Health Quality Ontario
The provincial advisor on the quality of health care in Ontario

Ontario Health Technology Assessment Series

Levonorgestrel-Releasing Intrauterine System (52 mg) for Idiopathic Heavy Menstrual Bleeding: A Health Technology Assessment

KEY MESSAGES

Up to one-third of women experience heavy menstrual bleeding, which can be painful, distressing, and disruptive to daily life. Often there is no specific cause, but treatment can make a woman's periods more manageable or even eliminate symptoms. Options include medications, various types of surgery, and a device called the levonorgestrel-releasing intrauterine system (LNG-IUS) that is inserted into the uterus and releases medication. This health technology assessment looked at how effective and cost-effective the LNG-IUS is for treating heavy menstrual bleeding.

We found that the LNG-IUS works well and costs less compared with other options to treat heavy menstrual bleeding. Women using the LNG-IUS said their quality of life improved and their periods were lighter. Although some women experienced mild side effects, women seemed to be generally satisfied with the treatment.

We also found that funding the LNG-IUS to treat heavy menstrual bleeding would result in cost savings to the Ontario health care system. Currently, the insertion procedure is publicly funded but the cost of the device is not, while several other treatment options are publicly funded in their entirety.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

Heavy menstrual bleeding affects as many as one in three women and has negative physical, economic, and psychosocial impacts including activity limitations and reduced quality of life. The goal of treatment is to make menstruation manageable, and options include medical therapy or surgery such as endometrial ablation or hysterectomy. This review examined the evidence of effectiveness and cost-effectiveness of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) as a treatment alternative for idiopathic heavy menstrual bleeding.

Methods

We conducted a systematic review of the clinical and economic evidence comparing LNG-IUS with usual medical therapy, endometrial ablation, or hysterectomy. Medline, EMBASE, Cochrane, and the Centres for Reviews and Dissemination were searched from inception to August 2015. The quality of the evidence was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We also completed an economic evaluation to determine the cost-effectiveness and budget impact of the LNG-IUS compared with endometrial ablation and with hysterectomy. The economic evaluation was conducted from the perspective the Ontario Ministry of Health and Long-Term Care.

Results

Relevant systematic reviews (n = 18) returned from the literature search were used to identify eligible randomized controlled trials, and 16 trials were included. The LNG-IUS improved quality of life and reduced menstrual blood loss better than usual medical therapy. There was no evidence of a significant difference in these outcomes compared with the improvements offered by endometrial ablation or hysterectomy. Mild hormonal side effects were the most commonly reported. The quality of the evidence varied from very low to moderate across outcomes. Results from the economic evaluation showed the LNG-IUS was less costly (incremental saving of $372 per person) and more effective providing higher quality-adjusted life years (incremental value of 0.05) compared with endometrial ablation. Similarly, the LNG-IUS costs less (incremental saving of $3,138 per person) and yields higher quality-adjusted life-years (incremental value of 0.04) compared with hysterectomy. Publicly funding LNG-IUS as an alternative to endometrial ablation and hysterectomy would result in annual cost savings of $3 million to $9 million and $0.1 million to $23 million, respectively, over the first 5 years.

Conclusions

The 52-mg LNG-IUS is an effective and cost-effective treatment option for idiopathic heavy menstrual bleeding. It improves quality of life and menstrual blood loss, and is well tolerated compared with endometrial ablation, hysterectomy, or usual medical therapies.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

BACKGROUND

Heavy Menstrual Bleeding

Heavy menstrual bleeding (menorrhagia) is excessive or prolonged menstrual bleeding, either alone or in combination with other symptoms that affect women of reproductive age.[1] This health technology assessment focuses on the management of heavy menstrual bleeding as defined by the Society of Obstetricians and Gynaecologists of Canada (adopting the definition from the UK National Institute for Health and Care Excellence): "excessive menstrual blood loss which interferes with a woman's physical, social, emotional, and/or material quality of life."[2,3] The term "abnormal uterine bleeding" includes heavy menstrual bleeding as well as several other variations to the menstrual cycle and other non-menstrual types of uterine bleeding that are beyond the scope of this review.[3]

Heavy menstrual bleeding can result from a number of underlying causes including cervical pathology, endometrial polyps, endometrial hyperplasia, cancers, fibroids, or systemic bleeding disorders.[3] It can also be idiopathic, meaning it occurs in the absence of any recognizable pelvic or systemic pathological condition; this is sometimes called cyclical dysfunctional uterine bleeding.[1] Women with idiopathic heavy menstrual bleeding tend to be younger than women whose heavy bleeding is due to organic causes such as fibroids, polyps, or endometrial hyperplasia.[4]

Population-based surveys from the mid-1960s and early 1970s estimated that the prevalence of "objective menorrhagia" (heavy menstrual bleeding of > 80 mL of blood loss per cycle) was about 10%.[5,6] In contrast, self-reported data suggest prevalence is on the order of 30%.[1] Experts we consulted estimate that 15% to 20% of women of reproductive age (15 to 55 years old) in Ontario are affected by heavy menstrual bleeding. The prevalence of heavy menstrual bleeding increases with age and peaks in perimenopause.[7] Defining the severity of the condition is a challenge, but a patient's perception of bleeding and its impact on her life is most important in considering treatment options and determining the degree of intervention.[3]

The pervasive impact of heavy menstrual bleeding is on a woman's quality of life, and its effects are biopsychosocial in nature. Focus groups have identified inconvenience, pain, self-consciousness, and social embarrassment as themes of the impacts of heavy menstrual bleeding on a woman's life.[8] Pain associated with bleeding is common and can be localized to the uterus or back, or it can manifest as a general sensation of cramping or heaviness.[8] The emotional toll of worry and embarrassment is compounded by the social impact of limitations in activities in general.[9] Heavy menstrual bleeding affects interpersonal relationships including sexual function,[5] and as many as two-thirds of women can experience mild to moderate depression.[10] There is evidence of economic impact in the form of lower earnings among women with excessive menstrual bleeding due to absence from work.[11] In the US, heavy menstrual bleeding accounts for an 8% loss in employee wages.[7]

If excessive bleeding is not treated effectively, approximately two-thirds of women will develop iron-deficiency anemia, which can produce fatigue, weakness, mood swings, weight loss, and impaired cognition.[12] Heavy menstrual bleeding is the most common cause of this anemia in developed countries,[12] and the anemia limits women's activities and negatively impacts their overall health and well-being.[9] Correction of anemia is associated with significant improvements in health-related quality of life in women with heavy menstrual bleeding.[13]

While in clinical practice a patient's own experience of heavy menstrual bleeding is key to understanding its impact on her life, research often involves quantifying the actual blood loss. Volume of blood loss can be assessed semi-quantitatively via the pictorial blood loss assessment chart (PBAC), self-report (e.g., diary keeping), or most objectively by the alkaline hematin lab test.[9] Using the PBAC method of blood loss measurement, women record and score the number and degree of saturation of the sanitary products they use, and the frequency and size of clots, and episodes of flooding over the course of a month.[14] The alkaline hematin method requires all used sanitary materials to be sent for laboratory analysis and is the standard for determining objective menorrhagia (blood loss > 80 mL per cycle). Both methods use standardized sanitary products to facilitate comparability between subjects. The alkaline hematin method is less commonly used owing to practicality.

