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Original Article

The Levonorgestrel Intrauterine System is an Effective Treatment in Women with Abnormal Uterine Bleeding and Anticoagulant Therapy

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ABSTRACT **Objective:** To evaluate the efficacy of levonorgestrel intrauterine systems (LNG-IUS) in obese women with AUB on anticoagulant therapy.

Design: Prospective observational case series (Canadian Task Force Classification II-3).

Setting: University affiliated teaching hospital.

Patients: Premenopausal women on Warfarin therapy.

Interventions: From January 2002 through January 2007, 10 women were identified from the senior author's clinical practice (G.A.V.). After clinical assessment, including Papanicolaou smear, endometrial biopsy, and pelvic sonography, the LNG-IUS was placed to treat their AUB.

Measurements and Main Results: The median and range of age, parity, and body mass index were 45 years (34-49), 1 (0-4), and 38 kg/m^2 (26-52), respectively. All women were receiving warfarin therapy (4-12.5 mg/d) for previous venous thromboembolism. Some patients had additional comorbid conditions and were at high risk for traditional medical or surgical therapies. After placement of the LNG-IUS, all women reported menstrual reduction at 3 and 6 months. By 12 months, 1 woman with large fibroids expelled the LNG-IUS and was treated with transfemoral uterine artery embolization. Two women had amenorrhea, and 7 had hypomenorrhea. At 2 to 5 years, 1 woman expelled the LNG-IUS and hysterectomy indicated extensive adenomyosis in a 195-g uterus, and 1 woman had hysteroscopic endometrial ablation, 4 were menopausal, 2 had amenorrhea, and 1 had hypomenorrhea. In the 5 women with uterine fibroids measuring 4.2 to 147 cm^3, the fibroids were reduced in volume by approximately 75% in 2, were no longer detectable in 1, were subsequently shown to be adenomyoma in 1, and required uterine artery embolization in 1.

Conclusion: In properly assessed and selected obese, premenopausal women with AUB receiving warfarin therapy and at high risk for traditional therapies, the LNG-IUS was an effective treatment in 70% of patients. Journal of Minimally Invasive Gynecology (2009) 16, 480–484 © 2009 AAGL. All rights reserved.

Keywords: LNG- IUS; Mirena; Menorrhagia; Warfarin; Thromboprophylaxis; Anticoagulant

Abnormal uterine bleeding (AUB), defined as change in any or a combination of frequency, duration or amount of bleeding is experienced by approximately 20% to 30% of premenopausal women [1,2]. In general, AUB is a common debilitating condition that results in reduced hemoglobin, adversely affects quality of life, and is associated with significant use of health care resources. The prevalence of AUB increases with age and peaks just before menopause in accordance with changes in steroidogenesis and serum sex hormones or lack of ovulation and serum progesterone [1,2].

In general, the menstrual cycle and amount of menstrual blood loss (MBL) are regulated by cyclic ovarian response to extraovarian stimuli and production of estrogen and progesterone. AUB then can be modulated by partial or complete suppression of ovarian steroidogenesis with a variety of agents including combined oral contraceptives, progestins, androgens (danazol) or gonadotropin-releasing hormone agonists [1,2]. In the presence of intrauterine polyps, found in 25% to 35%, and leiomyomas, found in 15% to 30% of

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women with AUB [3], effective treatments include hysteroscopic surgery or hysterectomy. In the absence of intrauterine disease, medical therapies, levonorgestrel intrauterine systems (LNG-IUS), and hysteroscopic and nonhysteroscopic endometrial ablation enjoy certain degrees of popularity in accordance with personal experience, training, expertise, and bias [1].

Among the general population of women with AUB, gynecologists occasionally encounter women with morbid conditions and ailments that may contribute to AUB in conjunction with age and hormonal, metabolic, and body mass index (BMI) changes. Such cases may include neuromuscular or bleeding disorders, cerebrovascular accidents, and thromboembolic events that may require prolonged thromboprophylaxis with anticoagulant agents. Under such circumstances, traditional therapies may be contraindicated, ineffective, refused, difficult, or quite risky to administer or perform.

