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Review article

Levonorgestrel intrauterine system: bleeding disorders and anticoagulant therapy

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Abstract

Hemostatic disorders in women are frequently associated with long-standing menorrhagia. This leads to significant morbidity and adversely affects quality of life. Management of these women poses a particular challenge; medical treatments may be contraindicated, and surgery carries additional risks. The levonorgestrel intrauterine system (LNG-IUS) has been shown to be highly effective in reducing menstrual blood loss in women with normal coagulation. It is also a reliable and reversible contraceptive. Data on the use of this system in women with bleeding disorders or those receiving anticoagulant therapy are limited. Analysis of data from four reported studies suggests that LNG-IUS is a viable and safe option for the management of menorrhagia in these women. Whether the underlying hemostatic disorders lead to a shorter duration of action or prolonged irregular bleeding/spotting post insertion is unknown and requires large prospective studies. Proper counselling remains crucial for patients' satisfaction.

Keywords: Levonorgestrel intrauterine system; Bleeding disorders; Anticoagulant therapy

1. Introduction

Disorders of hemostasis are frequently associated with bleeding complications. Women appear to be disproportionately affected with these disorders, and menorrhagia is the most common bleeding symptom. Management of menorrhagia in these women may pose many challenges to clinicians. They may be refractory to many medical treatments, whilst other pharmacological agents can be contraindicated for use. Furthermore, surgical treatment carries additional risks of bleeding or thrombotic complications. The levonorgestrel intrauterine system (LNG-IUS), primarily developed as a contraceptive device, is now increasingly used for the treatment of menorrhagia. With a high efficacy in reducing menstrual blood loss and minimal systemic side effects, it may provide a promising alternate treatment option for these women.

This review aims to discuss the magnitude of menstrual disorders affecting women with inherited bleeding disorders and those receiving anticoagulant therapy. It also addresses the difficulties in treating these women. Finally, it examines the available evidence for the use and effectiveness of LNG-IUS in the treatment of menorrhagia and the possible benefits for other gynecological problems. Areas for future research are also explored.

2. Inherited bleeding disorders

Inherited bleeding disorders in women are more common than previously suspected. Von Willebrand disease (VWD) is the most common inherited bleeding disorder with a prevalence of approximately 1% in the general population [1,2]. It is generally inherited in an autosomal manner, thus it affects both males and females equally. However, more women with VWD are symptomatic due to the hemostatic challenges of childbirth and monthly menstruation. In the United Kingdom Haemophiila Center Doctors' Organisation 2005 registry, women accounted for over 60% of the patient registered with VWD. VWD is classified into three main types according to whether the defect in von Willebrand factor (VWF) is quantitative (Types 1 and 3) or qualitative (Type 2). Type 1 is the most common, accounting for

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around 70% of all cases and is characterized by a partial deficiency in VWF. Type 3 involves a near or complete absent of VWF and is therefore severe. This is a rare disorder with a prevalence ranging from 0.1 to 5.3 per million [3]. There are four subtypes (2A, 2B, 2N, 2M) of Type 2 VWD. Type 1 and most Type 2 are transmitted as an autosomal dominant trait, whilst Type 3 and 2N are inherited in a recessive manner.

Hemophilia A and B are the most common severe inherited bleeding disorder. They result from deficiencies of coagulation factors VIII and IX, respectively. Their pattern of inheritance is X-linked recessive, hence, men inherit the condition and women are affected as carriers. Carriers of hemophilia are expected to have clotting factor levels around 50% of normal (normal range, 50–150 IU/dL). However, a significant number of carriers have a low factor level and a bleeding tendency. In a study by Plug et al. [4], 27.5% of carriers had a clotting factor level of ≤40 IU/dL. These carriers, as well as those with factor levels between 41 and 60 IU/dL, had an increased risk of bleeding compared to noncarriers.