The PBAC score is significantly correlated with objective menorrhagia defined by the alkaline hematin test in women with both normal and heavy menses.[15] A PBAC score of more than 100 reflects objective menorrhagia, with a sensitivity of 97% in heavy-bleeding populations[16] and 86% in the general female population.[14] A comparative study of the two methods found that, after adjustment for known confounders, the PBAC score is an independent predictor of menstrual blood loss of more than 80 mL.[15]

Treatment Options

The goal of treating heavy menstrual bleeding is to make menstruation manageable for a patient, and treatment options will reflect a woman's values and preferences as well as the unique clinical attributes of her condition. A number of systemic medications (oral or injected) may be prescribed as usual medical therapy to manage heavy menstrual bleeding. Hormonal medications may be beneficial both for reduction of menstrual blood loss and also for regulation of the menstrual cycle. Options may include combined oral contraceptives (estrogen and progestogens) or progestogens alone (oral, injection, or depot injection).[1] For women with predictable timing of bleeding, nonsteroidal anti-inflammatory drugs and antifibrinolytic drugs can be used to reduce bleeding.[3]

Medications that have some evidence of effectiveness include tranexamic acid, mefenamic acid, medroxyprogesterone acetate, combined oral contraceptives, and danazol.[17] In situations where other treatment options are contraindicated, gonadotropin-releasing hormone agonists may also be prescribed occasionally to treat heavy menstrual bleeding.[3] Table 1 describes these common medications.

Table 1: Overview of Usual Medical Therapies Available for Heavy Menstrual Bleeding

Medication	Drug Category	Dose/Regimen	Mechanism of Action	Side Effects
Tranexamic acid	Antifibrinolytic	During menstruation only	Inhibits breakdown of blood clots	Mild nausea, diarrhea
Mefenamic acid Naproxen	NSAID	During menstruation only	Inhibits prostaglandin production	Headaches, gastrointestinal issues
Norethisterone MPA	Progestogen	Days 5–26 of menstrual cycle	Suppresses endometrial growth and activity	Breast tenderness, bloating, headaches, breakthrough bleeding
COC	Estrogen and progestogen	21 or 28 days per cycle	Inhibits growth and development of endometrium	Nausea, headache, breast tenderness, weight change, altered libido, depression
Danazol	Androgen	Daily	Causes endometrial atrophy	Weight gain, headache, nausea, tiredness, acne, possible fetal damage

Abbreviations: COC, combined oral contraceptive; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug.
Source: Marjoribanks et al, 2010.[17]

Effective management with medical therapy is a key aim as it enables a woman to avoid more invasive, irreversible surgical treatments such as endometrial ablation or hysterectomy.[1] Endometrial ablation is a procedure to either destroy (ablate) or remove (resect) the lining of the uterus (endometrium).[18] This can be done via a number of techniques considered as either first generation (techniques developed in the 1980s, such as rollerball and laser ablation,) or second generation (developed in the 1990s, e.g., thermal balloon and microwave ablation).[19] First-generation ablation techniques generally require direct visualization of the endometrium via hysteroscope and a high degree of surgical skill on the part of the clinician, whereas second-generation techniques rely less on operator skill and more on the device for safety and efficacy.[19] Most ablation techniques are marketed as outpatient procedures.[19] Pregnancy can happen after endometrial ablation and has many risks, so women undergoing the procedure also need to use highly effective contraception such as sterilization, which can be done as part of the procedure, or (for their male partner) vasectomy.

Failure of the initial endometrial ablation can result in the need for either repeat ablation (this occurs in 3% to 7% of women who have had the procedure) or hysterectomy.[19] Treatment failure may result from the incomplete destruction of the endometrium, which allows endometrial cells to persist or regenerate, causing ongoing bleeding. Excessive destruction involving the cervix may result in hematometra (blood becoming trapped in the uterus), retrograde bleeding through the fallopian tubes, and significant pain.[18] These complications often lead to hysterectomy. A history of dysmenorrhea (painful menstruation), tubal ligation, or endometrial ablation performed in an operating room increase the likelihood of post-ablation hysterectomy.[20]

Hysterectomy is surgery to remove both the uterus and cervix (total hysterectomy) or just the uterus (subtotal or supracervical). Hysterectomy is one of the most common gynecologic procedures in the United States[20] and Canada,[21] and heavy menstrual bleeding is the main presenting problem in at least half of women who have a hysterectomy before age 60.[9] Removal of the uterus is considered the only definitive cure for heavy menstrual bleeding; however, women who retain their cervix can continue to experience cyclical bleeding after surgery.[22] With laparoscopic supracervical hysterectomy, as many as 17% to 24% of women may continue to have cyclical menstrual bleeding up to 3 years after surgery.[23,24] Laparoscopy is surgery that

uses small incisions and the use of a thin lighted tube to enable the surgeon to operate inside the body.

Even when surgery is uncomplicated, hysterectomy is the most invasive procedure for heavy menstrual bleeding and has a considerable recovery period.[25] The surgery usually requires general anesthetic and can be performed using various approaches. In descending order of duration of recovery time and invasiveness, the approaches are vaginal, laparoscopic (including robotic surgery), combination laparoscopic-vaginal, or abdominal (open).[19,26] The risks with hysterectomy are those associated with surgery and include postoperative infection (e.g., vaginal cuff cellulitis, urinary tract infection, wound infection, respiratory infection), blood clots (e.g., deep vein thrombosis, pulmonary embolism), and blood loss.[26] Hysterectomy-specific complications include potential injury to the nearby bladder or ureter, bowel injury, and rarely, nerve injury (e.g., femoral, iliohypogastric, ilioinguinal, or peroneal nerve), or vaginal cuff dehiscence (separation of the vaginal surgical incision) which can lead to in various degrees of evisceration (when the abdominal organs push through the surgical incision).[26] The risk of complications depends on several patient factors, such as older age, obesity, and comorbidities, as well as surgical technique.[26]

Ontario experts consulted for this report indicated that the surgical risks can be greater for women with higher body mass index (BMI), especially obese women, and therefore understanding the effectiveness of nonsurgical treatment options for heavy menstrual bleeding is of particular interest. This report examines the effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS), a hormone-releasing device described in the Technology section, below.

Patient Values and Preferences for Treatment

A patient's perception of her heavy menstrual bleeding and how it affects her quality of life is the most important information for the clinical management and the degree of intervention,[3] and multiple factors may influence individual treatment preferences. Clarifying a patient's values and preferences is a key part of decision-making in the management of heavy menstrual bleeding and has been shown to result in lower costs.[27] Women who want future pregnancies, have irregular menstruation, are unemployed, or have higher levels of anxiety are more likely to opt for conservative management.[28] On the other hand, women who express a preference for hysterectomy before getting treatment or who feel inconvenienced because they experience more symptoms of heavy bleeding have a higher likelihood of having a hysterectomy.[28]

A Dutch cohort study of women who had already chosen LNG-IUS, endometrial ablation, or hysterectomy for the management of idiopathic heavy menstrual bleeding sheds some light on complexities of women's decision-making about treatment.[29] Table 2 summarizes the information patients received about their options, the proportion who chose each treatment, and the main reasons for their preferences.