In this study we report our experience with 10 women with AUB, and various comorbidities and conditions, all of which required continuous warfarin therapy, treated with LNG-IUS (Mirena; Bayer Shering Pharma AG, Berlin, Germany). Review of these patient's records was approved by our university ethics committee (HSREB 13849 E).

Measurements and Main Results

From January 2002 through January 2007, we identified 10 women with AUB requiring thromboprophylaxis from the senior author's clinical practice (G.A.V.) at a university-affiliated teaching hospital. The median for age, parity and BMI were 45 years, 1 child (range 0-4), and 38 kg/m^2 (range 26-52), respectively. All women had experienced a variety of thromboembolic events including deep vein thrombosis, pulmonary embolism, or stroke and required continuous thromboprophylaxis with warfarin 4 to 12.5 mg daily. In addition, patients had a variety of comorbid conditions including diabetes, nephropathy, asthma, hypertension, angina, gastroesophageal reflux, atrial fibrillation, and depression. Two women with advanced multiple sclerosis were confined to wheelchairs with indwelling Foley catheter and were totally incapable of caring for themselves. Their menstrual bleeding was a major problem for themselves and their caregivers. All patients had Papanicolaou smear, endometrial biopsy, and sonohysterography before placement of the LNG-IUS. Endometrial histologic study was proliferative in 6, secretory in 3, and simple hyperplasia in 1. In 5 women, uterine fibroids were reported ranging in volume from 4.2 to 147 cm^3. The demographics, assessment and clinical outcomes of the 10 women are listed in the Table.

All women were reassessed at 3, 6, and 12 months and annually thereafter. At 3 months, all women reported significant menstrual reduction. At 6 to 12 months, a 45-year-old woman with the 2 largest fibroids measuring 75 cm^3 and 147 cm^3, respectively, expelled the LNG-IUS, and she was successfully treated with uterine artery embolization for unpredictable bleeding. Two women had amenorrhea, and 7 had further reduction of their bleeding. At 2 to 5 years, a 34-year-old woman expelled the LNG-IUS, and hysterectomy revealed extensive adenomyosis in a 195-g uterus. A 42-year-old woman underwent hysteroscopic endometrial ablation for unpredictable spotting, 4 women reached menopause, 2 had amenorrhea, and 1 had hypomenorrhea.

Two women with fibroids (patients 4 and 5) reached menopause, and their fibroids were reduced by approximately 75% in volume. In a third woman (patient 10) the fibroid was no longer detectable by transvaginal sonography. One woman (patient 8) with simple endometrial hyperplasia and a uterine mass of 31 cm^3 had development of hypomenorrhea but spontaneously expelled the LNG-IUS at 24 months. After vaginal hysterectomy, the uterus, weighing 195 g, showed extensive adenomyosis and proliferative endometrium with no evidence of leiomyoma or endometrial hyperplasia. The fifth woman (patient 9) with large fibroid uterus had development of hypomenorrhea but subsequently requested uterine artery embolization at 12 months for unpredictable spotting.

Discussion

Traditionally, premenopausal healthy women with AUB from benign causes are managed quite effectively with a variety of treatments including oral, transdermal, or injectable medications, intrauterine hormone-releasing systems, and surgical interventions including hysteroscopic and nonhysteroscopic procedures or hysterectomy [1]. However, gynecologists occasionally are faced with women experiencing AUB with multiple health disorders and ailments in which most of the above traditional therapies are contraindicated or quite risky to administer.

In this study, the senior author (G.A.V.) was referred 10 women with AUB, and a variety of comorbidities including obesity, all of whom required thromboprophylaxis for previous thromboembolic events. Under these conditions, estrogens are contraindicated because they increase the risk of thromboembolism, injectable agents cause injection site bleeding and hematomas, and surgical treatments require temporary discontinuation or alteration of the anticoagulants. Therefore the choices for contraception and treatment options for women with AUB on anticoagulant therapy are very limited. Under such circumstances, oral progestins or LNG-IUS may be the least risky choices of therapy, but data on their use and efficacy remain quite scanty.

