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Challenges of diagnosing and managing the adolescent with heavy menstrual bleeding

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ABSTRACT

Unpredictable, prolonged or heavy menstrual bleeding (HMB) may be expected for many adolescents soon after menarche. A decade of clinical experience and research has now established firmly that bleeding disorders (BD) are common in adolescents with HMB. Despite these advances, many questions remain, and several aspects of the diagnosis and management of BDs in adolescents are not supported by rigorous clinical trials. In this overview, four major areas will be discussed. First, we will discuss the frequency of BDs in young women with HMB. Up to 20% of older females with HMB are thought to have an underlying BD. Estimates from retrospective studies in adolescents suggest a prevalence that varies anywhere from 10 to 62%. Prospective studies with uniform hemostatic evaluation are needed to answer this question definitively. Second, we will review existing tools that help screen and diagnose adolescents with HMB with an underlying BD. Although identification of an underlying BD in older women with HMB is relatively straight forward, uncertainties remain for adolescents. Heavy menstrual bleeding in this age group may have different pathophysiological underpinnings than those in older women and may often be disregarded as anovulatory. There is an urgent need to develop novel tools, and evaluate existing diagnostic strategies in adolescents. Third, we will discuss the optimal medical management of HMB in young adolescents. As direct evidence is largely lacking, these areas are also subject to extrapolation from older women. Lastly, an important area- prediction, and management of future bleeding in those adolescents who are diagnosed with a mild BD-will be discussed. Throughout, areas of controversy and opportunities for further research are highlighted.

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1. Introduction

Menstrual problems are common in adolescence [1,2]. Adolescents frequently have irregular and/or painful cycles, but occasionally experience unpredictable, prolonged or excessive menstrual bleeding that can become a medical emergency [3–6]. Heavy bleeding not requiring medical attention is also associated with significant morbidity [7]. Heavy menstrual bleeding (HMB) is often multifactorial [8]. Of the possible causes, anovulation is likely to be the most common reason for HMB in this age group [9] but other causes, such as an underlying bleeding disorder (BD), are often present. Menstruation disrupts blood vessels, restoration of which requires an intact hemostatic system and successful interaction of platelets, clotting factors and fibrinolytic proteins. Bleeding disorders are increasingly being recognized in women with HMB [10,11]. Up to 10–35% of women report HMB at some point during their reproductive lives and up to 20% of these are eventually diagnosed with a BD [12]. Although less likely to present with spontaneous bleeding, such disorders can become particularly severe after hemostatic challenges such as surgery, trauma, menses or childbirth. Management of HMB in undiagnosed disorders of hemostasis maybe associated with unwanted risks and complications [13]. A growing body of evidence suggests that 10–62% adolescents with HMB may have an underlying BD [14–17]. Advances have been made in the management in patients with HMB; however, challenges still prevail in achieving optimal recognition and management. In this review, we will focus on gaps that exist in our present understanding related to adolescents with HMB. We will do so by addressing four specific clinical questions.

2. Search Methods

An extensive PubMed search was conducted to identify pertinent literature and evidence to answer our clinical questions. The terms 'adolescents', 'young women', 'women' 'heavy menstrual bleeding', 'abnormal uterine bleeding', 'menorrhagia', 'severe menorrhagia', 'acute menorrhagia' were entered without temporal limits using English language restriction to ensure that all potential articles were identified. These terms were cross-referenced with von Willebrand disease (VWD), platelet function defects (PFDs), coagulation factor deficiency and connective tissue disorders. We also screened the reference lists of most relevant review articles on HMB in adolescents for further studies not captured in our initial literature search.