Table 2: Summary of Most Common Reasons for Selection of Treatment for Heavy Menstrual Bleeding

Information Provided About Treatment Option	% Choosing	Most Common Reasons for Selection (% Citing Reason[a])
Levonorgestrel-releasing intrauterine system • Insertion in outpatient clinic • No anesthesia • Interim blood loss after insertion (several months) • Quick return to daily activities	16	• Want to avoid admission to hospital (39%) • Want to avoid general anesthesia (26%) • Want fast recovery (22%) • Do not want hysterectomy (22%)
Endometrial ablation • Day treatment • 20-minute procedure under anesthesia (general or regional) • Possible vaginal discharge after procedure (4–6 weeks) • Possible change in sexual experiences	67	• Do not want intrauterine system (22%) • Do not want hysterectomy (19%) • Prefer short hospital stay (15%)
Hysterectomy • Hospitalization for 5–7 days • Procedure under anesthesia (general or regional) • Possible complications from procedure or anesthesia • Recovery period of 4–6 weeks • Possible change in sexual experiences	17	• Want definitive solution to bleeding (85%)

[a]Proportions may add up to more than 100% as respondents could select more than one reason.
Source: Bourdez et al, 2004.[29]

Ontario gynecology experts reported that the treatment received by female relatives, cultural values around menstruation and amenorrhea (no menstruation), and misperceptions or lack of awareness about treatment options influence women's choices for treatment of heavy menstrual bleeding. In particular, the LNG-IUS is a type of intrauterine device (IUD), and misperceptions about IUDs persist despite the fact that most of the common concerns (e.g., pelvic inflammatory disease, difficult or painful insertion, infertility) are not based on evidence.[30] These misperceptions by both patients and providers can serve as barriers to women selecting an IUD, whether for contraception or treatment of heavy menstrual bleeding.[30] In addition, the chance of amenorrhea with the LNG-IUS is up to 40%, which may be undesirable to some women or in cultures that view menstruation as a natural and necessary cleansing process.[30,31] Globally, uptake of IUDs for contraception has been estimated by United Nations data to be nearly 14% of women aged 15 to 49 who are in committed relationships.[30] Despite widespread guidance from international and local authorities supporting IUD use in nearly all women, only 2.3% of women aged 15 to 50 in Canada use either copper IUDs or LNG-IUS for contraception.[30] Women's perceptions, beliefs, awareness of treatment options, and the experiences and choices of trusted others all contribute to shaping their treatment choices.

Technology

The 52-mg levonorgestrel-releasing intrauterine system **(**LNG-IUS) is inserted in the uterus and releases up to 20 mcg of levonorgestrel per day (mean 14 mcg/day).[32] Levonorgestrel is a progestogen that suppresses the endometrium, reducing the volume and duration of menstrual bleeding within a few months of use. The device is a polyethylene T-frame with a cylindrical drug reservoir. The 52-mg LNG-IUS is designed to be used for up to 5 years, after which the device should be removed or replaced if desired. The device can be inserted by obstetrician/gynecologist and many family physicians, and it can be removed by most physicians.[33]

During its 15 years of use, the LNG-IUS has been well studied. A great deal of published evidence documents its therapeutic benefits and side effects.[34] Some studies have estimated the LNG-IUS to be a good option for managing heavy menstrual bleeding in upwards of 85% of women.[35] Research has found that the decrease in menstrual blood loss is usually seen within the first 3 months after the device is inserted,[36] and the reduction can be so large[37] that it has even lead women to cancel scheduled surgery.[36,38] While intermenstrual bleeding (spotting) and mild hormonal side effects are very common during the first few months, they tend to decrease and disappear with time.[33] There is evidence for clinical effectiveness in women with different underlying causes such as uterine fibroids,[39,40] adenomyosis,[41] and heavy menstrual bleeding resulting from anticoagulant medication.[42] However, questions remain about whether the LNG-IUS has a role as a high-quality treatment alternative compared with other options, including hysterectomy and endometrial ablation, to manage idiopathic heavy menstrual bleeding.

The LNG-IUS is very safe and minimally invasive, but not risk-free.

- Uterine perforation (when the device partially breaks through the outer surface of the uterus or is inadvertently inserted through the uterus into the abdominal cavity) occurs in 1.4 per 1,000 insertions (ranges reported 0.3 to 2.6 per 1,000).[33,43,44] The primary risk factor for perforation is breastfeeding[45,46] or postpartum insertion (this risk decreases over time but is elevated up to 36 weeks after delivery).[33]
- Expulsion of the device has been reported to occur in as many as 5% of cases,[33] though large cohort studies have estimated the rate of device expulsion to be 0% per year for nulliparous women (those who have never given birth) and 0.2% for parous women (who have given birth).[47] Historical concerns about increased risk of adverse events in nulliparous women have not been substantiated by further investigation.[48]
- In the long-term, the LNG-IUS is associated with a slightly elevated risk of breast cancer,[49] and women with current or recent breast cancer (within 5 years) are contraindicated for any treatment with progestogens.[32] At the same time, a protective effect for endometrial, ovarian, pancreatic, and lung cancers was seen in the same large cohort.[49]
- Use of the LNG-IUS is also associated with increased appearance of ovarian cysts; however, a large study found that the cysts did not cause symptoms and spontaneously resolved in 94% of cases following removal of the device.[50]

Regulatory Information

The Mirena LNG-IUS 52 mg (Bayer, Inc.) is licensed by Health Canada as a drug product for contraception and for the treatment of idiopathic heavy menstrual bleeding for up to 5 years.[33] At the time of writing, Mirena was the only LNG-IUS product currently licensed in Canada for both of these indications. A 13.5-mg LNG-IUS is licensed in Canada for up to 3 years, but it is

indicated for contraception only. The use of LNG-IUS has also been explored as a treatment for endometriosis, adenomyosis, endometrial hyperplasia, and heavy menstrual bleeding due to small fibroids, and as an adjunct to estrogen replacement therapy.[7] However, these all remain off-label uses in Canada.

Context

The Canadian, American, and British guidelines addressing the role of the LNG-IUS for the treatment of heavy menstrual bleeding are summarized in Table 3. The guidance from the UK National Institute for Health and Care Excellence (NICE) on heavy menstrual bleeding explicitly recommends the LNG-IUS as the first-line medical treatment above oral or injectable medical options.[2]

Table 3: Existing Guidelines for the Levonorgestrel-Releasing Intrauterine System for Heavy Menstrual Bleeding

Organization, Guideline	Year	Summary of Recommendations
SOGC, Endometrial Ablation in the Management of Abnormal Uterine Bleeding[51]	2015	The LNG-IUS should be discussed prior to any surgical option for women with abnormal uterine bleeding and a normal uterine cavity.
SOGC, Menstrual Suppression in Special Circumstances[52]	2014	The Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception identifies abnormal uterine bleeding as a medical indication for menstrual suppression. Combined or progesterone-only hormonal products (including LNG-IUS) can be used continuously to obtain menstrual suppression.
SOGC, Abnormal Uterine Bleeding in Pre-Menopausal Women[3]	2013	Combined oral contraceptive pills, depot medroxyprogesterone acetate, and LNG-IUS significantly reduce menstrual bleeding and should be used in women with abnormal uterine bleeding who desire effective contraception.
University of Texas at Austin, Evaluation and Management of Ovulatory Heavy Menstrual Bleeding (HMB) in Primary Care[53,a]	2012	LNG-IUS should be first-line therapy for heavy menstrual bleeding for women preferring contraception lasting for 5 years.
NICE, Heavy Menstrual Bleeding (Clinical Guidance 44)[2]	2007[b]	If pharmaceutical treatment is appropriate and both nonhormonal and hormonal treatments are acceptable, the LNG-IUS should be considered first, followed by tranexamic acid/NSAIDs/combined oral contraceptives, then norethisterone/injected long-acting progestogens.

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; NICE, National Institute for Health and Care Excellence; NSAID, nonsteroidal anti-inflammatory drug; SOGC, Society of Obstetricians and Gynaecologists of Canada.
[a]From the School of Nursing, Family Nurse Practitioner Program.
[b]Guidance update is in progress as of March 2015 with anticipated publication in August 2016.

