Original Study

Levonorgestrel-Releasing Intrauterine Device Use in Female Adolescents with Heavy Menstrual Bleeding and Bleeding Disorders: Single Institution Review

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A B S T R A C T

Study Objective: To identify complications and efficacy of the levonorgestrel-releasing intrauterine device (LNgIUD) in adolescents with heavy menstrual bleeding (HMB) and bleeding disorders (BD).
Design, Setting, and Participants: A retrospective chart review of 13 postmenarchal adolescent girls with HMB/BD who underwent placement of an LNgIUD.
Interventions: Placement of an LNgIUD.
Main Outcome Measures: Primary outcome was to identify complications from placement of an LNgIUD. Secondary outcome was to evaluate the efficacy of the LNgIUD in adolescents with BD.
Results: Thirteen patients met study criteria. The mean age of diagnosis of HMB was 14.08 ± 1.75 years. BD or bleeding risk factor diagnoses included low von Willebrand (VW) activity in 5, type I VW disease in 5, type IIM VW disease in 1, low VW activity and factor 7 deficiency in 1, and acquired VW disease and factor 7 deficiency in 1. Before LNgIUD placement, other hormonal therapy (n = 13) and hemostatic therapy (antifibrinolytic agents, desmopressin acetate; n = 8) yielded poor control of HMB. The LNgIUD was placed using anesthesia with periprocedure hemostatic therapy with no complications. All patients reported significant improvement in HMB after LNgIUD placement and 60% achieved amenorrhea, with mean time to improvement of 94 ± 69 days. Mean hemoglobin and ferritin levels increased after LNgIUD placement compared with before LNgIUD placement values ($P = .02$, $P = .0085$, respectively). Use of supplemental hormonal and hemostatic agents decreased (n = 4) after LNgIUD placement. None required LNgIUD removal; 1 spontaneously expelled the LNgIUD with subsequent replacement.
Conclusion: Study results indicated the LNgIUD is an effective therapeutic option in postmenarchal adolescents with HMB due to BD/bleeding risk factor with minimal complications, high compliance rate, improvement in HMB and anemia, and no periprocedural bleeding with hemostatic management.
Key Words: Heavy menstrual bleeding, Adolescent, Levonorgestrel-releasing IUD, Bleeding disorder

Introduction

Heavy menstrual bleeding (HMB) is a common problem affecting women in their reproductive years with an estimated prevalence of 9%-14%.[1,2] In women with bleeding disorders (BD), the prevalence is much higher.[3,4] In the adolescent population, several studies have reported an increase of BD in patients who present with HMB with a prevalence ranging from 10%-48%.[5–9] In a study on causes of abnormal uterine bleeding in adolescents who were hospitalized for HMB, hematologic disease (33%) ranked second, next to anovulation (46%).[5] HMB is often the first sign in diagnosing adolescents with BD and it is estimated that 44% of adolescents who present to clinics with HMB might have an underlying coagulopathy.[8] Management options of HMB in adolescents with BD include hormonal and/or hemostatic treatment. Because of the desire to preserve future fertility, surgical management is reserved for life-threatening hemorrhage in the adolescent population. A common treatment for HMB is hormonal therapy, usually in the form of the combined oral contraception (COC) pill, containing estrogen and progesterone.[10] Management with COC in the adolescent often proves to be a challenge because of compliance. As a result, daily hormonal therapy might not be the best option in this unique group, and dire consequences such as need for transfusion and hemorrhagic shock might arise if the hormonal medication is not used appropriately to control HMB with menstrual cycles. This can cause significant distress, affect school performance, and affect quality of life in these adolescents affected by HMB. The use of subcutaneous depot medroxyprogesterone acetate and long-acting reversible contraception such as the etonogestrel implant or the levonorgestrel-releasing intrauterine device (LNgIUD)

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reduce the challenge of compliance. Long-acting reversible contraception is also noted to have the highest rate of satisfaction and continuation of all reversible contraceptives.[11]

Although increased uterine bleeding is a concern with placement of an intrauterine device in women with BD, studies exclusively on LNgIUD use in women with HMB due to inherited BD reveal it is an effective long-term treatment in this population. However, the median age of women in these studies were older than 38 years.[4,12] There are limited data on LNgIUD use in adolescents with HMB due to BD, with no study on this exclusive patient population. We hypothesized that the LNgIUD would be a safe, effective, alternate treatment option for HMB in adolescents with BD. We sought to test our hypothesis by conducting a retrospective chart review on adolescent girls with HMB/BD who underwent placement of an LNgIUD at our institution.

