Original research article

Contraceptive and noncontraceptive benefits of the LNG-IUS in a vertically integrated HMO☆

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Abstract

Background: The study was conducted to assess outcomes among women using the levonorgestrel-releasing intrauterine system (LNG-IUS).

Study Design: The data were collected via a retrospective claims database analysis of 152 women. Two nested cohorts were further distinguished based on length of follow-up: two and three continuous years (n=73 and n=29, respectively).

Results: Over 90% had a single insertion, and fewer than 4% experienced an LNG-IUS-related complication. Thirteen percent of women experienced menorrhagia in the year preceding insertion; this figure dropped to 12.5%, 1.2% and 0% in the 1, 2 and 3 years postinsertion. Mean number of gynecology-related visits decreased from four to two in the overall cohort, from seven to four in the cohort with 2 years of follow-up and from nine to four in the cohort with 3 years of follow-up.

Conclusion: LNG-IUS use prevented pregnancy in all patients and was associated with decreased vaginal bleeding starting in the second year postinsertion.

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Keywords: LNG-IUS; Retrospective; Outcomes

1. Introduction

In 2001, there were 1.4 million physician visits in the United States for excessive uterine bleeding [1]. Every year, more than 5% of women aged 30–49 years present to their general practitioner with menorrhagia, and more than 12% of referrals to gynecologists are related to menorrhagia [2]. Menorrhagia is typically defined as prolonged and/or heavy menstrual bleeding (i.e., total menstrual blood loss of more than 80 mL per cycle) occurring cyclically and over several consecutive cycles [3]. Other terms used to describe disturbances of menstruation include abnormal uterine bleeding (AUB) and dysfunctional uterine bleeding (DUB). These terms have been heavily debated over time [4]; however, regardless of the classification of the type of bleeding, women with heavy menstrual bleeding have a 43% prevalence of anemia [5] and a 60% probability of undergoing a hysterectomy within 5 years [6].

Traditional medical management for irregular, heavy bleeding has consisted of tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), oral progestins or oral contraceptives. However, these treatments are often ineffective, requiring many women to undergo subsequent surgical procedures such as endometrial resection, endometrial ablation or hysterectomy [7]. The levonorgestrel-releasing intrauterine system (LNG-IUS), a contraceptive marketed as Mirena®, provides a viable alternative to invasive surgery in women with irregular, heavy bleeding. While relatively new to the US market (the LNG-IUS was approved by the FDA in late 2000) and unpopular among US women, the device was studied extensively in Europe [8–13] for more than a decade prior to receiving US approval and has proven to be effective in the treatment of heavy menstrual bleeding [14].

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The LNG-IUS produces substantial (albeit readily reversible) morphologic effects on the endometrium [15] as endometrial growth is suppressed by continuous exposure to levonorgestrel [16]. Over time, this has been shown to produce reduced menstrual flow, with up to 50% of users becoming amenorrheic after 12 months (substantially higher than the 20% reported in package labeling) [17,18]. The effect on menstrual flow has led researchers to examine the LNG-IUS as a treatment for menorrhagia, an indication already approved for this device in several countries [7,19,20]. The LNG-IUS has proven considerably more effective than NSAIDs in menorrhagia management [20]. In addition, the LNG-IUS has been found to be as effective as oral norethisterone in treating menorrhagia. In one study, the LNG-IUS reduced menstrual blood loss by an average of 94% after 3 months, comparable to the 87% reduction in long-cycle oral norethisterone users [19]. Method satisfaction differed dramatically; however, following three cycles of treatment, 76% of the LNG-IUS group wished to continue treatment compared with 22% of the norethisterone users.

The objectives of this retrospective pre-post cohort study were to describe a real-world population of women who have received LNG-IUS and assess the contraceptive and noncontraceptive benefits over time.