Equity Issues

There are two costs associated with the use of the 52-mg LNG-IUS: the cost of the insertion procedure by a physician and the purchase of the product itself from a pharmacy. All Canadian provinces and territories provide coverage for the physician component of the LNG-IUS (exam, insertion, removal), but none provide universal coverage for the drug product itself, which costs about $340 (Ontario Ministry of Health and Long-Term Care, written communication, June 2015). In Ontario, the 52-mg LNG-IUS is publicly funded only for women over 65 years of age or

on social assistance or eligible for the Trillium Drug Program. Similarly, three other provinces (Nova Scotia, Newfoundland and Labrador, and Saskatchewan) provide restricted public coverage of the drug for eligible older women, women on social assistance, or through other income-based coverage. The LNG-IUS is covered under Health Canada's Non-Insured Health Benefit for First Nations and Inuit women.[54,55]

Those women of reproductive age preferring this treatment option and not eligible for coverage under the above described Provincial policies have to pay for the device. Given that this option is fully funded only for seniors and women with significant economic disadvantage, a potential inequity in access to this therapy exists among the majority of women in Ontario and across Canada.

Research Questions

Clinical Evidence Review

What is the effectiveness of the 52-mg levonorgestrel-releasing intrauterine system for idiopathic heavy menstrual bleeding, compared with each of the following treatment options?

- Hysterectomy
- Endometrial ablation
- Usual medical therapy

Economic Evidence Review

What is the evidence from previous research on the cost-effectiveness of the LNG-IUS compared with endometrial ablation, hysterectomy, or nonsurgical intervention in women with heavy menstrual bleeding?

Primary Economic Evaluation

What is the cost-effectiveness, within the context of the Ontario Ministry of Health and Long-Term Care, of the LNG-IUS compared with surgical interventions (hysterectomy and endometrial ablation) in women with heavy menstrual bleeding?

Budget Impact Analysis

What is the potential budget impact in Ontario of publicly funding the LNG-IUS for treatment of heavy menstrual bleeding compared with hysterectomy and endometrial ablation?

CLINICAL EVIDENCE REVIEW

Objective

The objective of the clinical evidence review was to assess the effectiveness of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) for treatment of heavy menstrual bleeding, compared with hysterectomy, endometrial ablation, and usual medical therapy.

Methods

Literature Search

In scoping the state of knowledge on the topic, we discovered a large number of recent, high-quality systematic reviews that, collectively, have broadly and comprehensively examined treatments for heavy menstrual bleeding. We therefore developed a review approach targeting systematic reviews. We applied a study design filter to the search strategy to return systematic reviews, health technology assessments, and meta-analyses of randomized controlled trials (RCTs) comparing LNG-IUS 52-mg to hysterectomy, endometrial ablation, or usual medical therapy.

We performed a literature search on August 17, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database, for studies published from inception to August 17, 2015.

Search strategies were developed by medical librarians using medical subject headings (MeSH). See Appendix 1 for full details, including all search terms.

Literature Screening

A single reviewer screened the abstracts and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. We used DistillerSR to review citations, and reasons for exclusion of full-text articles are reported in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

Inclusion Criteria

- English-language full-text publications
- Studies published before August 17, 2015
- Systematic reviews, health technology assessments, meta-analyses of randomized controlled trials; if none identified, randomized controlled trials meeting all other inclusion criteria
- Women of reproductive age with idiopathic heavy menstrual bleeding
- 52-mg LNG-IUS that delivers up to 20 mcg levonorgestrel per day, indicated for heavy menstrual bleeding and approved for up to 5 years
- Comparison with at least one of:

  - total or supracervical (subtotal) hysterectomy via vaginal, laparoscopic, robotic, or abdominal surgical approach
  - endometrial ablation or resection with first- or second-generation techniques
  - usual medical therapy (systemic medications) consisting of nonsteroidal anti-inflammatory drugs, antifibrinolytics, combined hormonal contraceptives, oral progestogens, depot-medroxyprogesterone acetate, danazol, or gonadotropin-releasing hormone agonists
- Reporting outcomes of interest

Exclusion Criteria

- Animal or in vitro studies
- Quasi-randomized studies, observational or therapeutic studies, editorials, case reports, commentaries
- Menopausal women or those seeking treatment for perimenopausal menstrual bleeding, or menorrhagia due to structural or pathological causes (e.g., fibroids, cancer, polyps, adenomyosis, endometriosis, systemic bleeding disorders)
- Intrauterine systems releasing different doses of levonorgestrel, other progestogens, or other medications, or other 52-mg levonorgestrel products with differing guidance on indications or administration
- Noncomparative studies or those using an ineligible or inactive comparator (e.g., placebo, observation)
- Not reporting outcomes of interest

Outcomes of Interest

Primary outcome:

- Quality of life (overall or health-related as measured by a validated tool)

Secondary outcomes:

- Menstrual bleeding (measured by pictorial blood loss assessment chart (PBAC), self-report, or alkaline hematin test)
- Satisfaction/acceptability (measured by a validated tool, if evaluated separately from quality of life)
- Complications/side effects/adverse events of the intervention and all comparators

Data Extraction

Data on study context, methods, population, intervention, comparator, outcomes, results, and risk of bias items were extracted by a single reviewer based on the information available in the published articles. Data included study eligibility criteria and population characteristics (age, parity, medical history, socioeconomic characteristics, obesity status, etc.); information on the LNG-IUS procedure (location of insertion), surgical approach to hysterectomy or endometrial ablation technique (device, location, administering clinician) and type of medical therapy; and information related to all defined outcomes.

Statistical Analysis

Statistical synthesis was not appropriate due to methodological heterogeneity in the studies we identified; thus, we analyzed the studies in a narrative synthesis.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[56] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Expert Consultation

We sought expert consultations on the use of the 52-mg LNG-IUS for idiopathic heavy menstrual bleeding. Members consulted included physicians in the specialty areas of gynecology and family medicine. The role of the expert advisors was to provide important contextual information on the use of the LNG-IUS, including expertise on the health condition, patients, diffusion of the technology, or clinical issues that contextualize the research question to Ontario. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 311 citations published up until August 17, 2015. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment. Seventeen systematic reviews on LNG-IUS (including two health technology assessments) were identified. We hand-searched the reference lists of the systematic reviews, along with health technology assessment websites and other sources, to identify additional relevant studies. One additional citation (a health technology assessment) was identified, for a total of 18 systematic reviews.

Systematic Reviews Identified

Each of the 18 systematic reviews compared the LNG-IUS with one or more of usual medical therapy, endometrial ablation, and/or hysterectomy. The earliest was published in 2001 and the two most recent in 2015. Table 4 summarizes the scope of the identified systematic reviews from the literature search.

No systematic review met all inclusion criteria for our clinical evidence review. The published systematic reviews varied in their overall objectives and in their definition of the population with heavy menstrual bleeding. While most did include the population of interest, they combined it with mixed, ineligible populations which precluded their authors from making conclusions about idiopathic heavy menstrual bleeding. Thus, we used the 18 systematic reviews to identify eligible RCTs that only included women with idiopathic heavy menstrual bleeding. We obtained the full texts of all RCTs included in all of the systematic reviews to assess their eligibility against our inclusion and exclusion criteria. Figure 1 shows the flow of citation assessment and the reasons articles were excluded.

