Menorrhagia in women with congenital disorders of hemostasis

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Ovulation, menstruation, pregnancy and delivery, abortion, and post-partum period may be characterized by excessive bleeding in a “normal” woman and women with congenital disorders of hemostasis are definitely at greater risk. The most frequent problem for a woman during reproductive life is by far represented by menorrhagia. Menstruation is part of the hemostatic process. Formation of a platelet plug occurs by the interaction of platelets through glycoprotein receptors on platelet membranes with von Willebrand factor present on the subendothelium of the vessel wall of endometrium surface. Concomitantly, a fibrin clot is generated by thrombin formed by activation of the clotting system through FVII-Tissue factor pathway and the clot is part of the hemostatic plug together with the adherent platelets. Menorrhagia occurs in about 10% of women in the general population (1). It is subjectively reported as excessive menstrual blood loss, but this perception needs to be objectively assessed due to the different psychological and behavioral awareness of menstrual bleeding in a given woman. In the past, alkaline hematin extraction of hemoglobin from pads or towels has been used to quantitate menstrual blood losses. This method is however cumbersome, time-consuming, requires specialized lab and involves collection and saving of sanitary material by women. A pictorial blood assessment chart with semiquantitative assessment of blood losses has been recently adopted, with reasonable sensitivity and specificity (2). A consensus has been reached among the experts to define menorrhagia as menstrual blood losses > 80 ml by objective measurement. The relevance of such an objective definition is illustrated by the fact that up to 40% of women with losses greater than 80 ml may consider their period as moderate or scanty, and conversely, that 15% of women with losses < 20 ml may consider their period as “heavy” (1). Menorrhagia may be the presenting manifestation of a congenital bleeding disorder in women (3-5). In some studies, a primary coagulation defect was found in 20% of adolescents admitted to hospital for menorrhagia (6). Furthermore, menorrhagia is a valuable predictor for a bleeding disorder and is now considered as a sentinel symptom for inherited mild coagulopathies (4). In some studies, up to 20% of women with objectively documented menorrhagia may have mild von Willebrand disease (VWD) (6). In a recent study including 150 consecutive women with objectively confirmed menorrhagia without anatomical or hormonal causes, 14% had mild VWD and 3% mild FXI deficiency (4). Other studies, which adjusted VWF level by blood group, found a percentage ~ 10% of VWD (6). Thus, women with menorrhagia, especially if accompanied by other bleedings such as epistaxis or after tooth extraction, should be assessed for VWD or other inherited mild clotting factor deficiencies. The few data available on rarer inherited bleeding disorders (afibrinogenemia, FV, FVII, FX, FXIII, severe VWD) show high rates of menorrhagia (50 to 70% of cases) in the affected women (7-12). A lower prevalence is likely in women with FXI deficiency, characterized by an heterogeneous bleeding tendency not always directly related to the circulating FXI level (3). Female carriers of hemophilia A and B, which are X-linked bleeding disorders due to the deficiency of FVIII and FIX, usually do not suffer from bleeding symptoms. However, extreme Lyonisation is observed in about 10-15% of them and thus a bleeding tendency may occur when FVIII or FIX is < 20%. A recent Dutch study showed that hemophilia carriers with low FVIII/FIX levels more often reported excessive blood loss during menstrual period and that the risk of requiring iron suppletion was 80% increased in women with FVIII/FIX level ≤ 40% compared with those with a FVIII/FIX level ≥ 60% (13).

No data are available on the prevalence and severity of menorrhagia in patients with inherited mild platelet function defects (e.g., storage-pool disease). The rare patients with Bernard-Soulier syndrome (an autosomal recessive bleeding disorder caused by deficiency of glycoprotein lb on platelet membrane) and, especially, Glanzmann Thrombasthenia (an autosomal recessive bleeding disorder caused by the deficiency of glycoprotein IIb/IIIa on platelet membrane) may suffer from severe and recurrent uterine bleeding, requiring blood and platelet transfusions (14,15). Often, combined estroprogestinic treatment is not sufficient to completely avoid the risk of excessive bleeding associated with menstruation in these patients (16).

Women with menorrhagia due to a causative hemostatic bleeding disorder have a poor quality of life and the lack of recognition of the coagulation cause of the symptom may lead to inappropriate treatment (e.g. excessive number of hysterectomy). The treatment of menorrhagia rests on the use of antifibrinolytic aminoacids (e.g. tranexamic acid), correction, if present, of iron deficiency anemia, use of combined estroprogestinic pill, substitutive
treatment with appropriate factor concentrate or desmopressin. The latter compound has
been demonstrated to be safe and effective, when self-administered as nasal spray or by
subcutaneous route, as home-treatment in women with mild VWD or mild platelet dysfunction
disorders (17,18).

In conclusion, menorrhagia in women with congenital disorders of hemostasis is frequently
observed, even in mild deficiencies, and may often affect the quality of life. In some cases,
menorrhagia is the only significant bleeding observed and often prompts detailed
investigations which allows the demonstration of a specific hemostatic. Prompt diagnosis and
prophylaxis or treatment of menorrhagia may significantly improve the quality of life. For rarer,
severe inherited disorders of hemostasis gynecological complications are anticipated by the
diagnosis usually occurring in infancy so that specific prophylactic treatment can be efficiently
adopted in most cases.

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