Materials and Methods

A retrospective chart review of postmenarchal girls aged 21 years or younger with HMB and diagnosis of BD and bleeding risk factors (RF) who subsequently underwent LNgIUD placement between May 2008 and December 2014 at our institution formed the study population. The LNgIUD (Mirena, Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ) is a T-shaped device containing 52 mg levonorgestrel that is placed within the uterine cavity and releases 20 μg of levonorgestrel every 24 hours over 5 years with daily plasma levels varying from 150 to 200 pg/mL. The study was approved by the institutional review board at Baylor College of Medicine. Charts were reviewed for basic demographic characteristics, laboratory studies including hemoglobin, hematocrit, ferritin levels, and pictorial blood assessment chart (PBAC) score before and after LNgIUD placement, HMB therapy before and after LNgIUD placement, periprocedure hemostatic therapy, intraoperative complications from LNgIUD placement, and outcome of HMB at last follow-up. Descriptive statistics and *t* tests were used; *P* value $< .05$ determined statistical significance.

Results

A total of 13 adolescent girls with HMB and a diagnosis of BD/RF were included in the study. Characteristics of the study population are shown in Table 1. The mean age of menarche of the study population was 10 ± 1.07 (range, 9-13) years. The mean age of diagnosis of HMB was 14.08 ± 1.75 years. BD/RF diagnoses included low von Willebrand (VW) activity in 5, type I VW disease (VWD) in 5, type IIM VWD in 1, factor 7 deficiency in combination with acquired VWD in 1, and low VW activity in 1 participant.

PBAC score before LNgIUD placement was available for 46% (6 of 13) of the girls with a mean score of 581.1 ± 376.6. For the remaining participants, description of bleeding from chart review was changing 1-2 pads every hour because of soiling during the menstrual cycle.

Before LNgIUD placement, 100% of the girls had tried other treatment modalities for HMB including hormonal therapy (COC pill, norelgestromin/ethinyl estradiol transdermal patch, etonorgestrel/ethinyl estradiol vaginal ring, progestin only pill, and depot medroxyprogesterone acetate or a combination of hormonal therapy; n = 13) and hormonal therapy combined with hemostatic therapy (desmopressin acetate, aminocaproic acid, tranexamic acid; n = 8), which yielded poor control of HMB.

Table 1
Characteristics of Adolescents with BD Who Received the LNgIUD for HMB

	N (%)
Age at menarche (years)	
Median	10
Range	9-13
Age at diagnosis of BD (years)	
Median	14
Range	12-17
Bleeding Disorder	
Low von Willebrand (VW) Activity	5 (38.5)
Type I VW Disease (VWD)	5 (38.5)
Type IIW VWD	1 (7.7)
Low VW and factor 7 Deficiency	1 (7.7)
Acquired VWD and factor 7 deficiency	1 (7.7)
Analgesia at time of insertion	
General anesthetic	13 (100)
Peri-procedure hemostatic treatment	
Desmopressin acetate	5 (38.5)
Aminocaproic acid	8 (61.5)
Tranexamic acid	5 (38.5)
HMB treatment: before/after LNgIUD	
Combined oral contraceptive pill	10 (76.9)/1 (7.7)
Ortho-Evra patch	4 (30.8)/0 (0)
NuvaRing	1 (7.7)/0 (0)
Progestin only pill	1 (7.7)/0 (0)
Depo, medroxyprogesterone	4 (30.8)/0 (0)
Desmopressin acetate	3 (23.1)/2 (15.4)
Aminocaproic acid	8 (61.5)/1 (7.7)
Tranexamic acid	3 (23.1)/2 (15.4)
Complications of LNgIUD insertion	
Bleeding, uterine perforation, malposition, infection, pelvic pain	0 (0)
Expulsion (subsequent replacement)	1 (7.7)

BD, bleeding disorders; HMB, heavy menstrual bleeding; LNgIUD, levonorgestrel-releasing intrauterine device; VW, von Willebrand; VWD, von Willebrand disease. NuvaRing is from Merck and Co, Inc (Kenilworth, New Jersey), and the Ortho-Evra patch is from Janssen Pharmaceuticals (Beerse, Belgium).

