A SYSTEMATIC REVIEW OF THE LEVONORGESTREL INTRAUTERINE SYSTEM AND ITS USE FOR WOMEN WITH HEAVY OR PROLONGED BLEEDING

by

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LEVONORGESTREL INTRAUTERINE SYSTEM USE AMONG WOMEN WITH HEAVY OR PROLONGED BLEEDING

MEC Condition: Heavy or prolonged bleeding
MEC Method: LNG-IUS

ABSTRACT

Objective: To determine from the literature whether it is safe for women with heavy or prolonged bleeding to use the levonorgestrel intrauterine system (LNG-IUS) and to update the evidence prepared for the 2014 MEC Guideline Development Group meeting.

Methods: We searched MEDLINE and Cochrane databases for articles (in all languages) published in peer-reviewed journals from April 2006 to July 2013 for articles relevant to heavy or prolonged bleeding and LNG-IUSs. We also used articles identified from a previous systematic review that spanned January 1966 to March 2006. We used standard abstract forms and grading systems to summarize and assess the quality of the evidence.

Results: Our search from April 2006 to July 2013 resulted in 218 articles, from which we identified 24 studies that met our systematic review criteria. The previous systematic review identified 20 studies and 2 systematic reviews, of which 12 met our inclusion criteria. Overall we included 36 articles from January 1966 to July 2013. “Good” quality evidence from these articles suggested that women with menorrhagia who use LNG-IUSs usually experience decreases in bleeding quantity and pain and increases in hemoglobin and serum ferritin levels. Evidence suggests that some women experience reduction in fibroid size. The studies reported few serious adverse events.

Conclusion: "Good" quality evidence suggests that it is safe and potentially beneficial for women with heavy or prolonged bleeding to use LNG-IUSs.

Body of Evidence Grading: II-3, Good

INTRODUCTION

Heavy menstrual bleeding or menorrhagia is a considerable problem for many women. The use of the contraceptive levenorgestrel intrauterine system (LNG-IUS) may reduce menstrual blood loss. The current (2009) WHO recommendation states that there are no restrictions for the use of the LNG-IUS as a contraceptive method for women with heavy or prolonged bleeding (Category 1) and the advantages of using this method generally outweigh the theoretical or proven risk for women continuing this method (Category 2)[1]. The objective of this review is to determine whether it is safe for women with heavy or prolonged bleeding to use the LNG-IUS. This review also serves as an update of the evidence prepared for the 2014 Guideline Review Committee meeting.

METHODS

We searched MEDLINE for all articles (in all languages) published in peer-reviewed journals between April 2006 and July 2013 for evidence relevant to L-IUS use among women with heavy or prolonged menstrual bleeding. The following search strategy was performed in MEDLINE: *(levonorgestrel AND (intrauterine devices[mesh] OR iud OR iucd OR ius OR intrauterine system OR intra-uterine system OR intrauterine device OR intra-uterine device)) or mirena* AND (menorrhag* OR ((menstru* or bleeding) AND (heavy or excessive)) or hemorrhage*).* Reference lists from articles identified by the search, as well as key review articles, were searched to identify additional articles. We did not attempt to identify unpublished articles or abstracts from scientific conferences nor did we contact any subject matter experts. All study designs were included. Randomized control trials were studied as single arm trials because we wanted to focus on the safety of the LNG-IUS and not the comparative treatment effect for bleeding. We

did not include any literature reviews and instead included the individual articles the reviews were based on.

Selection Criteria

We selected studies that examined the safety and related effects of the LNG-IUS among women with heavy or prolonged menstrual bleeding, including changes in bleeding patterns, changes in hemoglobin or serum ferritin levels, increase or decrease of bleeding-associated pain, and serious adverse events. Serious adverse events are defined as any treatment related medical occurrence that is either life threatening, requires hospitalization, or results in incapacity.[2]

Study Quality Assessment

The evidence was summarized and systematically assessed using standard abstract forms[3]. The quality of each individual study was assessed using the United States Preventative Services Task Force (USPSTF) grading system[4]. We were primarily interested in the safety of the LNG-IUS used for contraception and treatment, but not in the comparative treatment effects of the LNG-IUS versus other treatments for bleeding abnormalities. Therefore we treated randomized control trials and cohort studies as single arm studies for the purposes of this systematic review.

Data Synthesis

We assessed the heterogeneity of the included studies by examining their respective study designs and participant characteristics. Due to the diversity in the types of studies included, we were unable to estimate summary measures of effect. Alternatively, we synthesized results by three types of outcomes most pertinent to women with menorrhagia. These included the primary outcomes of changes in bleeding patterns and pain associated with bleeding, as well as serious adverse events. Secondary outcomes were L-IUS expulsions, changes in fibroid size, and changes in hemoglobin and serum ferritin levels.