2. Materials and methods

2.1. Database description and study design

This study utilized a retrospective pre-post cohort design, with data extracted from the Henry Ford Health System (HFHS) linked claims database. HFHS is a large, vertically integrated health care system serving the primary and specialty health care needs of residents in the Midwestern United States; care is provided to over 2.5 million patient contacts annually. Approximately 60% of HFHS members are part of a large, nonprofit, mixed-model HMO (Health Alliance Plan, or HAP) that includes a substantial number of Medicare and Medicaid patients. For HAP enrollees, the database contains information for all health-related encounters that occurred within or outside of HFHS for the duration of HAP enrollment.

2.2. Patient population

The patient population was selected from the HFHS database using the following inclusion criteria: (1) patients 18 years of age and older, (2) at least one insertion of an LNG-IUS between 2000 and 2005 [based on Henry Ford and Health Care Procedure Coding System (HCPCS) [21] codes, see Table 1] and (3) at least 1 year of continuous HAP enrollment both pre- and post-LNG-IUS insertion. Index date was defined as the first date of insertion of an LNG-IUS appearing in the database. Fig. 1 presents the study cohort in schematic form.

Analyses were performed on the overall patient population as well as on two nested subpopulations: those with 2 years of continuous HAP enrollment both pre- and postindex date and those with 3 years. Patients were included in all analyses for

<table>
<thead>
<tr>
<th>F/u Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year pre, 1 year post</td>
<td>152</td>
</tr>
<tr>
<td>2 years pre, 2 years post</td>
<td>73</td>
</tr>
<tr>
<td>3 years pre, 3 years post</td>
<td>29</td>
</tr>
</tbody>
</table>

Fig. 1. Study cohorts and follow-up schematic.
which they had full follow-up; that is, patients included in the 3-year analysis were also included in the 1- and 2-year analyses (Fig. 1).

2.3. Statistical analyses

The study database was checked for accuracy, consistency and completeness; data cleaning was performed as necessary. Descriptive statistics were performed at baseline to summarize the demographic characteristics of each of the study populations. Frequencies (for categorical variables) and distributions (for continuous variables) were examined for the following variables: age at index date, race, Charlson Comorbidity Index, parity (having previously given birth to an offspring), gravidity (having previously been pregnant) and use of hormonal contraception (oral, transdermal, injectable or vaginal, based on National Drug Codes) in the year preceding insertion of the LNG-IUS.

Year of LNG-IUS insertion (i.e., index year) and duration of HAP enrollment pre- and postinsertion were reported. Removal of the LNG-IUS was determined by an algorithm that searched the database for any of the following events: (1) A Current Procedural Terminology (CPT) Plus code [22] for removal of an intrauterine device, (2) a second IUD insertion code or (3) an ICD-9 diagnosis code [23] for an LNG-IUS-related complication (see Table 1 for codes). The first date of any of the above events was considered the date of removal; if none of the above were present, the LNG-IUS was assumed to have remained intact for the duration of the postinsertion follow-up. Distribution of mean length of time on the LNG-IUS was calculated for patients with an identified removal; frequencies of additional insertions and related complications were calculated for the patient populations.

Contraceptive and noncontraceptive outcomes were examined and compared in the pre- and postinsertion periods. Frequencies of menorrhagia, AUB, DUB, dysmenorrhea and anemia were determined in the pre- and postindex periods using ICD-9 codes. A time-trend analysis was conducted to determine rates of relevant bleeding disorders in the year preindex and in 1-year increments over 3 years postinsertion; each increment included all patients with full HAP follow-up.