Table 4: Systematic Reviews with Relevance to the Levonorgestrel-Releasing Intrauterine System for Heavy Menstrual Bleeding

Author, Year	Objective	Search Dates (Records Screened, N)	Databases Searched	LNG-IUS Comparator(s)
Lethaby et al, 2015[25]	Determine the effectiveness, acceptability, and safety of progesterone or progestogen-releasing IUDs in achieving a reduction in HMB	Up to Jan 2015 (609)	Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register; CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO; MetaRegister of Clinical Trials; US NIH Clinical Trials Register; WHO International Clinical Trials Registry Portal; Web of Knowledge register	Medical therapy EA Hysterectomy
Bitzer et al, 2015[57]	Provide a comprehensive summary of the efficacy and safety of available medical treatments of HMB	Up to Mar 2013 (2,552)	MEDLINE; EMBASE	Medical therapy EA Hysterectomy
Uhm and Perriera, 2014[58]	Focus on the efficacy of hormonal contraceptive methods in the treatment of HMB in reproductive-aged women	Up to Feb 2014 (734)	PubMed	Medical therapy
Qiu et al, 2014[34]	Compare the effects of the LNG-IUS with conventional medical treatment in reducing HMB	Up to Apr 2014 (1,198)	MEDLINE; EMBASE; CENTRAL	Medical therapy
Hartmann et al, 2013[59]	Evaluate interventions and direct comparisons among treatments that are often used and promoted as first-line choices with the goal of clearly describing their effectiveness and potential harms for use in primary care settings	1980 to Sep 2011/Jun 2012 (1,775)	MEDLINE; CINAHL; EMBASE	Medical therapy Hysterectomy
Lethaby et al, 2013[60]	Investigate the effectiveness of NSAIDs in achieving a reduction in menstrual blood loss in women of reproductive years with HMB	Up to Jul 2012 (NR)	Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register; CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO; trial registers; citation indices; LILACS; PubMed; OpenSIGLE; Google/Google Scholar	Medical therapy
Matteson et al, 2012[61]	Compare hysterectomy and less invasive alternatives for AUB in 7 clinically important domains	Up to Jan 2011 (5,503)	MEDLINE	Hysterectomy
Kauntiz and Inki, 2012[62]	Review the clinical evidence and provide and update on the risk and benefits of using the LNG-IUS in the management of HMB	Up to Apr 2011 (NR)	MEDLINE; EMBASE	Medical therapy EA Hysterectomy
Duckitt and Collins, 2012[9]	Answer the following clinical questions: What are the effects of medical treatments for menorrhagia? What are the effects of surgical treatments for menorrhagia? What are the effects of endometrial thinning before endometrial destruction in treating menorrhagia?	Up to Jun 2011 (NR)	MEDLINE; EMBASE; CDSR; Cochrane Library; DARE; HTA database	Medical therapy EA Hysterectomy
Middleton et al, 2010; Bhattacharya et al, 2011[63,64]	Determine the clinical effectiveness and cost-effectiveness of hysterectomy, 1st- and 2nd-generation EA, and Mirena for the treatment HMB	Up to May 2010 (556)	Cochrane Library; MEDLINE; CINAHL; Meta-Register of Controlled Trials; International Standard Randomised Control Trial Number register	EA Hysterectomy

Author, Year	Objective	Search Dates (Records Screened, N)	Databases Searched	LNG-IUS Comparator(s)
Blumenthal et al, 2011[65]	Review the literature for economic and HRQOL data associated with the use of the LNG-IUS in the management of HMB	Up to Jul 2010 (NR)	MEDLINE; EMBASE	EA Hysterectomy
Marjoribanks et al, 2010[17]	Compare the effectiveness, safety, and acceptability of surgery versus medical therapy for HMB	Up to Mar 2010 (NR)	Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register; CENTRAL; MEDLINE; EMBASE; PsycINFO	EA Hysterectomy
Kaunitz et al, 2009[35]	Compare the effects of LNG-IUS and EA in reducing HMB	Up to Jan 2009 (NR)	MEDLINE; EMBASE	EA
Lethaby et al, 2008[66]	Investigate the effectiveness of oral progestogen therapy taken either during the luteal phase or for a longer course of 21 days in achieving a reduction in menstrual blood loss in women of reproductive years with HMB	Up to Apr 2007 (NR)	Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register; CENTRAL; MEDLINE; EMBASE;	Medical therapy
Iavazzo et al, 2008[67]	Review the role of TBEA as an alternative in treating AUB	1994 to May 2007 (NR)	PubMed	EA
NICE, 2007[2]	Offer best practice advice on the care of women with HMB	Up to Jun 2006 (NR)	MEDLINE, EMBASE, CINAHL, British Nursing Index, PsycINFO, CENTRAL, Cochrane Library, DARE, NHS EED, NHS CRD	Medical therapy EA Hysterectomy
Varma et al, 2006[68]	Expand on past reviews by incorporating recent advances and performing an up-to-date systematic review focused entirely on LNG-IUS, evaluating the quality of supporting evidence and, where available, present information relating to adverse events, cost-effectiveness, and HRQOL	1996 to 2005 (NR)	MEDLINE; EMBASE; CENTRAL; CDSR; DARE; National Research Register; MRC Clinical Trials Register; NHS CRD	Medical therapy EA Hysterectomy
Stewart et al, 2001[69]	Determine whether the LNG-IUS (currently licensed for contraceptive use) may reduce menstrual blood loss with few side effects	Up to Mar 1999 (143)	MEDLINE; CINAHL; EMBASE; Grateful Med; BMJ Website Archiving Facility; Cochrane Library; Best Evidence; NHS CRD; Internet search engines	Medical therapy EA

Abbreviations: AUB, abnormal uterine bleeding; BMJ, British Medical Journal; CENTRAL, The Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; CINAHL, Cumulative Index of Nursing and Allied Health Literature; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; EA, endometrial ablation; EED, Economic Evaluation Database; EMBASE, Excerpta Medica database; HMB, heavy menstrual bleeding; HRQOL, health-related quality of life; HTA, health technology assessment; IUD, intrauterine device; LILACS, Latin American and Caribbean Health Sciences Literature; LNG-IUS, levonorgestrel-releasing intrauterine system; MRC, Medical Research Council; NICE, National Institute for Health and Care Excellence; NIH, National Institutes of Health; NHS, National Health Service; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; TBEA, thermal balloon endometrial ablation; WHO, World Health Organization.