RESULTS

The search strategy identified a total of 218 articles. After reviewing the titles and abstracts of these articles, as well as the full article when necessary, we included 36 new articles. Four studies[20-21, 32-33, 35-36, 42-43] are included that have follow-up reports available.Original report and follow-up report are cited together in this review and treated as if they were one article. For the purpose of this review, we focused on the results from the most recent follow-up. In addition, one article in French was translated to English.[28]

All studies enrolled women with either objective or subjective menorrhagia. We did not include any articles that focused exclusively on women with specific conditions or medications that caused or contributed to menorrhagia.The studies were conducted in 19 different countries spanning 5 continents, the majority based in Asia. There are 16 observational studies,[5-7, 9-10, 13, 15, 22-23, 27-28, 34, 38, 40-42, 44] 4 cohort studies[11, 14, 16, 39], and 16 randomized control trials[8, 12, 17-21, 24-26, 29-33, 35-37, 43]. Again, because we were primary interested in the safety of the LNG-IUS for women with menorrhagia, and not in the comparative treatment effects, we considered RCT and cohort studies as non-comparative. The studies ranged in initial sample size from 15 to 483 women with LNG-IUS insertions, and the ages of the participants, which were provided in 20 studies, ranged from 18 to 55. The follow-up times for these studies varied, with 5 studies having follow-up times between 6 and 12 months, 16 studies with 12 months of follow-up, and 15 studies ranging from 12 months to 5 years.

The results are organized by the three types of outcomes most pertinent to L-IUS use among women with menorrhagia. These include: 1) bleeding associated outcomes, 2) pain associated with bleeding (dysmenorrhea) and 3) secondary outcomes including serious adverse events, expulsions and changes in fibroid size.

1. Bleeding Associated Outcomes

Bleeding associated outcomes include:

- Bleeding quantity
- Changes in bleeding patterns, including development of spotting and amenorrhea
- Blood serum levels of hemoglobin, hematocrit, and serum ferritin

A. Bleeding quantity

L-IUS insertion among women with menorrhagia often resulted in dramatic changes in bleeding quantity during follow-up. It was generally found that bleeding quantity decreased as more time passed. The most common measurement for bleeding quantity was the Pictoral Blood Loss Assessment Chart (PBAC), a standardized but subjective blood loss scoring method. PBAC measurements were used in 14 studies from pre-L-IUS insertion to follow-up[6, 8, 10-12, 17, 23-24, 26, 28, 30-31, 35-37, 43]. Generally, a PBAC score of 75 is considered eumenorrheic and a score over 100 is menorrhagic[43], although there are no official guidelines for score correlation. Different studies used varying cut off points to define abnormally heavy, normal, and light bleeding.

Mean PBAC scores were reported in 8 studies,[10-11, 28, 30-31, 35-37, 43] with baseline scores ranging from 107 to 490 and follow-up scores ranging from 7 to 55. Eleven studies reported a significant decrease in PBAC scores from baseline to follow-up.[6, 8, 10, 17, 23-24, 26, 30-31, 35-36, 43] Gupta et al (2006)[11], which did not report significance tests, found a 98.6% reduction in PBAC score from baseline to follow-up. Significant changes in PBAC score before final follow-up was reported in Reid et al's 6-cycle study of women with objectively proven idiopathic menorrhagia[31] ($p<.001$ from baseline to 3, 6 and 12 months and $p<.005$ between baseline, cycle 3 and cycle 6, respectively).Busfieldet al[30] also reported PBAC scores during intermediate follow-up periods. Starting from a baseline mean of 490, PBAC scores dropped to 125 by 3 months, 72.1 by 6 months, 41.1 by 12 months, and 20.6 by 24 months.

Other methods besides PBAC were used to measure bleeding quantity. Gupta et al (2013)[12] used the Menorrhagia Multi-Attribute Score (MMAS)and found the mean improved significantly by 13.4 points over two years. Xiao et al[38]and Shabaan et al[19]used milliliters to measure bleeding quantity. Xiao found a

mean reduction from 124.2 mL at baseline to 2.7 mL by 36 months, with an average reduction of 86.3%.Shabaan reported a reduction from 300 mL at baseline to 44.4 mL by 12 months. Kaunitz et al[21] did not report baseline or follow-up scores but found a mean decrease in bleeding of 128.8 mL, with 80% of women experiencing a 70% decrease in bleeding by 6 months. Henshawet al[39], used a scale of 0 to 50 to determine mean bleeding score, with 50 corresponding to the heaviest bleeding. Henshaw reported a significant change from the mean baseline score of 30.7 to the mean follow-up score of 8.2 ($p<.0001$).