A deficiency in other plasma clotting factors (fibrinogen; prothrombin; factor V, VII, X, XI, XIII) or a quantitative or qualitative defect in platelets can also cause bleeding symptoms of varying severity. These rarer coagulation disorders are generally inherited as autosomal recessive traits with severe forms expressed in homozygotes or compound heterozygotes.

3. Menorrhagia in women with hemostatic disorders

Disorders of hemostasis are commonly associated with excessive menstrual blood loss. In a survey of 99 women with Type 1 VWD from four hemophilia centers in the United States, 79% reported their periods to be heavy, 71% required medical attention and 13% required hysterectomy for control of menorrhagia [5]. In a study by Ragni et al [6], 93% of 38 women with VWD suffered from heavy menstruation. Menorrhagia was the most common initial bleeding symptom leading to the diagnosis of the disease in 53% of them. In an international survey of 44 women with more severe forms of VWD, 80% had at least one episode of severe menorrhagia requiring blood product therapy [7]. In our center, using the pictorial blood assessment chart (PBAC) [8], menorrhagia (defined by a score of more than 100) was reported in 74%, 57% and 59% of 66 women with VWD, 30 carriers of hemophilia and 20 Factor XI (FXI)-deficient women, respectively, compared to 29% in the age-matched control group [9]. Women with these disorders also had significantly longer periods (25% bled for more than 8 days compared to only 4% in the control group) and more episodes of flooding and passage of clots [9]. Menorrhagia is a long-standing problem for these women and usually starts from menarche. Menorrhagia since menarche was reported in 65% of women diagnosed with a bleeding disorder, compared to only 9% in those with normal coagulation [10]. Heavy menstruation has also been reported in women with platelet disorders or a deficiency in prothrombin, fibrinogen, factor V, factor VII, factor X or factor XIII. In a review of published series, menorrhagia was reported in 35–98% of women with these disorders [11].

Iron deficiency anemia is consequently prevalent among women with bleeding disorders. A past or present history of anemia was reported in 64% of 81 menstruating women with Type 1 VWD, compared with 34% of 150 menstruating controls [5]. There is also a high rate of surgical interventions for menorrhagia, including hysterectomy. A hysterectomy rate of 23–26% has been reported among women with VWD [7,12]. Hysterectomy is often performed at a relatively young age and prior to the diagnosis of the bleeding disorder. There has been a report of hysterectomy as early as 14 years of age [7]. Menstruation also has a significant negative impact on the quality of life of these women. A striking difference in health-related quality of life has been reported between males and females with VWD, with a significantly poorer score in women [13]. It is likely that this burden of morbidity reflects the adverse effects of menorrhagia. Over a third of women with inherited bleeding disorders had to cut down the time spent at work and other activities or accomplished less as a result of their menstruation [14].

Data on menstruation and the prevalence of menorrhagia in women on anticoagulant therapy is very limited. In a small study by van Eijkeren et al. [15], the mean menstrual blood loss measured by the alkaline hematin method was 98 mL (range, 9–239 m/L) in 11 women receiving anticoagulant therapy; five (45%) had menorrhagia (menstrual blood loss of more than 80 mL). Of the six women with normal menstrual loss, two had losses in the high-normal range (60–80 mL). In our center, nine (82%) of the 11 women on anticoagulant therapy had menorrhagia defined by a pictorial blood assessment chart score of greater than 100 (ongoing study). Five women developed intermenstrual bleeding, and six women reported adverse effect on their quality of life during menstruation after the start of their anticoagulant therapy.

Choices for contraception and the treatment options of menorrhagia in women on anticoagulant therapy are limited. Combined oral contraceptives are usually contraindicated because of their increased risk of thromboembolic disorders. Copper-containing intrauterine devices are associated with a further increase in menstrual loss. Many clinicians are also very reluctant to use antifibrinolytics in women with a thrombotic tendency. Progestogens alone are therefore the treatment of choice for these women.

4. Levonorgestrel intrauterine system for treatment of menorrhagia in women with hemostatic disorders

The LNG-IUS is well established as an effective, long-acting and reversible contraceptive. It is associated with a significant reduction in menstrual blood loss as early as the