most common complaints of women in reproductive age (1, 3). Excessive uterine bleeding can be caused by functional and hormonal defects such as uterine fibroids and ovarian cysts (4).

Also, coagulation abnormalities account for

remarkable number of HMB cases. It has been shown that inherited deficiencies of coagulation factors are detectable in 10-15% of menorrhagia patients (5). Coagulation factors play pivotal role in clotting pathway, each responsible for a specific reaction. Inherited deficiency of the factors cause coagulation disorders including hemophilia and von Willebrand disease (VWD) (6).

First line coagulation screening tests include prothrombin time (PT), partial thromboplastin time (PTT), bleeding time (BT), and platelet count (Plat) which are frequently used in HMB evaluation. PT determines the blood clotting tendency and coagulation extrinsic pathway status by analysis of factors I (fibrinogen), II (prothrombin), V, VII, and X, while PTT represents the intrinsic and common pathway functions. BT verifies the vessel constriction and plug formation and could be affected by certain vascular disorders, platelet abnormalities and VWD (7).

It should be noted that some of the coagulation diseases occur in mild forms, which increase the susceptibility to HMB. However, these patients are not generally under proper medical care. Genetic variants including single nucleotide polymorphisms (SNP's) should also be borne in mind which make the patient susceptible to HMB without fully manifesting the disease. Given this evidence, in addition to diagnosed coagulopathy patients, other women who are suffering from heavy bleeding should be screened (8). Since many of these predisposed young women do not seek medical treatment, community-based screening can be an advantage over screening for those referring to medical centers.

Considering the high impact of menorrhagia on patients educational, social and psychological conditions and consequently the quality of life, we designed this study to achieve a low cost and effective strategy for HMB screening. We particularly aimed to investigate the correlation between prolonged menstrual bleeding (PMB) and first line coagulation screening tests.

## Methods

***Participants.*** Participants were identified based on the data collected via more than 700 questionnaires distributed to high school and university female students. The questionnaire contained general health records of their medical history as well as menstrual bleeding status. They were asked to record the bleeding duration and symptoms of menstrual periods in a row. Reviewing the questionnaires and volunteers' interview revealed that 98% of the contents reflected in the questionnaire were accurate and reliable.

A case-control study comprising PMB and non-PMB groups was designed to determine correlation between extended bleeding and hematological traits variations.

From the respondents to questionnaires, a group of 43 PMB cases and a control group comprising 104 non-PMB age-matched women were selected. Patients with a definitive diagnosis of HMB such as uterine fibroids and ovarian cysts were excluded from the study.

The participants contributed to this study, on a volunteer basis and signed a written informed consent approved by the ethics committee of Iran University of Medical Sciences, Tehran, Iran.

***Hematological assessments.*** The patients and normal individuals were referred to Comprehensive Hemophilia Care Center Tehran, Iran for blood tests. In the first step, the complete blood count (CBC) was assessed which routinely included the following: white blood cell count (WBC), red blood cell count (RBC), red cell distribution width (RDW), Hb (hemoglobin), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and Plat. Supplemental blood types test and RH were also performed.

First line coagulation screening tests included BT, PT, PTT were analyzed by the same laboratory technician and setup. Complementary tests including coagulation factor antigens were performed in cases where first line coagulation screening suspected of a kind of coagulopathy.

***Statistical analysis.*** The collected data were statistically analyzed using SPSS version 16. Correlation studies of the quantitative and qualitative data were performed by ANOVA and chi-square tests, respectively. T-test was used to compare differences

between two independent parameters that normally distributed and the Mann-Whitney U test was applied to not normally distributed data. The p value <0.05 was considered statistically significant.

# Results

***Menstrual characteristics.*** According to the data obtained from the cases' questionnaires, mean age was 19.96 year with a standard deviation of 2.18 while the controls mean age was 18.12 ±3.05.

At initial interview, 88.3% of cases and 81.9% of controls experienced menarche longer than 3 years. Seventy-eight percent of cases and 75% of controls reported spectra of dysmenorrhea which could be considered as the hypothalamic–pituitary–gonadal axis development. Along with dysmenorrhea, premenstrual symptoms are other common signs of ovulatory cycle's occurrence. Thus, questions were posed in the case of symptoms such as headache, irritability, gastrointestinal symptoms and etc. Forty-two percent of the cases reported that they always experience these symptoms, whereas, 28% of them had the symptoms occasionally. These values for the controls were 63% and 22%, respectively. Statistical analysis showed no significant difference in prevalence of non- ovulatory cycles between the two groups.