B. Changes in bleeding patterns

a. Amenorrhea

Twenty-two papers reported on the number of women who became amenorrheic during follow-up[5-7, 9, 13, 16-18, 22-24, 26, 29-30, 32-38, 40-42, 44]and 3 papers reported on trends in amenorrhea progression.[7, 22, 30] Five studies[5, 16, 32-33, 38, 41]found that more than 50% of women were amenorrheic, with follow-up periods ranging from 1 to 5 years. These numbers may be slightly inflated as 2 studies reported combined percentages from amenorrhea, hypomenorrhea, and oligomenorrhea.[5, 32-33]Twelve studies reported amenorrhea rates from 25-50%[6, 13, 18, 22-24, 30, 34, 36, 38, 41-42, 44] with follow-up times ranging from 6 months to 5 years. Six studies reported amenorrea rates from 0% to 25%[7, 9, 17, 26, 29, 37] with follow-up times ranging from 6 months to 2 years.

In studies that reported trends in amenorrhea progression, Desai et al[7] noted that no women had amenorrhea at 3 months, 22.5% of women presented with amenorrhea at 6 months, and that number did not increase by 1 year. Palmaraet al[22] reported that 13.6% of women were amenorrheic at 6 months and that increased to 31.8% by 1 year. Busfield et al[30] found a steady increase in amenorrhea rates: 5.6% of women had amenorrhea at 3 months, 9.4% at 6 months, 20% at 12 months, and 35% at 24 months.

b. Spotting

Ten studies[7, 10, 16-17, 22, 26, 29, 34, 38, 40] reported the number of women who experienced spotting at follow-up. Although most studies did not define an objective spotting measurement, spotting is generally

understood to be bleeding between menstrual periods. The number of women who experienced spotting ranged from 0% to 32.5% with follow-up times ranging from 6 months to 4 years. Desai et al[7] found that spotting initially decreased to 32.5% at 6 months from 60% at 3 months, but no further decreases were found by 1 year. Palmaraet al[22], conversely, reported that 13.6% of women experienced spotting at 6 months, but no women experienced spotting by 1 year.

C. Blood serum levels

a. Hemoglobin

Twenty[5-6, 8-9, 11, 13, 15, 17-18, 20-21, 23-25, 28-29, 32-33, 35-36, 38, 40, 43] studies reported changes in mean hemoglobin levels from baseline to follow up. Seventeen studies[5-6, 8-9, 11, 13, 17-18, 23, 25, 28-29, 32-33, 35-36, 38, 40, 43] found a significant increase in mean hemoglobin levels; 3 studies[15, 20-21, 24] did not report on significance. Normal hemoglobin levels range from 12 to 18 g/dL, but mean baseline values in the studies ranged from 9.1 to 12.6 g/dL. After device insertion all studies reported an increase in hemoglobin values, with follow up values ranging from 12.13 to 14.41 g/dL. Follow up times ranged from 6 months to 5 years. No studies reported a decline in hemoglobin levels.

b. Hematocrit

Two studies[5, 13] reported changes in mean hematocrit levels from baseline to follow up. Hematocrit measures the percentage of blood that is made up of red blood cells. Tasciet al[5] found that the mean increased 3.98% over 12 months. Kohet al[13] reported a significant increase of hematocrit levels from 37% to 40% by 6 months (p=0.05).

c. Serum ferritin

Nine studies[9, 15, 20-21, 24, 28, 32-33, 35-36, 38, 41-42] reported changes in mean serum ferritin levels after insertion. Serum ferritin measures the iron storage level in blood. Different tests and units of measurement were used in different studies. However, eight studies[9, 15, 20-21, 24, 28, 32-33, 35-36, 38]with follow-

up times from 6 months to 5 years found serum ferritin levels increased over time after insertion. However, Barrington et al[42] found no significant change after 5 years. Four studies[28, 32-33, 35-36] found that increases in mean serum ferritin levels were significant. The other 4 studies[9, 15, 20-21, 24] did not report on significance. No studies reported decreases in serum ferritin levels.

2. Pain associated with bleeding (dysmenorrhea)

Nine studies[6, 10, 14 23, 28, 34-36, 39, 41-42] examined changes in dysmenorrhea and pelvic pain from insertion to follow-up. All 9 studies found a general improvement in subjective pain scores by end of the follow-up period. Chattopdhyayet al[6] found that 85% of women were completely relieved of dysmenorrhea by 3 months and 100% by 6 months. Lee et al[15] found 76.1% of women had complete dysmenorrhea relief by 12 months. Kriplani reported that 77.5% of women had no dysmenorrhea by 3 months, and by 24 months no women reported any pain.

