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Review article

Use of Levonorgestrel Intrauterine System for Medical Indications in Adolescents

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A B S T R A C T

The levonorgestrel intrauterine system (LNG-IUS) is an underused contraceptive method in adolescent populations. In addition to being a highly effective, reversible, long-acting contraception, the LNG-IUS has many noncontraceptive health benefits including reduced menstrual bleeding, decreased dysmenorrhea and pelvic pain related to endometriosis, and menstruation suppression in teens with physical or developmental disabilities. The LNG-IUS can also provide endometrial protection in teens with chronic anovulation, and may be used to treat endometrial hyperplasia and cancer. This review examines the evidence supporting the use of the LNG-IUS in adolescents for these noncontraceptive benefits.

The levonorgestrel intrauterine system (LNG-IUS) (Mirena [Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ]) is an alternative means of providing many noncontraceptive health benefits that adolescents experience with oral contraceptive pills (OCPs), the most popular form of birth control among adolescents [1]. Among teen OCP users, 82% report using the pill for noncontraceptive reasons, most commonly for menstrual pain (47%) and menstrual regulation (40%) [2]. However, OCP compliance among adolescents is particularly poor, with a reported average of three missed pills per month and discontinuation rates of 67%–88% at 12 months [3,4]. In addition, not all adolescents may be candidates for OCPs, such as those with migraine headache with aura, coagulopathies, or other medical comorbidities [5].

The LNG-IUS is a T-shaped device with a vertical stem containing a reservoir of 52 mg levonorgestrel, which initially releases 20 μg levonorgestrel per day and is effective for 5 years of use [6]. The LNG-IUS causes a profound suppression of the functional endometrium as well as thickening of the cervical mucus [6,7]. This local effect on the endometrium contributes to its high efficacy as contraception, as well as its noncontraceptive health benefits. This article summarizes these noncontraceptive benefits of the LNG-IUS and examines the evidence supporting this use in adolescents.

Heavy Menstrual Bleeding

Assessing menstrual irregularities in adolescents is difficult because of the normal variability in cycle length before the establishment of consistently ovulatory cycles. In adults, the mean blood loss per menstrual cycle is 30 mL and chronic blood loss of >80 mL is associated with anemia [8]. Practically, menstrual bleeding requiring a change of pad or tampon every 1–2 hours is considered excessive, especially if menstrual duration is >7 days [8]. Menorrhagia or heavy menstrual bleeding (HMB) in adolescents is most often associated with anovulation and bleeding disorders [9,10]. Anovulatory but reasonably regular bleeding with a statistically derived normal cycle length of approximately 20–45 days in teens is common in early cycles and may not necessitate treatment [11]. However, significant deviation outside the parameters noted above may

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represent disease, including early manifestations of common conditions including polycystic ovary syndrome (PCOS) or eating disorders, as well as uncommon conditions such as primary ovarian insufficiency [11]. Consideration should be given to evaluating cycles with a length >90 days before the initiation of therapy (either combination hormonal therapy or the LNG-IUS), because this represents the 95th percentile for cycle length, even in the first gynecologic year [8].

Heavy menstrual bleeding in adolescents is also associated with bleeding disorders [9,10], although the subjective nature of quantifying menstrual loss makes this assessment challenging. The prevalence of bleeding disorders in adolescents with HMB ranges between 10.4% and 48% [12,13]. Of adolescents presenting with menstrual hemorrhage at menarche, nearly 50% were found to have a bleeding disorder [14]. von Willebrand disease and platelet dysfunction represent the most common bleeding disorders; factor deficiencies are less common [12,14,15]. von Willebrand disease occurs in about 1% of the general population and frequently presents with HMB in the adolescent years.

The use of LNG-IUS has been well studied in the treatment of idiopathic HMB in adults. A reduction in menstrual blood up to 86% at 3 months and 97% at 12 months has been reported by one study involving women with a mean age of 38 years [16]. Another study demonstrated an 83.8% decrease in menstrual blood loss at 12 months and an 85% decrease at 36 months in women with a mean age of 35 years, who used LNG-IUS [17]. In addition, those women in the study who used LNG-IUS had a significant increase in hemoglobin concentration and serum ferritin level. When comparing LNG-IUS with low-dose combined OCPs in adult women aged 20–50 years with HMB, the mean reduction in menstrual blood loss in the LNG-IUS group was significantly greater compared with the OCP group at 12 months (87.4% versus 34.9%; $p = .013$) [18]. Similarly, a Cochrane review concluded that LNG-IUS was more effective than cyclic norethindrone as treatment for HMB [19].