***Hematological assessments: Anemia.*** PMB and non-PMB groups were evaluated for the correlation between menstruation longer than seven days and hematological indices. ANOVA test showed that there was a significant association between PMB and RBC (p value, 0.04). The mean values of indices in two groups are indicated in Table-1. As shown, the significant association was only observed for RBC but not for the other parameters emphasizing a weak association between prolonged menstruations and developing anemia. Since Iron therapy affect anemia, the analyses were weighted for this confounding factor in the exact logistic model. However, the results remained unchanged, suggesting that our analysis was not markedly affected by Iron supplements. Previous reports have shown a link between PMB and anemia, however, our study did not reach significant results in this regards. This discrepancy can stem from the prevalence of anemia in the healthy group due to nutritional causes.

**Table 1**- The mean values of CBC indices in case and control groups

| Hematological parameters | Cases Mean±SD | Controls Mean±SD | *p value* | 95% confidence interval (CI) |
|---|---|---|---|---|
| **RBC($10^6$/µl)** | 4.7±.3 | 5.12±.6 | .040 | 4.7-4.9 |
| **Hb(g/dl)** | 12.61±1.3 | 13.1±1.0 | .289 | 12.7-13.3 |
| **Hct(%)** | 40.71±2.0 | 40.89±2.2 | .268 | 39.7-41.0 |
| **MCV(fl)** | 85.91±4.4 | 84.99±3.7 | .191 | 81.7-84.4 |
| **MCH(pg/cell)** | 27.82±2.1 | 27.37±2.4 | .430 | 25.9-27.4 |
| **MCHC(g/dl)** | 32.36±1.6 | 32.39±1.4 | .553 | 31.7-32.6 |
| **RDW (%)** | 12.38 | 12.50 | .345 | 12.6-13.2 |
| **Plat(x1000)** | 278±73 | 258±48 | .126 | 248-281 |

RBC; Red Blood Cell count, Hb; hemoglobin, Hct; hematocrit, MCV; Mean Corpuscular Volume , MCH; Mean Corpuscular Hemoglobin, MCHC; Mean Corpuscular Hemoglobin Concentration, RDW; Red cell distribution Width, Plat; Platelets

***Hematological assessments: Blood Types.*** Statistical analysis showed interesting results regarding blood groups. By comparing the two groups, we observed a significant correlation between PMB and blood types (p value, 0.008 and $\chi 2$, 20.64). Data analysis showed that 53.4% of PMB cases had O blood type vs. 33.6% of control group. Regarding blood types A and AB the differences were not significant as they were almost equal in both groups. Blood type B was detected in 21.1% of controls, but there was only one B blood type case in PMB group (2.4%). Figure 1 shows the distribution of blood types in both groups. It should be noted that our results revealed no link between prolonged menstruation and RH.

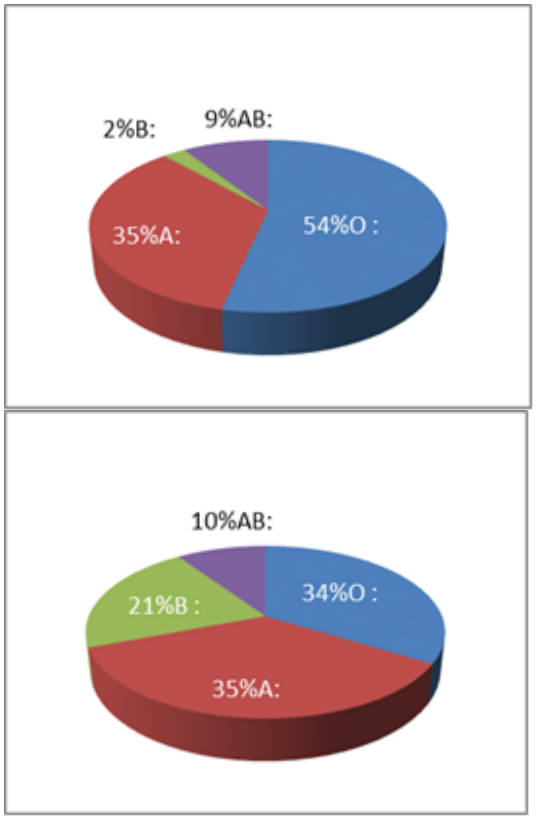


**Figure 1** – The percentage of the blood types in control (Up) and case (Down) groups.

***Hematological assessments: coagulopathies.*** A significant correlation was observed between PMB and BT testing results (p value, 0.018). However the differences between Plat, PT and PTT in two groups were not statistically significant (Table-1 and Table-2).