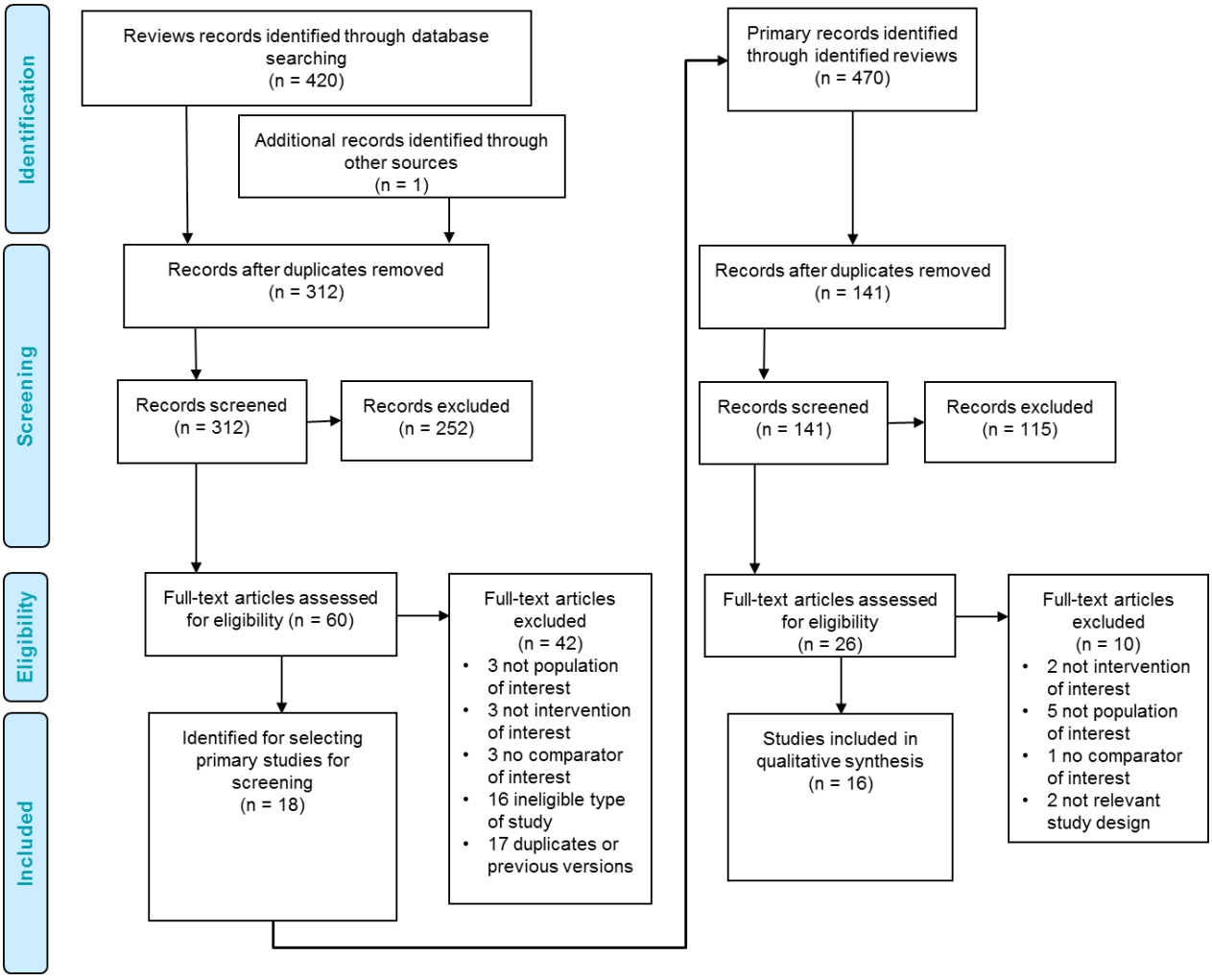

Figure 1: PRISMA Flow Diagram for Clinical Evidence Review

Source: Adapted from Moher et al, 2009.[70]

Randomized Controlled Trials

From the 18 systematic reviews summarized in Table 4, we obtained 26 unique RCTs evaluating the LNG-IUS. We excluded 10 of these studies: two that investigated LNG-IUS with alternative dosage,[71,72] three that included populations with heavy menstrual bleeding due to structural or pathological causes,[39-41] one that was of a mixed population (heavy menstrual bleeding and endometrial hyperplasia),[73] one whose population was women experiencing iatrogenic heavy menstrual bleeding from anticoagulant medication,[42] one study without a comparator of interest,[74] and two others because they did not use randomized study designs.[75,76]

Ultimately, 16 RCTs reported in 23 articles met the inclusion criteria for our review.[77-99] Where multiple articles reported on the same study and results, we extracted data from the article that reported the most comprehensive and up-to-date data on each outcome. We hand-searched the reference lists of the included studies, along with health technology assessment websites and other sources, and no additional relevant studies were identified.

We also identified two ongoing relevant RCTs.[25] One comparing the LNG-IUS to endometrial ablation is expected to close recruitment in December 2015 (NTR2984).[100] The other trial is comparing the LNG-IUS with combined oral contraceptives and is expected to be completed in January 2017 (NCT02002260, ClinicalTrials.gov).

Of the 16 included RCTs, two compared the 52-mg LNG-IUS with hysterectomy, nine compared it with endometrial ablation techniques, and five compared it with medical therapies. All included RCTs stated that they excluded women with heavy menstrual bleeding as a result of anatomical, structural, and pathological causes (Table 5).

Table 5: Included RCTs Evaluating the 52-mg Levonorgestrel-Releasing Intrauterine System for Idiopathic Heavy Menstrual Bleeding

Author, Year	Country, No. Sites (if > 1)	Recruitment Period	Sample Size (% Lost to Follow-Up)	Heavy Menstrual Bleeding Criteria[a]
Compared with hysterectomy				
Sesti et al, 2012[77]	Italy	Apr 2008 – Sep 2010	72 (0)	Score ≥ 100 PBAC
Hurskainen et al, 2001, 2004; Heliovaara-Peippo et al, 2013[78-80]	Finland, 5	Oct 1994 – Sep 1997	236 (6)[b]	Referred to gynecologist
Compared with endometrial ablation				
Ghazizadeh et al, 2011[81]	Iran	NR	104 (12)	Score ≥ 100 PBAC
De Souza et al, 2010[82,83]	Brazil	Jan 2005 – Mar 2007	58 (10)	> 80 mL according to PBAC
Shaw et al, 2007[84]	UK	Nov 2001 – Oct 2003	66 (35)	Score ≥ 120 PBAC[c]
Tam et al, 2006[85]	China	NR	44 (25)	Documented history
Busfield et al, 2006[86]	New Zealand	Mar 1999 – Jul 2001	79 (18)	Self-described
Malak and Shawki, 2006[87]	Egypt	NR	60 (7)	Score ≥ 100 PBAC
Barrington et al, 2003[88]	UK	NR	50 (12)	NR
Kittelsen and Istre, 1998; Istre and Trolle, 2001; Rauramo et al, 2004[89-91]	Norway	Mar 1993 – Oct 1995	59 (31)	Score 75 PBAC + 60mL
Crosignani et al, 1997[92]	Italy	NR	70 (1)	Score ≥ 100 PBAC
Compared with usual medical treatment				
Gupta et al, 2013, 2015[93,94]	UK, 63	Feb 2005 – Jul 2009	571 (26)	RCOG definition[d]
Shaaban et al, 2011[95]	Egypt	May 2003 – Mar 2004	112 (15)	Self-described
Kaunitz et al, 2012, 2010[96,97]	US, Canada, Brazil, 55	Jun 2006 – Jun 2008	165 (12)	> 80 mL alkaline hematin
Reid and Virtanen-Kari, 2005[98]	England	May 1996 – Dec 1998	51 (18)	> 80 mL alkaline hematin
Irvine et al, 1998[99]	UK	NR	44 (18)	> 80 mL alkaline hematin

Abbreviations: PBAC, pictorial blood loss assessment chart; NR, not reported; RCOG, Royal College of Obstetrics and Gynaecology guidelines.
[a]A score of > 100 on the PBAC reflects objective menorrhagia determined by the alkaline hematin method (i.e., > 80 mL blood loss per cycle).
[b]Proportion lost to follow-up at 10 years.
[c]Mean PBAC score over 2 cycles.
[d]Guideline defines menorrhagia as heavy cyclical menstrual blood loss over several consecutive cycles without any intermenstrual or postcoital bleeding; study investigators defined several as 3 consecutive cycles.

Methodological Quality of the Included Studies

Complete results of our analysis of the methodological quality of the body of evidence and risk of bias for included studies are presented in Appendix 2.

