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Bleeding patterns with the levonorgestrel-releasing intrauterine system when used for heavy menstrual bleeding in women without structural pelvic pathology: a pooled analysis of randomized controlled studies☆

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Abstract

Background: The study was conducted to characterize the changes in bleeding pattern over time in women receiving the levonorgestrel-releasing intrauterine system (LNG-IUS) for heavy menstrual bleeding (HMB). The reduction in menstrual blood loss volume has been well documented elsewhere.

Study Design: Post hoc pooled analysis of the impact of the LNG-IUS on bleeding patterns in four comparator studies of medical and surgical treatment options for HMB. We enrolled women aged ≥ 18 years with HMB without organic pathology. The change in the number of bleeding and spotting (B/S) days and bleeding patterns was assessed over the duration of the studies pooled.

Results: One hundred and sixty-three women received the LNG-IUS in randomized trials. Relative to pretreatment baseline, there was a transient increase in the mean number of bleeding days in the first month of treatment, which returned to baseline by the second month and declined thereafter. Although the number of spotting days also increased during the first month of treatment, these declined with continued use but remained elevated relative to baseline during the first year of treatment.

Conclusion: In women with HMB, the LNG-IUS is associated with an initial increase in number of B/S days that improve over time.

Keywords: Amenorrhea; Contraception; Heavy menstrual bleeding; Levonorgestrel-releasing intrauterine system (LNG-IUS)

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1. Introduction

The contraceptive reliability of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®, Bayer HealthCare, Berlin, Germany) is well established, with efficacy comparable to female sterilization [1–3], but with the added advantage of rapid return of fertility upon removal. Women using the LNG-IUS for contraception experience a change in their menstrual bleeding pattern [1,4]. This change is characterized by an initial increase in the number of bleeding and spotting (B/S) days during the first few months following insertion, after which a reduction in the number of B/S days occurs with the proportion of women with amenorrhea or infrequent bleeding increasing to 16% and 57%, respectively, over the first year of LNG-IUS use [5]. Nearly 30% of women using the LNG-IUS have amenorrhea by the fourth year, a rate that is further increased with subsequent consecutive LNG-IUS use [6].

The profound reduction in blood loss achieved with the LNG-IUS makes it an effective option for the treatment of heavy menstrual bleeding (HMB). HMB, objectively defined, for research purposes, as blood loss ≥ 80 mL per menstrual cycle [7], has a prevalence of up to 14% in women of reproductive age from the general population in studies where menstrual blood loss (MBL) was measured using objective assessments such as the alkaline hematin method (National Institute for Clinical Excellence 2007 guidelines) [8]. In studies based solely on women's perceptions of the heaviness of their bleeding episodes, prevalence rates as high as 50% have been reported [9].

The efficacy of the LNG-IUS in reducing MBL in women with HMB without recognizable structural pelvic pathology is well established; median reductions of MBL have ranged from 83% to 97% over 3–12 months of treatment in prospective studies using objective assessments of MBL [10–12]. Similar effects are seen with less rigorous methodology; mean reductions of 71% to 97% in bleeding scores have been observed in randomized controlled studies using the subjective pictorial blood assessment chart (PBAC) to quantify MBL [13]. Collectively, these studies demonstrate the efficacy and tolerability of the LNG-IUS in reducing the volume of uterine bleeding in women with HMB [14], but in contrast to women using the LNG-IUS for contraception, details of the number of bleeding and/or spotting days observed with long-term treatment have not been reported.

The purpose of this current study, therefore, was to characterize the bleeding pattern in women using the LNG-IUS solely for the treatment of HMB. We pooled data from four randomized, comparative studies [including one unpublished study (data on file; Bayer HealthCare)] where similar inclusion and exclusion criteria were applied and bleeding diary data were collected [11,12,15,16] with the aim to assess, for the first time, the number of bleeding and/or spotting days experienced by women receiving treatment with the LNG-IUS for HMB and to better define the bleeding pattern among a larger population. These studies focused primarily on the changing volume of MBL over the first 12 months of LNG-IUS use.

2. Methods

2.1. Study design and participants

In this post hoc pooled analysis, we focused on analyzing the number of bleeding and spotting days and bleeding patterns from four randomized studies that compared the efficacy of the LNG-IUS with that of medroxyprogesterone acetate (MPA) [11], tranexamic acid (unpublished observations), mefenamic acid [12] and transcervical endometrial resection [15,16] for the treatment of HMB without organic pathology (Table 1). The primary focus of our analysis was on bleeding pattern (which is not adequately addressed in the published literature in women with HMB).

Table 1
Characteristics of randomized controlled trials pooled

Study	Location/Date	Treatments	Duration
Kaunitz et al. 2010 (ClinicalTrials.gov: NCT00360490) [11]	Fifty-five centers in the United States, Canada and Brazil between July 2006 and June 2008	LNG-IUS (n=82) Oral MPA acetate (10 mg once daily for 10 days beginning on Day 16 of each cycle) (n=83)	6 cycles (30-day cycles) of treatment
Unpublished study	Single center in Sweden between 1995 and 1998	LNG-IUS (n=29) Oral tranexamic acid (2×500 mg four time daily for a maximum of 5 days from the onset of menstruation) (n=30)	12 cycles of treatment
Reid et al. 2005 [12]	Two centers in the UK between 1996 and 2003	LNG-IUS (n=25) Oral mefenamic acid (500 mg three times daily for the first 4 days of each menstrual cycle) (n=26)	Six cycles of treatment
Istre et al. 2001 (for year 1 data) [15] Rauramo et al. 2004 (for data through year 3) [16]	Single center in Norway between 1993 and 1998	LNG-IUS (n=30) Transcervical endometrial resection (n=29)	Initially planned for 12 months of treatment but extended to 36 months before first patient was enrolled