LNG-IUS consists of a polyethylene, barium-coated frame (32 $\times$ 32 mm) to make it radiopaque with a containing reservoir (52 mg) around its vertical stem [4]. The system initially releases levonorgestrel approximately 20 μg/d via a drug-controlling membrane, decreasing to approximately half of that by 5 years and to less than 10 μg/d from 5 to 7 years. The average release within the first 5 years is approximately 14 μg/d. Interestingly, clinical observations indicate that the efficacy of the LNG-IUS may diminish after the third year of placement for noncontraceptive uses (personal observations). LNG is absorbed from the uterine cavity very

Table
Ten obese premenopausal women with AUB and thromboprophylaxis treated with LNG-IUS

Date	Age (Yrs)/ Parity	BMI kg/m^2	Comorbidities	Pre-LNG-IUS Endometrial Biopsy	Clinical Outcomes (months)						
					3	6	12	24	36	48	60
01/2002	47/4	28	DVT/PE Diabetes, MS Nephropathy	Proliferative	Hypomen	Hypomen	Hypomen	Hypomen	Ameno	Menopause	Died from Nephropathy
02/2003	48/3	37	DVT, Asthma Hypertension	Secretory	Hypomen	Hypomen	Hypomen	Hypomen	Ameno	Menopause	Ameno
01/2004	42/1	26	DVT, Stroke Atrial fibrillation	Proliferative	Hypomen	Hypomen	Hypomen	Hypomen	Hypomen	Hypomen	
02/2004	45/0	52	DVT, PCOS Fib. 38 cm^3	Secretory	Hypomen	Hypomen	Hypomen Fib. 13 cm^3	Hypomen Fib. 10 cm^3	Menopause Removed Fib. 10 cm^3	Menopause	Menopause
11/2004	49/1	38.1	DVT Fib. 12 cm^3	Proliferative	Hypomen	Ameno	Ameno Fib. 14 cm^3	Ameno	Ameno Fib. 3 cm^3	Menopause	
7/2004	42/3	32.4	DVT/PE, MS	Proliferative	Hypomen	Hypomen	Hypomen	Menorrhagia HEA			
09/2005	41/0	48.5	DVT Depression	Proliferative	Hypomen	Ameno	Ameno	Ameno	Ameno		
07/2005	34/1	41	DVT/PE ? Fib. 31 cm^3	SEH	Hypomen	Hypomen	Hypomen	Expelled Hysterectomy Uterus 195 g Adenomyosis			
11/2005	45/3	36.6	DVT, Stroke Fib.1, 147 cm^3 Fib.2, 75 cm^3	Proliferative	Hypomen	Hypomen Expelled	Menorrhagia UAE	Hypomen Fib. 1.60 cm^3 Fib. 2.15 cm^3			
01/2007	47/1	39	DVT, Hypertension Fib. 4.2 cm^3	Secretory	Hypomen	Hypomen	Hypomen	Ameno. Fib. 0 cm^3			

MS = Multiple sclerosis; SEH/CEH = simple/complex endometrial hyperplasia; DVT/PE = deep vein thrombosis/pulmonary embolism; HEA = hysteroscopic endometrial ablation; UAE = uterine artery embolization; Fib. = fibroid; Ameno = amenorrhea; Hypomen = hypomenorrhea.

rapidly, reaching sustained serum levels of 150 to 200 pg/mL within a few hours of placement [5,6].

The effects of LNG-IUS in women with menorrhagia has been reviewed from both cohort and randomized studies. In general, after placement of the LNG-IUS in women with menorrhagia, MBL was reduced by 79% to 97%, with patient satisfaction and continuation rates being 72% to 94% and 65% to 88%, respectively [7-12]. On the basis of the above evidence and on the limited treatment options, in our group of 10 women we elected to use the LNG-IUS after obtaining informed consent. A literature search revealed 1 case report of apparent interaction between warfarin and levonorgestrel. A 35-year-old woman was taking warfarin 7 mg daily. After 2 doses of levonorgestrel 0.75 mg given 12 hours apart for emergency contraception, the woman's international normalized ratio rose from 2.1 to 8.1 in 3 days [13]. Current evidence suggests that the risk of thromboembolism is not increased in patients using levonorgestrel containing oral contraceptives [14]; however, there is no evidence to support the same in women who already had a thromboembolic event and are currently on thromboprophylaxis.