Results for Quality of Life

Nine studies evaluated quality of life using various validated assessment tools.[77,79,82,85-87,92,93,95] The most common assessment tool used for general quality of life was the Short Form 36 (SF-36), comprised of eight multi-item dimensions of quality of life that are scored from 0 to 100 (higher scores indicate less disability). Dimensions include general health, physical functioning, mental health, social functioning, vitality, pain, and physical and emotional role functioning.[101] Other generic quality of life assessment tools used were the EuroQol (EQ) EQ-5D and the EQ visual analogue scale (EQ-VAS).[102] The EQ-5D is a five-dimension measure of quality of life (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that asks a respondent to rank each dimension into three states (no problems, some problems, extreme problems).[103,104] Alternatively, the EQ-VAS asks respondents to mark on a line their perception of their overall health, from best imaginable to worst imaginable.

One study measured health-related quality of life using the Center for Disease Control and Prevention's Healthy Days Measure (HRQOL-4).[95] This instrument consists of four items: self-rated health and the number of days in the past 30 days that the respondent has experienced physically unhealthy days, mentally unhealthy days, and activity limitation days.[105,106]

Another single study evaluated health-related quality of life with the Psychological General Well-Being Index, which is focused on overall psychological wellness including anxiety, depressed mood, positive well-being, self-control, general health, and vitality, but does not include any evaluation of physical health.[107]

One study used a disease-specific quality of life measure in addition to general assessments.[93] The menorrhagia multi-attribute scale (MMAS) asks women with heavy menstrual bleeding to report their experience with practical difficulties, social life, psychological health, physical health and well-being, work/daily routines, and family life/relationships.[108] The MMAS instrument has been validated using the SF-36, EQ-5D, and Sexual Activity Questionnaire and seeks to capture the subjective experience of heavy menstrual bleeding.[109]

Of the eight RCTs that reported on quality of life outcomes, the majority (75%) found significant improvement in quality of life from baseline, within both the LNG-IUS and comparator groups (medical therapy or surgery).[77,79 86,87 93,95] Given that the measures and metrics (i.e., timing of measurements and summary statistics reported) were heterogeneous among these studies, we were unable to conduct a quantitative synthesis of the data. Quality of life results are summarized narratively, by comparator, below.

LNG-IUS Versus Hysterectomy

Two studies compared the effect on quality of life of the LNG-IUS and hysterectomy (Table 6).[77,79] Both studies used the SF-36 questionnaire to measure quality of life, and one study[79] also used the EQ-5D. The characteristics of the study populations were generally similar between studies with regard to age, body mass index, and parity. Sesti et al[77] reported that all participants were Caucasian, and the Hurskainen et al study[79] described the educational attainment in the study groups as being similar (LNG: 32% elementary, 44% lower secondary,

24% upper secondary; hysterectomy: 28% elementary, 40% lower secondary, 32% upper secondary).

Table 6: Quality of Life Studies of Women Receiving LNG-IUS or Hysterectomy

Author, Year	Hysterectomy Type(s) (n[a])	LNG-IUS (n[a])	Age, Years, Mean (SD)	BMI, Mean (SD)	Parity, Mean (SD)	Baseline Menstrual Bleeding, Mean (SD)
Sesti et al, 2012[77]	Laparoscopic supracervical (36)	Mirena (36)	41.7–47.5 (5.9–7.4)	24–24.5 (3.4–3.9)	1.8–2.0 (0.9–1.3)	PBAC score 911–937 (330–344)
Hurskainen et al, 2001[79]	Vaginal 28%, abdominal 20%, laparoscopic 52% (117)	Mirena (119)	43 (3.4)	25.8 (4.8)	2.1 (1.1)	128–130 mL (116)

Abbreviations: BMI, body mass index; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial blood loss assessment chart; SD, standard deviation.

[a]Number of participants randomized to each study arm.

In the Hurskainen et al trial,[79] 55 women randomized to the LNG-IUS group went on to have hysterectomy during the 10 years after randomization. Most of these subsequent surgeries occurred within the first 5 years after randomization, including 44% (24 women) within the first year and 47% between 12 months and 5 years (26 women). Only 9% (5 hysterectomies) occurred between years 5 and 10 of the study.[79] No women in the Sesti et al trial[77] discontinued their LNG-IUS treatment.

In both studies, all dimensions of quality of life improved significantly from baseline within both treatment groups. To compare between the groups, the Hurskainen et al study[79] reported change in quality of life from baseline, whereas the Sesti et al study[77] reported the quality of life scores at the various assessment points. Therefore, we could not combine the data from these studies. Table 7 outlines the measures and dimensions of quality of life where results differed significantly between the treatment groups in each study.

Table 7: Quality of Life Results in Women After LNG-IUS or Hysterectomy

Author, Year	QOL Measure	Follow-Up	QOL Results	*P*
Sesti et al, 2012[77]	SF-36	3 mo	**LNG > Hyst** • Emotional role functioning • Physical role functioning • Mental health	< .05
	SF-36	6 mo	**LNG > Hyst** • Emotional role functioning • Physical role functioning • Mental health	< .05
	SF-36	1 y	**LNG > Hyst** • Emotional role functioning • Physical role functioning • Social function • Mental health • Vitality	< .05
	SF-36	2 y	**LNG > Hyst** • Emotional role functioning • Mental health Hyst > LNG • Less pain	< .05 < .05
Hurskainen et al, 2001[79]	EQ-5D	1 y	**No difference[a]**	.90
	SF-36		Hyst > LNG • Less pain[a]	.01
	EQ-5D	5 y	**No difference[a]**	.60
	SF-36		**No differences**	.60–.90
	EQ-5D	10 y	**No difference[b]**	.94
	SF-36		**No differences**	0.39–0.91

Abbreviations: EQ-5D, EuroQol 5-dimensions; Hyst, hysterectomy; LNG, levonorgestrel-releasing intrauterine system; mo, months; QOL, quality of life; SF-36, 36-item short-form survey; y, years.
[a]Reduction expressed as magnitude of change from baseline pain assessment.
[b]No significant difference in EQ-5D change from baseline, nor change between 5 and 10 years.

Table 8 shows the overall study findings for quality of life, by follow-up time. In the Sesti study,[77] which compared LNG-IUS and laparoscopic supracervical hysterectomy, only the dimensions of general health, physical function, and vitality did not show a difference from pre-treatment levels at 1-year follow-up. The differences found in some SF-36 dimensions at each time point favoured greater scores in the LNG-IUS group, with the exception of less pain in the hysterectomy group at 1 year[79] and 2 years.[77]

Table 8: Quality of Life Improvement by Follow-Up Time: LNG-IUS vs. Hysterectomy

Author, Year	Follow-Up	QOL Improvement: LNG-IUS vs. Hysterectomy	*P*
Sesti et al, 2012[77]	3 mo	**LNG better** • 3[a] of 8 SF-36 dimensions **No difference** • 5 of 8 SF-36 dimensions	< .05
Sesti et al, 2012[77]	6 mo	**LNG better** • 3[a] of 8 SF-36 dimensions **No difference** • 5 of 8 SF-36 dimensions	< .05
Sesti et al, 2012[77]	1 y	**LNG better** • 5[b] of 8 SF-36 dimensions **No difference** • 3 of 8 SF-36 dimensions	< .05
Hurskainen et al 2001[79]		Hysterectomy better • 1[c] of 8 SF-36 dimensions **No difference** • All EQ-5D dimensions	.01 .90
Sesti et al, 2012[77]	2 y	**LNG better** • 2[d] of 8 SF-36 dimensions Hysterectomy better • 1[c] of 8 SF-36 dimensions	< .05 < .05
Hurskainen et al 2001[79]	5 y	**No difference** • All SF-36 dimensions • All EQ-5D dimensions	.60–.90 .60
Hurskainen et al 2001[79]	10 y	**No difference** • All SF-36 dimensions • All EQ-5D dimensions	.39–.91 .94

Abbreviations: EQ-5D, EuroQol 5-dimensions; LNG, levonorgestrel-releasing intrauterine system; mo, months; QOL, quality of life; SF-36, 36-item short-form survey; y, year

[a]Emotional role functioning, physical role functioning, and mental health dimensions of SF-36.