The LNgIUD was inserted in the operating room using general anesthesia in all participants because of the presence of a BD for placement in a controlled situation in the event of heavy bleeding. All participants received hemostatic prophylaxis periprocedure: 15.4% received desmopressin acetate (2 of 13), and all patients received antifibrinolytic agents (aminocaproic acid, 8 of 13 [61.5%]; and tranexamic acid, 5 of 13 [38.5%]). There were no periprocedure bleeding complications.

All patients reported significant improvement in HMB after LNgIUD placement with mean time to improvement of 94 ± 69 days (Fig. 1). Eight patients (61.5%) achieved amenorrhea or occasional spotting only. The mean hemoglobin after LNgIUD placement increased to 13.4 g/dL (range, 12.0-14.8 g/dL) from the mean hemoglobin before LNgIUD placement of 11.1 g/dL (range, 3.0-15.9 g/dL; Fig. 2*A*), which was statistically significant ($P = .02$). The mean ferritin level after treatment increased to 34.1 ng/mL (range, 12-67 ng/mL) from the mean ferritin level before treatment of 16.2 ng/mL (range, 2-28 ng/mL; Fig. 2*B*), which was statistically significant ($P = .0085$). The use of supplemental hormonal/hemostatic agents decreased after

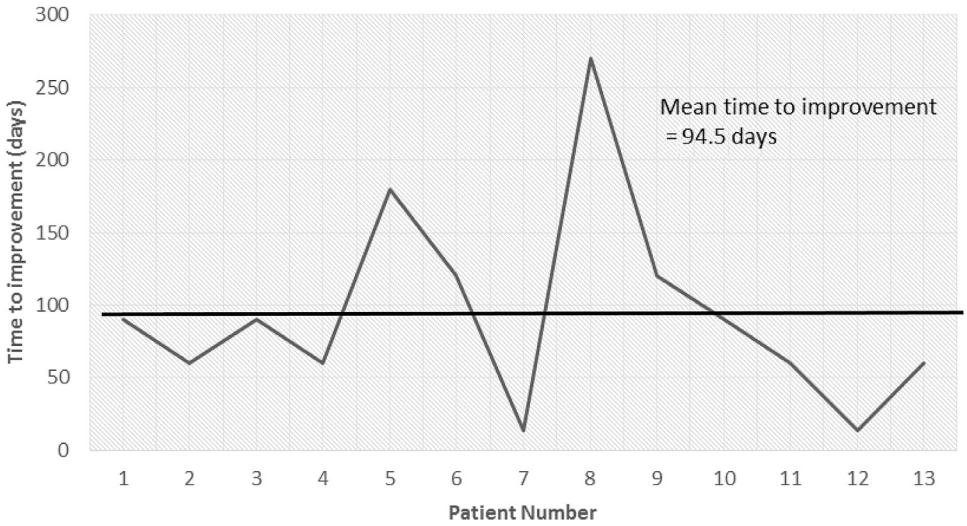

Fig. 1. Time to improvement in heavy menstrual bleeding after levonorgestrel-releasing intrauterine device insertion.

LNgIUD placement (n = 4). Two patients required tranexamic acid for occasional spotting, 1 patient required a course of desmopressin, and another required a COC taper, aminocaproic acid and tranexamic acid for light breakthrough bleeding after LNgIUD placement. None required LNgIUD removal; 1 patient spontaneously expelled the LNgIUD but had subsequent successful replacement. No patient was found to have other complications after LNgIUD placement including severe bleeding, uterine perforation, malposition, infection, or pelvic pain.

Discussion

The LNgIUD has been reported to increase hemoglobin concentration and serum ferritin levels, significantly reduce menstrual blood loss, and improve quality of life.[13,14] Currently there are limited data on the use of LNgIUD in women with BD and no dedicated studies in adolescents with BD.