Gorgen et al[10] used a Visual Analogue Scale to subjectively measure pain and found that scores decreased from mean 4.32 to 3.55 by 6 months.Istreet al[36] asked women the number of days they experienced pain and reported a significant decrease in days with mild, moderate, and severe pain (p=0.001) by 36 months.

Radesicet al[34] was the only study to report any increase in pelvic pain or dysmenorrhea, with 3.8% of women reporting an increase in pain by 4 years. However, 11.5% reported no change in pain and 73% of women found that pain decreased by 4 years after insertion.

3. Secondary outcomes

A. Serious adverse events

Serious adverse events are defined as any treatment related medical occurrence that is either life threatening, requires hospitalization, or results in incapacity[2]. Many studies reported “adverse effects” which were defined as spotting and expulsions, which are addressed elsewhere, or general quality of life complaints that are not addressed in this review. Two studies[8, 12] reported serious adverse events which

were non-treatment related. Three studies[30-31, 35-36] reported serious adverse events. Raumaro et al[35-36], reported one case of edema, 3 cases of endometriosis, and 2 cases of pelvic inflammatory disease by 36 months. Reid et al[31] reported after 6 months that one woman experienced hypertension, but was found to have a strong family history, and one woman was diagnosed with chlamydial endometritis, which was successfully treated.Busfieldet al[30] reported that one woman developed actinomycoses by 24 months.

B. Expulsions

Frequency of L-IUS expulsion was reported in 15 studies[7, 9, 11, 14, 19-21, 23, 26, 29, 31, 34-36, 38, 40-42] and ranged from 1.8% to 21.7%. Six studies[9, 14, 19, 20-21, 34-36] had expulsion rates from 1.8- 4.9%, 3 studies[7, 11, 23]had expulsion rates from 8-10%, and 6 studies[26, 29, 31, 38, 40-42] had expulsion rates from 11-21.7%. Follow-up time ranged from 6 months to 5 years.

C. Changes in fibroid size

Although we did not include studies that focused exclusively on women with menorrhagia due to fibroids, many of our studies examined women with fibroids alongside women with idiopathic menorrhagia. One study, Tasciet al[5], reported on changes in fibroid size after insertion of the LNG-IUS. Tasci et al found that out of 25 women with fibroids, 20 saw a significant decrease in fibroid size ($p=0.04$).

DISCUSSION

The general consensus from 36 articles included in this review is that LNG-IUS use for treatment of menorrhagia is extremely safe and effective. All studies that examined bleeding quantity after insertion found that bleeding dramatically decreased; as a result, blood serum levels of hemoglobin, hematocrit, and serum ferritin increased in all studies except one. Barrington et al[37] did not find any change in serum ferritin levels. No studies found that bleeding quantity increased and no studies found that blood serum levels of hemoglobin, hematocrit, or serum ferritin decreased. All studies, except one,[34] reporting on

dysmenorrhea or pelvic pain found that pain decreased after insertion, and the vast majority of women experienced total relief of pain. Over one-third of studies reported LNG-IUS expulsions, although in over half of those studies 10% or less of patients experienced expulsions.

The quality of the studies ranged from “very poor” to “good” with most studies given a “fair” rating. However, from the homogeneity of results across the studies, as well as the presence of many “good” quality studies, we conclude that the overall body of evidence is of “good” quality. However, synthesizing the outcomes of interest across the studies presented some difficulty because of the variations in the subjective measuring tools for bleeding quantity and dysmenorrhea, as well as the difference in definitions of what constituted menorrhagia. Many of the studies had low follow-up rates and small sample sizes. One of the biggest concerns in these studies was that they focused on older women who often did not need the LNG-IUS for contraceptive purposes, and were in fact nearing menopause. This may not be entirely representative of our target population, although it is likely that issues of safety are similar.

Despite the limitations, we found an overwhelming amount of evidence that the LNG-IUS is safe to use for women with menorrhagia and may provide a beneficial effect.

CONCLUSION

Body of evidence grading: II-3, Good

“Good” quality evidence from 36 studies show that women with menorrhagia and LNG-IUSs usually experience dramatic decreases in bleeding quantity and dysmenorrhea, as well as increased hemoglobin, hematocrit, and serum ferritin levels. Studies reported few adverse events.

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Conflicts of Interest
There are no conflicts of interest

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