2.1. Clinical question no. 1: How common are bleeding disorders in young adolescents with heavy menstrual bleeding?

The majority of studies on diagnosis of BDs in women with HMB have focused on adults. There is mounting evidence that BDs are another common, yet unidentified cause of HMB in adolescents. Key advances in this field include a move toward development of multidisciplinary clinics specifically for adolescents and young women with HMB [18], looking for BDs beyond VWD and specifically, the incorporation of platelet aggregation and release testing to screen for PFDs [19]. Vo and colleagues retrospectively reviewed data on 105 adolescent girls aged 8–18 years without a known hematologic condition, referred to an adolescent hematology clinic for HMB [15]. Sixty-two percent of patients were diagnosed with a BD, including a relatively high proportion (36%) with platelet storage pool defects (PSPD). Young women with BDs in this study were more likely to report 'irregular' menstrual cycles compared to those without a bleeding disorder, a counter-intuitive notion that irregularity in cycles automatically signifies anovulation and not an underlying BD. Subjects with BDs perceived their periods as 'heavy' or 'very heavy' and most had ≥4 days of heavy bleeding per cycle. An important detail of this study was that the diagnosis of PSPD was based largely on platelet electron microscopy (EM) and platelet aggregation studies were not uniformly performed. The diagnosis of delta-granule storage pool deficiency was based on a local definition of an average of ≤3.68 delta granules per platelets. A lack of standardized reference ranges for platelet EM limits the widespread applicability of these results. In addition, of the 105 girls evaluated, 62% were diagnosed with a BD, a number which is much higher than the published prevalence of BDs in other studies of women with HMB. Additionally, personal histories of other bleeding or family history of bleeding were not obtained. Diaz et al performed a retrospective chart review of 131 girls with HMB aged 7–17 years of age [20]. First tier testing included screening coagulation studies and von Willebrand (VW) disease (VWD) panel (VW factor (VWF) antigen (Ag), VWF: ristocetin (RCo) co-factor activity and VWF multimers. VWD was diagnosed accordingly to NHLBI guidelines [21] with VWF: RCO and/or VWF antigen ≤30%. Whole blood platelet aggregation with secretion analysis was performed only after first tier testing was negative. The diagnosis of PFD required detection of at least 2 abnormalities in platelet aggregation and/or secretion as per published guidelines [22,23]. A hemostatic abnormality was identified in 53% of young girls with HMB - 21% with a definitive BD and 32% with a risk factor for bleeding, namely low VWF levels. This study also showed PFD to be the most common (11%) hemostatic disorder. No clinical variables were able to discriminate girls with or without a BD. It is well known that a higher percentage of patients are diagnosed with a BD when evaluated at Hemophilia Treatment Centers (HTCs) [24], so these numbers, 62% and 53% respectively, evaluated at multidisciplinary clinics are likely over representations. A more recent cross sectional study surveyed University students with pictorial blood assessment chart (PBAC) scores <100, who underwent hemostatic testing [25]. Nearly 14% of the study subjects were diagnosed with a BD. One could argue that a higher frequency of BDs in this 'general' cohort was due to the higher cut off (VWF: Ag and/or VWF: RCo <45% for type O and <50% for non-O blood types) selected for diagnosis of VWD but at the same time, PFD testing did not include release defects, so it is possible that a proportion of young women with a BD were also missed [25]. Table 1 provides an overview of all published studies of BDs in the adolescent age group.

Despite advances in the recognition and diagnosis of BDs in adolescents with HMB, problems persist. Prospective studies with objective menstrual flow and frequency assessments, and standardized hemostatic testing, particularly in terms of the laboratory definition of VWD, and the definition of a PFD are needed to determine the true frequency of BDs. Prospective studies are needed for both the primary care and HTC settings, as referral bias would be hard to eliminate in studies carried out at HTCs. Finally, given the escalating costs of laboratory testing, future studies should include a cost-effectiveness analysis [26].

2.2. Clinical question no. 2: how can we accurately identify and diagnose an underlying bleeding disorder in adolescents presenting with HMB?

It has been suggested that an underlying bleeding diathesis should be considered in the differential diagnosis of all women evaluated for HMB, regardless of age [27]. Wide ranges of reported prevalence, difficulty in discerning normal from excessive menstrual bleeding, the semi-empiric use of hormonal therapy and the mundane nature of the