Case reports of adolescents with BD who had LNgIUD placed reported significant improvement in HMB.[15,16] Historically, there has been a reluctance to place intrauterine devices in adolescents because of provider concern for pelvic inflammatory disease, perceived difficulty in insertion because of nulliparity, and the risk of expulsion.[17,18] A retrospective review of 233 adolescent and young women ages 11-21 years who underwent LNgIUD placement reported that it is a safe and reliable option in this patient population with few complications and no serious adverse events.[19] The American College of Obstetricians and Gynecologists Committee on Adolescent Health Care supports LNgIUD use in appropriate candidates with HMB including adolescent girls.[11,20] and it is our institutional practice to offer this choice of hormonal therapy to adolescents, including those with HMB and BD. The lack of information in the literature prompted us to review our experience in this patient population, to analyze the benefits and risks of LNgIUD in adolescents with HMB and BD.

The LNgIUD has been reported to be efficacious in controlling menstrual bleeding in adult women with HMB.[1,12,21] These studies reported decreased number of bleeding days or amenorrhea and an improvement in quality of life. Kingman et al[12] performed a prospective pilot study on 16 women aged 15-50 years (mean age, 30.8 years) with inherited BD, who had an LNgIUD inserted after other medical treatment had failed. Over a 9-month follow-up period, 56.3% (9 of 16) became amenorrheic with the remaining showing an improvement in the PBAC score. All women showed significant improvement in hemoglobin concentration, and none reported side effects. Our study showed similar findings, that the LNgIUD can be used as effective therapy for HMB in adolescents with BD, with 60% of the patients achieving amenorrhea or occasional spotting. In addition, higher ferritin and hemoglobin levels and improved quality of life were noted in the adolescents after insertion.

Reported adverse effects of the LNgIUD in women with hemostatic disorders include potential risk of bleeding at the time of insertion, expulsion, irregular spotting/bleeding, persistent/recurrent HMB, ovarian cysts, and potential risk of recurrence of thrombotic disease.[3,22] Patients with BD are potentially at risk of bleeding at the time of insertion. Chi et al specifically investigated the response to hormonal and nonhormonal treatment in adolescents with HMB due to BD.[23] Of the 153 adolescents studied, 5 (ages 16-19 years) had the LNgIUD placed. All were given hemostatic prophylaxis prior to intrauterine device placement, 2 had placement using general anesthesia, and the remaining 3 had placement using local anesthetic in the clinic setting. No complications including bleeding during placement were reported. In another study,[4] reporting on 3-year long-term follow-up of LNgIUD use in 26 adult women with BD, prophylactic hemostatic coverage was given to 81% of the participants (21 of 26) at the time of insertion. No bleeding insertion complications were reported. In our study, all patients had placement of the LNgIUD using general anesthesia with prophylactic hemostatic coverage; there were