Frequency of hysterectomy was calculated in the patient population. Numbers of obstetric- and gynecology-related encounters within the health care system (based on ICD-9 and CPT codes) were calculated for the pre- and postinsertion periods among nonhysterectomized women only. The rationale for excluding hysterectomized women was that hysterectomy, by definition, could occur only in the postindex period. A comparison of obstetric-related encounters from the preindex to the postindex period would therefore be biased because women cannot become pregnant posthysterectomy; a comparison of gynecology-related encounters would be biased as well because hysterectomy was associated with a postindex surge in resource utilization that could not be borne in the preindex period. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Population description

Results from the descriptive analysis are summarized in Table 2. Overall, the population of patients with 1 year of HAP enrollment pre- and postinsertion consisted of 152 women (mean age, 35 ± 8). The 2-year population consisted of 73 women (mean age, 35 ± 8), while the 3-year population size was 29 (mean age, 36 ± 7). The overall patient

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1 The Charlson Comorbidity Index is a summary measure of disease burden based on International Classification of Diseases, Ninth Edition (ICD-9) [22] diagnosis codes for chronic conditions in the year prior to index date and scaled from 0 to 34 with 34 representing the highest comorbidity burden [23].

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Table 2 Patient characteristics at baseline and patterns of LNG-IUS use

<table>
<thead>
<tr>
<th>Patient characteristics at baseline</th>
<th>One year pre and post</th>
<th>Two years pre and post</th>
<th>Three years pre and post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at index date in years (SD)</td>
<td>34.6 (7.5)</td>
<td>35.0 (7.7)</td>
<td>36.0 (6.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>68 (45)</td>
<td>33 (45)</td>
<td>12 (41)</td>
</tr>
<tr>
<td>White</td>
<td>64 (42)</td>
<td>35 (48)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (13)</td>
<td>5 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Mean Charlson Comorbidity Index (SD)</td>
<td>0.4 (0.7)</td>
<td>0.5 (0.8)</td>
<td>0.4 (0.6)</td>
</tr>
<tr>
<td>Parous, n (%)</td>
<td>107 (70)</td>
<td>55 (75)</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Gravidous, n (%)</td>
<td>117 (77)</td>
<td>57 (78)</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Contraceptive use preindex, n (%)</td>
<td>69 (45)</td>
<td>46 (63)</td>
<td>20 (69)</td>
</tr>
<tr>
<td>Index year, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>36 (24)</td>
<td>30 (41)</td>
<td>22 (76)</td>
</tr>
<tr>
<td>2003</td>
<td>51 (34)</td>
<td>32 (44)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>2004</td>
<td>57 (37)</td>
<td>11 (15)</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>8 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of HAP enrollment in years (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preindex</td>
<td>6.5 (4.9)</td>
<td>7.3 (4.6)</td>
<td>7.4 (3.8)</td>
</tr>
<tr>
<td>Postindex</td>
<td>2.3 (0.9)</td>
<td>3.0 (0.6)</td>
<td>3.4 (0.3)</td>
</tr>
<tr>
<td>Patterns of LNG-IUS use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of LNG-IUS insertions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>139 (91)</td>
<td>68 (94)</td>
<td>28 (97)</td>
</tr>
<tr>
<td>Two</td>
<td>12 (8)</td>
<td>4 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Three</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Number of patients with LNG-IUS removal during postinsertion period, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>41 (27%)</td>
<td>24 (33%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Two</td>
<td>15 (10)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mean time to removal in months (SD)</td>
<td>5 (4)</td>
<td>9 (7)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Number of patients with LNG-IUS-related complications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>4 (2.6%)</td>
<td>3 (4.1%)</td>
<td>1 (3.5%)</td>
</tr>
</tbody>
</table>

* Among the subset of patients who had an LNG-IUS removal within the postinsertion period of interest.
population was healthy (mean Charlson Comorbidity Index was 0.4 ± 0.7), and over 40% of women self-reported being African American. Over 76% of women were identified as gravidous, and 70% were parous at baseline.

3.2. Patterns of LNG-IUS use

The patterns of LNG-IUS use are also summarized in Table 2. Over 90% of women in all study populations had a single LNG-IUS insertion, while 3–8% of women had two insertions and 1% or fewer had three insertions over the duration of follow-up. Among women who had the LNG-IUS removed before the end of follow-up (24–33% of patients), mean time to removal ranged from 5 months for the 1-year population to 13 months for the 3-year populations. Four patients (2.6%), 3 patients (4.1%) and 1 patient (3.5%) experienced an LNG-IUS-related complication (e.g., expulsion, perforation or infection) in the 1-, 2- and 3-year populations, respectively.