Unfortunately, there are no dedicated studies on the use of LNG-IUS in adolescents with HMB. However, one study that randomized young women (18–25 years old) with regular menstrual cycles to receive LNG-IUS or OCPs for contraception reported a significantly higher rate of decreased bleeding in the LNG-IUS group (49.3% versus 22%; $p = .001$), although bleeding was assessed subjectively [20]. In a New Zealand cohort study of 133 adolescents who received LNG-IUS, 58% of subjects identified HMB as the primary indication for use [21]. Although limited conclusions can be drawn from this study, it is worthwhile to report an 85% continuation rate at 1 year, which suggests a high level of efficacy.

Growing evidence supports the use of LNG-IUS for HMB in women with bleeding disorders [22,23]. There have been four published studies, totaling 77 subjects, on bleeding disorders among adults treated with LNG-IUS [23–26]. A decrease in menstrual blood loss was reported in 68%–100% of these subjects. Up to 56% reported amenorrhea at 9 months, with an associated increase in hemoglobin concentrations [26]. In looking at long-term efficacy and safety, one study observed 26 adult women with inherited bleeding disorders treated with LNG-IUS for >12 months [23]. Only three of 26 women experienced a return of heavy bleeding before 5 years, which resolved with replacement of the LNG-IUS. One additional study looked specifically at different treatments for HMB in adolescents with bleeding disorders [27]. The study included five adolescents (four with von Willebrand disease and one with hemophilia A carrier) who were treated with LNG-IUS after failing other medical management. All of the adolescents reported a reduction in menstrual blood loss with no adverse effects except irregular bleeding, which was well tolerated.

There are potential safety concerns regarding the use of LNG-IUS in women with bleeding disorders, including bleeding risk at time of insertion. This is particularly important for women with severe inherited bleeding disorders, who may require hemostatic coverage for the insertion. In a series of 26 adult women with inherited bleeding disorders, "prophylactic hemostatic cover" with tranexamic acid with or without desmopressin was successfully used in 21 women with severe disorders for the insertion of LNG-IUS [23]. The remaining five women had mild bleeding disorders and did well without such prophylactic coverage. Another potential concern with using LNG-IUS in women with severe bleeding disorders is the increased risk of ovarian cyst formation, which is reported in about 12% of all users [28,29]. Although most of these cysts resolve spontaneously, for women with severe bleeding disorders, there is a potential risk of hemorrhage into the cyst [22,30,31]. Suggested management options include ultrasound screening for women at high risk for bleeding, as well as ovarian suppression with combined hormonal contraception to prevent the formation of hemorrhagic ovarian cysts [23,32].

Dysmenorrhea and Endometriosis

Dysmenorrhea, or painful menses, is the most common gynecologic problem among adolescents, with a reported prevalence between 60% and 93% [33–36]. Dysmenorrhea is the leading cause of recurrent short-term school absenteeism and can significantly interfere with daily life activities [33,34]. Primary (or functional) dysmenorrhea accounts for most cases of dysmenorrhea among adolescents. It is associated with normal ovulatory cycles and no pelvic pathology, and has a clear pathologic etiology involving an overproduction of prostaglandins within the endometrium [33,37].

Secondary dysmenorrhea may account for at least 10% of adolescents with dysmenorrhea, and refers to painful menses associated with pelvic abnormalities, most commonly endometriosis [38,39]. Biopsy-proven endometriosis has been diagnosed in patients as young as 10 years old [40]. Although it is difficult to determine the incidence of endometriosis in adolescents, it has been reported as high as 45%–70% in a referral population for chronic pelvic pain [41].

Data specifically examining the use of LNG-IUS for dysmenorrhea are limited. However, the secondary outcome of reduction in dysmenorrhea has been reported in numerous LNG-IUS trials [42–47] and observational studies [48–50]. One study looking at long-term acceptability of LNG-IUS in women (25–47 years old) found a reduction in menstrual pain from 60% before use to 29% at 36 months of use [49]. Specific to adolescent and young adult females (18–25 years old), a randomized trial to receive LNG-IUS or OCPs for contraception demonstrated a more significant alleviation of dysmenorrhea in the LNG-IUS group at 1 year ($p = .021$) [20].

More evidence exists regarding the use of LNG-IUS for the treatment of pain related to endometriosis in adults, although data are limited by small sample sizes. Several prospective studies have demonstrated a decreased rate in dysmenorrhea and pelvic pain related to endometriosis with the LNG-IUS [51–54]. There has been one randomized controlled trial