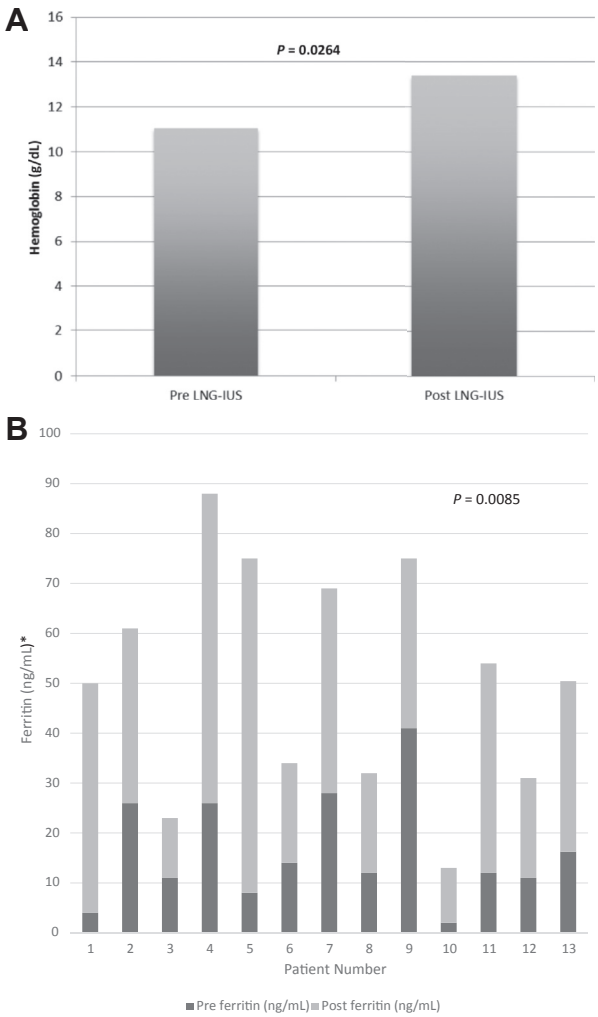

Fig. 2. (A) Hemoglobin concentration before (Pre LNG-IUS) and after (Post LNG-IUS) levonorgestrel-releasing intrauterine device insertion. (B) Serum ferritin levels before (Pre ferritin) and after (Post ferritin) levonorgestrel-releasing intrauterine device insertion. * Normal reference range, 10-70 ng/mL.

no bleeding insertion complications intraoperatively or periprocedure. Comanagement with a hematologist is essential to optimize periprocedure hemostasis on the basis of the type of BD, and this will help avoid periprocedure bleeding and might in turn contribute to successful insertion of the LNgIUD.

Another concern in placing the LNgIUD in patients with BD is persistent/recurrent HMB. Schaedel et al[24] performed a retrospective study on 28 women with hemostatic disorders after placement of the LNgIUD for HMB spanning 6 years; 68% (19 of 28) experienced improvement. Of these 19 patients, 7 had the initial LNgIUD removed for varying reasons ranging from breakthrough/irregular bleeding, increased bleeding, lost coil strings, and severe back pain. Nonetheless, all patients in this study reported that replacement of the LNgIUD reversed their previously reported symptoms that had prompted their removal request. In our study all of the adolescents experienced less bleeding. PBAC score before LNgIUD placement was available for 46% (6 of 13) of the girls with a mean score of 581.1 ± 376.6, confirming severe HMB in these patients. PBAC score has been shown to be an accurate perception of the degree of menstrual blood loss and a score greater than 100 has been associated with clinically significant HMB.[25] After insertion, 60% (8/13) became amenorrheic and an increase in hemoglobin concentration was noted. Because our study was a retrospective review, PBAC score after LNgIUD placement was not uniformly available in all patients but this can be used as a measure to assess response to LNgIUD in future trials because the score can play a role in diagnosing and monitoring response to treatment in patients with HMB.[25]

Expulsion and malposition are well recognized side effects of LNgIUD placement. In 2013, Rimmer et al[26] evaluated expulsion rates in women with BD who had an LNgIUD placed; this was the first study to investigate expulsion and malposition specifically in women with BD. Of the 20 women with complete follow-up, 3 had expulsion (15%). When rates of malposition were included, the rate increased to 25% (5 of 20), which was higher than the previously reported expulsion rates among women without BD of 5%-10%. In the study by Chi et al[4] expulsion of the intrauterine device occurred in 8% (2 of 26). In our study, there were no discontinuations and our expulsion rate was low at 7.7% (1 of 13). This is considerably lower than in the study by Rimmer et al[26] and similar to the study by Chi et al.[4] In addition, there were no reports of infection and no participants in our study experienced severe bleeding after insertion.

To our knowledge, this study is the first to investigate the efficacy and complications of the use of the LNgIUD in an exclusive adolescent population with HMB and BD. Notable shortcomings of our study are the small sample size and the retrospective nature of the study. Because BD are relatively uncommon, a prospective, multicenter study would enable inclusion of a larger number of adolescents with BD and HMB and complete analysis of all variables to confirm our study findings regarding the efficacy and side effects of the LNgIUD. Long-term outcome data in our patient population is not yet available, and continued follow-up of our patients is planned to assess long-term efficacy. In conclusion, our study results indicate that the LNgIUD can be an effective therapeutic option to reduce HMB in adolescents with BD. In addition, it appears to be associated with minimal complications, good compliance rate, and improvement in anemia. Appropriate hemostatic therapy for insertion administered in conjunction with a hematologist can decrease or avoid periprocedure bleeding complications.

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