3.3. Contraceptive benefits of the LNG-IUS

No patient experienced a pregnancy while the LNG-IUS was inserted. The mean number of obstetric-related encounters in the health system among nonhysterectomized women in the pre- and postinsertion periods is presented in Table 3. The mean numbers of preinsertion visits were 6 ± 8 in the 1-year population, 9 ± 13 in the 2-year population and 9 ± 12 in the 3-year population. The mean number of postinsertion obstetric visits was zero (or close to zero) for all populations.

3.4. Noncontraceptive benefits of the LNG-IUS

Fig. 2 shows the percentage of patients experiencing any one, two or three bleeding outcomes using a time-trend analysis. Each patient with bleeding was counted only once per year of follow-up; fewer than 25% of the study population experienced a bleeding disorder at any point during the study. Among those patients who did have bleeding, most (~73%) experienced only a single bleeding outcome, and no patient experienced all four bleeding events (the maximum number of separate bleeding conditions experienced by any one patient was three). The percentage of patients experiencing bleeding disorders was not markedly different in the year immediately following insertion compared to the year preinsertion; however, there was a notable decline in bleeding outcomes in the second year following insertion, with no patient experiencing irregular, heavy bleeding in the third year. Fig. 3 shows a time-trend analysis of each individual bleeding condition. Fewer than 14% of patients experienced menorrhagia or AUB, fewer than 6% had DUB or dysmenorrhea and fewer than 3% became anemic. The prevalence of each bleeding outcome was similar in the 1-year preinsertion and 1-year postinsertion periods, and the prevalence of all bleeding outcomes except DUB decreased in the second year postinsertion to frequencies lower than in the preinsertion period (menorrhagia and AUB by approximately 88%; dysmenorrhea and anemia by 100%). By the third year postinsertion, none of the women in the study population experienced a bleeding outcome.

Mean numbers of gynecology-related visits pre- and post-LNG-IUS are presented in Table 3. The number of gynecology-related visits decreased in the postindex period for all follow-up periods (from four visits to two in the 1-year population, from seven visits to four in the 2-year population...
and from nine visits to four in the 3-year population). Family planning advice was the most common reason for a gynecologist visit both pre- and postindex; other reasons included menorrhagia in the preindex period and IUD-related inquiries (i.e., checking, insertion and removal) in the postindex period.

4. Discussion

Data from this study demonstrate both the contraceptive and noncontraceptive clinical benefits of the LNG-IUS in a real-world population of women. The contraceptive benefits of the LNG-IUS have already been firmly established; once inserted, it is over 99% effective at preventing pregnancy [24]. Noncontraceptive benefits demonstrated in this study include a reduction in vaginal bleeding symptoms that became more apparent over time, as well as a concurrent reduction in health care system utilization. Results of the bleeding analysis are consistent with clinical trial literature establishing the LNG-IUS as an effective treatment for a variety of bleeding disorders. In a systematic review published in 2001, the LNG-IUS was found to reduce menstrual blood loss by 74% to 97% in women with irregular, heavy bleeding, a significantly greater effect than that of medical regimens such as tranexamic acid (44%, p < .01) and flurbiprofen (21%, p < .001) [25]. Given these findings, US physicians should provide ample counseling to patients on the benefits of LNG-IUS, which may raise acceptance to levels seen in their European counterparts.