**Table 2-** The mean values of First line coagulation screening tests in case and control groups

| Hematological parameters | Cases Mean±SD | Controls Mean±SD | *p value* | 95% confidence interval (CI) |
|---|---|---|---|---|
| BT | 3.88±.7 | 3.27±.4 | .018 | 3.3-3.6 |
| PT | 10.13±.3 | 10.05±.1 | .696 | 10-10.1 |
| PTT | 32±2 | 33.4±2.5 | .082 | 31.8-33.1 |

BT; Bleeding Time, PT; Prothrombin Time, PTT; Partial Thrombin Time

The results of first line coagulation screening tests revealed that six out of 43 cases were suspected of having some type of coagulation disorder. Complementary tests confirmed the presence of FVII deficiency in one patient but not a pathogenic condition in the remaining patients. However, the specialist suggested further follow-up over a longer period for other five cases. The FVII deficiency patient suffered from menorrhagia, chronic nosebleeds and easy bruising and had FVII level of 33%.

## Discussion

Abnormal uterine bleeding is partly caused by hormonal dysfunction and uterine disorders; however, there are still other cases due to various underlying diseases that need to be identified. At puberty, menstrual cycles without ovulation are common in the first three years which root in the lack of hypothalamic-pituitary axis development and impaired ovarian LH secretion (9). These periods are associated with adequate levels of LH and FSH required for ovulation induction and secretion of estrogen, but not enough for oocyte maturation and ovulation (4). In our study, given the reported symptoms and clinical examination, anovulatory cycles were observed in less than 10% of the subjects. A retrospective study on the patients attended the adolescent gynecology clinic revealed hypothalamic-pituitary-ovarian axis immaturity in 28 out of 73 patients following a negative bleeding disorder screening (10).

The second most common cause of HMB in adolescents is hereditary or acquired coagulation disorder (11). Retrospective studies showed the prevalence of menorrhagia in 10-62% of adolescents compared to 20% in older females (12). On the other side, the menorrhagia due to bleeding disorder was reported in most of the patients (13). Considerable evidence indicate that 5-36% of adolescents with HMB suffer from VWD, 2-44% from platelet function defects, 13-20% from thrombocytopenia, and 8-9% from clotting factor deficiencies that implies a dispersed distribution in populations (14).

Owing this fact, first line coagulation screening tests are recommended for the detection of inherited bleeding disorders or predisposed people. Abnormal test results may direct physicians to the assessment of specific coagulation factor (15). In our study, PMB

showed a significant association with BT test. As it was mentioned earlier, BT is influenced by thrombocytopenia, platelet disorders and VWD (16). Type 1 VWD is the most common type of the disease with mild symptoms or asymptomatic phenotype. In addition, females with heterozygous type 2 or type 3 VWD are either clinically asymptomatic or may present only mild bleeding tendency (17). The clinical diagnosis of such cases is a complex issue, as the variations in VWF levels possibly lead to prolonged bleeding time with mild hematological index changes (18). A recent cohort study reported a newly diagnosed type 2A VWD patient among 40 adolescents with PMB upon their initial presentation to the hospital. In the rest of the subjects coagulation assay results were in the normal ranges (19). By studying 120 Irish women with low VWF levels, Lavin et al showed HMB in 89% of the cases. They reported that 89.2% of low VWF cases had blood group O vs. 55% of the general population (20).

In this regard, the other finding by our study revealed a correlation between blood types and menorrhagia.

The bleeding tendency in various diseases can be directly affected by blood groups. Previous studies in duodenal ulcers bleeding and post-tonsillectomy hemorrhage showed that individuals with O blood group were at higher risk. Researchers attribute this effect to the blood groups links with the VWF (21). An important regulator of VWF levels in blood are blood group antigens. It has been previously shown that VWD and the Factor 8 display decreased level of 25-30% in individuals with blood type O (22). ABH antigenic determinants have been localized on the N-linked oligosaccharide chains of plasma VWF. ABO group affects VWF plasma clearance rates as the half-life of the protein in O blood type is 40% of the individuals with other blood types (23). The impact of blood groups on the VWF plasma levels also makes it difficult to diagnose type 1 VWD since the normal range of VWF antigen in individuals with O blood group is lower than conventional normal values (24). However, in a study of more than 4,000 samples, no association was found between O blood type and early postpartum hemorrhage (PPH)(25). It can be concluded that the influence of blood group on adolescent menorrhagia is more specific and can be considered as an evaluation indicator.

The number of adolescents admitted to hospitals due to severe menstrual bleeding is significant. To date an agreed approach is not applied and since HMB profoundly affects the patients' health, it is necessary to formulate a guideline for early identification of patients at high risk (26).

## Conflicts of Interest

The authors have stated that they have no interests which might be perceived as posing a conflict or bias.

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