Association of menstrual bleeding and anticoagulant therapy has been reported in a small number of women. Van Eijkeren et al [15] measured MBL in 6 premenopausal women with various congenital or acquired bleeding disorders and in 11 women using oral anticoagulant therapy. The mean MBL, by alkaline hematin method, was 98 mL (9-239 mL) in women receiving anticoagulant therapy. Five (45%) had menorrhagia (MBL $>$ 80 mL). Of the remaining 6 women, 2 had blood losses in the high normal range (60-80 mL). The authors concluded that oral anticoagulants increase MBL [15].

Kadir and Chi [16] in a review article reported that 9 of 11 (82%) women with bleeding disorders on anticoagulant therapy had menorrhagia (pictorial blood loss assessment chart score $>$ 100). Five women had development of intermenstrual bleeding, and 6 reported adverse effects on their quality of life during menstruation after the start of their anticoagulant therapy [16]. Because the prevalence of menorrhagia in the general population is 20% to 30%, the above studies indicate that bleeding disorders and anticoagulant therapy significantly increase the risk of AUB up to 80%.

The efficacy and use of the LNG-IUS in anticoagulated women with bleeding disorders has been reported in small studies. Pisoni et al [17] treated 16 women with menorrhagia associated with warfarin with the LNG-IUS. The LNG-IUS treatment was associated with a reduction of MBL in 87% of women, 4 (25%) of whom became amenorrheic, and 75% were very satisfied or satisfied with their treatment. In a follow-up study, the same authors reported on 17 women with menorrhagia on warfarin therapy. MBL was reduced in 10 (58.8%) women, with 4 (23.5%) reporting amenorrhea, no change in MBL in 1 (5.9%), increase in MBL in 2 (11.8%), and 2 did not remember. Twelve (70.6%) women were either very satisfied or satisfied with the LNG-IUS therapy [18].

Shaedel et al [19] reported on 2 women with hemostatic disorders on warfarin with the LNG-IUS. The LNG-IUS was removed 7 days after placement in 1 woman because of abdominal pain and 1 month later in the other because she had development of transverse sinus thrombosis. Nineteen of 28 (68%) women with hemostatic disorders (not on anticoagulants) experienced improvement of menstrual bleeding with the LNG-IUS [19].

Finally, Lukes et al [20] reported on 7 premenopausal women with hemostatic disorders and AUB treated with the LNG-IUS. Four women were using anticoagulants, 3 warfarin and 2 aspirin. A reduction of BML and improved quality of life was reported by 5 (71%) women [20].

Based on the above limited data, Kadir and Chi [16] in their review article concluded that the LNG-IUS is a safe and attractive option for women with hemostatic disorders, which may obviate the need for surgical interventions in these women. Their review, however, did not include any women without bleeding disorder and previous thromboembolism requiring current anticoagulants.

To our knowledge, this is the first report of women with AUB, without apparent hemostatic disorders requiring thromboprophylaxis treated with the LNG-IUS. As the table indicates, all women had comorbid conditions that may or may not have contributed to their AUB and MBL. One patient with insulin-dependent diabetes had multiple sclerosis and end-stage nephropathy. After placement of LNG-IUS, the insulin requirements did not change. A randomized trial demonstrated that the LNG-IUS had no adverse effect on glucose metabolism in diabetic women at either 6 weeks or 6 months [21].

All of our patients were overweight (BMI $>$ 25 kg/m^2). Eight were obese (BMI $>$ 30 kg/m^2), and 6 were morbidly obese (BMI $>$ 35 kg/m^2). As a rule, obesity is associated with many chronic diseases, as well as clinical conditions including venous thromboembolism, diabetes, hypertension, and menstrual disorders including uterine neoplasia [22]. Obesity currently is reaching epidemic proportions in the developed world. In 1999 to 2002, 62% of U.S. women aged 20 years or older were overweight (BMI $>$ 25 kg/m^2), and 30% were obese (BMI $<$ 30%/m^2) [22]. Under the circumstances, health care providers will encounter more and more women with similar conditions and ailments to those of our present study. Our experience therefore with this small group of patients, indicating that 7 of 10 women (70%) were effectively and safely treated with the LNG-IUS, may be of considerable benefit and value to both patients and therapists.

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