Four women (2.6%) underwent a hysterectomy during study follow-up. While no claims can be made as to whether more hysterectomies were avoided due to LNG-IUS use, avoidance of surgery has been a demonstrated benefit of the LNG-IUS in the published reports. Studies have reported that 64% to 82% of women slated for bleeding-related hysterectomies opted to forego the procedure after using the LNG-IUS for treatment, compared with fewer than 20% of those using traditional medical management [7,26–28]. Additionally, Bongers et al. [3] have shown that 77% of women with irregular, heavy bleeding whose medical therapies fail go on to have a surgical procedure. In 30% of these cases, a hysterectomy is necessary to treat persistent bleeding. Thus, approximately a quarter (23%) of the women who present with irregular, heavy bleeding and are unsuccessful with medication therapy eventually have a hysterectomy. While our sample size was insufficient to show a statistically significant reduction in bleeding, no patient in the study population experienced a bleeding disorder by the third year postinsertion, compared with 25% of patients in the year prior to insertion. Additionally, in a randomized trial, the LNG-IUS scored as well in the treatment of bleeding as hysterectomy at 12 months in terms of health status, health-related quality of life and psychological well-being [27]. Given the high percentage of women with these bleeding conditions who have required hysterectomy in the past, the LNG-IUS has the potential to substantially reduce the frequency of this major, invasive surgery.

Trussell et al [29] found intrauterine contraception to be the most cost-effective form of birth control if left intact for over 3 years. An analysis establishing the cost-effectiveness of the LNG-IUS in the treatment of bleeding was out of the scope of this study; however, our results suggest greater cost-effectiveness with a longer duration of use. The economic benefits derived from preventing invasive and costly procedures such as ablation or hysterectomy to treat irregular, heavy bleeding are potentially high and should be investigated further.

Our study has several limitations. The LNG-IUS was FDA-approved as a contraceptive device in 2000, limiting the amount of follow-up obtainable within the study population. Additionally, intrauterine contraception is used by approximately 1% of women of childbearing age in the United States, further limiting our sample size. Our database search did not yield enough study subjects to make meaningful statistical comparisons from the pre-to the postindex period; small sample size was a particular problem in studying subpopulations with longer follow-up, where long-term benefits of the LNG-IUS may be more apparent. Additionally, claims data provide an imperfect proxy for true resource utilization and may not reflect all clinical nuances experienced by the population. Indeed, there was a degree of overlap in terms of classifying the following bleeding episodes: menorrhagia (excessive regular menstrual bleeding, included in the same ICD-9 code as frequent menstrual bleeding), dysmenorrhea (pain during regular menstruation), DUB (excessive menstrual bleeding in the absence of structural abnormality, included in the same ICD-9 code as functional uterine hemorrhage), AUB (absent, infrequent, postcoital, intermenstrual or irregular bleeding) and anemia (including iron deficiency, non-autoimmune hemolytic anemia and acute posthemorrhagic anemia) [23].

The HFHS population is drawn from a single large, urban area in the United States whose population may not perfectly mirror that of the United States overall, particularly in terms of racial composition and personal physician practice patterns (we do not know the demographics or numbers of physicians responsible for the 152 insertions, for example). Furthermore, HAP members represent a unique subsection of the Henry Ford population. Although it is difficult to generalize our study findings for the overall U.S. population, or for overall physician prescribing patterns, LNG-IUS-related complication rates found in our study are comparable to that of the general population for expulsion (2–10% spontaneous expulsions within the first year) [24], perforations (1 per 1000 correct insertions lead to a perforation) [30] and pelvic inflammatory disease (1.6 cases per 1000 woman-years of IUD use) [31]. It should be noted that the rate of pelvic inflammatory disease reported in this article is for the copper IUD and therefore may be higher than noncopper IUD rates.
To the best of our knowledge, this study represents the first analysis of patterns of LNG-IUS use and subsequent contraceptive and noncontraceptive outcomes in a real-world managed care population. Further study of the economic benefits of the LNG-IUS is needed, particularly with respect to the potential impact on budgets for the treatment of bleeding disorders. As the LNG-IUS remains on the market for a longer period of time in the United States, it will become possible to study its impact in larger patient populations with longer follow-up.

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