[b]Emotional role functioning, physical role functioning, mental health, vitality, and social function dimensions of SF-36.

[c]Pain dimension of SF-36.

[d]Emotional role functioning and mental health dimensions of SF-36.

Overall, in these two RCTs the improvement in quality of life offered by LNG-IUS was either superior or not significantly different than the benefit of hysterectomy.

LNG-IUS Versus Endometrial Ablation

Five studies compared the impact on quality of life of LNG-IUS and endometrial ablation techniques.[82,85-87,92] Table 9 summarizes the study characteristics. Ages of study participants were generally similar across RCTs, but few studies reported information on body mass index (BMI)[86,92] and parity.[82,87,92] One RCT stipulated failure of medical therapy as an eligibility criteria,[85] and one recruited women scheduled for hysterectomy.[87]

Table 9: Quality of Life Studies of Women Receiving LNG-IUS or Endometrial Ablation

Author, Year	Ablation Technique (n[a])	LNG-IUS (n[a])	Age, Years, Mean (SD)	BMI, Mean (SD)	Parity, Mean (SD)	Baseline Menstrual Bleeding, Mean (SD)
de Souza et al, 2010[82]	ThermaChoice TBEA (30)	Mirena (28)	42–43.4 (0.7)	NR	2.4–2.6 (0.2–0.4)	PBAC score 492–522 (56.8–90.3)
Tam et al, 2006[85]	ThermaChoice TBEA[b] (22)	Mirena (22)	44.1–44.7 (2.7–3.5)	NR	NR	PBAC score 460–534 (270–525)
Busfield et al, 2006[86]	ThermaChoice TBEA (41)	Mirena (42)	NR (range 40–49)	28.9–29.7 (5.4–8.0)	NR	PBAC score 490–502 (419–422)
Malak and Shawki, 2006[87]	Endometrial resection (30)	Mirena (30)	46.3–47.7 (1.3–1.4)	NR	1.9–2.4 (0.3–1.9)	PBAC score 316–346 (143–152)
Crosignani et al, 1997[92]	Endometrial resection (35)	Mirena (35)	43.8–45.4 (3.8)	24.0–25.3 (3.0–4.4)	1.6–1.8 (0.9–1.1)	PBAC score 181–204 (59.4–82.9)

Abbreviations: BMI, body mass index; LNG-IUS, levonorgestrel-releasing intrauterine system; NR, not reported; PBAC, pictorial blood loss assessment chart; SD, standard deviation; TBEA, thermal balloon endometrial ablation.

[a]Number of participants randomized to each study arm.

[b]Preoperative thinning of the endometrium was performed with either danazol or gonadotropin-releasing hormone agonists.

Three studies measured general quality of life using the SF-36,[85,86,92] one study used the EQ-VAS,[87] and another single study used the Psychological General Well-Being Index.[82] All studies measured quality of life at the end of 1 year, with only one evaluating after 2 years[86] and another at 5 years.[82] The quality of life findings of these studies are summarized in Table 10.

Table 10: Quality of Life Results in Women After LNG-IUS or Endometrial Ablation

Author, Year	QOL Measure	Follow-Up	QOL Results	*P*
de Souza et al, 2010[82]	PGWBI	5 y	**No difference between groups**	.247
Tam et al, 2006[85]	SF-36	1 y	EA > LNG • General health perception • Mental health	 .024 .021
Busfield et al, 2006[86]	SF-36	3 mo 1 y 2 y	**No differences** **No differences** **No differences**	NR
Malak and Shawki, 2006[87]	EQ-VAS	6 mo 1 y	**No differences** **No differences**	NR
Crosignani et al, 1997[92]	SF-36	1 y	**No differences**	NR

Abbreviations: EA, endometrial ablation; EQ-VAS, EuroQol visual analogue scale; LNG, levonorgestrel-releasing intrauterine system; mo, month; NR, not reported; PGWBI, Psychological General Well-Being Index; QOL, quality of life; SF-36, 36-item short-form survey; y, year.

Two studies reported no significant change in quality of life within treatment groups compared with baseline.[82,85] Two other studies found significant improvements within treatment groups from baseline.[86,87] The fifth study did not report change within groups from baseline.[92]

Three studies found no significant differences in any of the domains of quality of life between women treated with LNG-IUS compared with those receiving endometrial ablation.[86,87,92] Psychological well-being did not differ between the endometrial ablation and LNG-IUS groups, at baseline or at 5 years post-treatment.[82] The Tam et al study[85] found that participants treated

with endometrial ablation had statistically significantly superior general health and mental health status at 1 year post-treatment compared with the LNG-IUS group, and no differences in the other six dimensions of quality of life. The quality of life results across the body of evidence did not appear to differ among studies at low risk of bias[86,87] or at higher risk of bias.[82,85,92] Table 11 shows the overall study findings for quality of life, by follow-up time.

Table 11: Quality of Life Improvement by Follow-up Time: LNG-IUS vs. Endometrial Ablation

Author, Year	Follow-Up	QOL Improvement: LNG vs. EA	*P*
Busfield et al, 2006[86]	3 mo	**No difference** • All SF-36 dimensions	NR
Malak and Shawki, 2006[87]	6 mo	**No difference** • EQ-VAS	NR
Tam et al, 2006[85]	1 y	EA better • 2[a] of 8 SF-36 dimensions **No difference** • 6 of 8 SF-36 dimensions	.021–.024
Busfield et al, 2006[86]		**No difference** • All SF-36 dimensions	NR
Malak and Shawki, 2006[87]		**No difference** • EurQol VAS	NR
Crosignani et al, 1997[92]		**No difference** • All SF-36 dimensions	
Busfield et al, 2006[86]	2 y	**No difference** • All SF-36 dimensions	NR
de Souza et al, 2010[82]	5 y	**No difference** • All PGWBI dimensions	.247

Abbreviations: EA, endometrial ablation; ; EQ-VAS, EuroQol visual analogue scale; LNG, levonorgestrel-releasing intrauterine system; mo, months; NR, not reported; PGWBI, Psychological General Well-Being Index; QOL, quality of life; SF-36, 36-item short-form survey; y, year
[a]General health perception and mental health dimensions of SF-36.

Both LNG-IUS and endometrial ablation improved quality of life, and most of the five studies found that the improvement in quality of life offered by LNG-IUS was not significantly different from the benefit of endometrial ablation.

LNG-IUS Versus Usual Medical Therapy

Two studies compared the effect of the LNG-IUS with usual medical therapies on quality of life (Table 12).[93,95] The ECLIPSE trial (Effectiveness and Cost-effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care Against Standard Treatment for Menorrhagia) by Gupta et al[93,94] used a menorrhagia-specific assessment tool to measure health-related quality of life. The second study by Shaaban et al[95] used the HRQOL-4 tool from the Centers for Disease Control and Prevention to evaluate quality of life.

Table 12: Quality of Life Studies of Women Receiving LNG-IUS or Usual Medical Therapy

Author, Year	Medications (n[a])	LNG-IUS (n[a])	Age, Years, Mean (SD)	BMI, Mean (SD)	Parity, MD (Range)	Baseline Menstrual Bleeding, Mean (SD)
Gupta et al, 2013[93]	Mefenamic acid, tranexamic acid, norethindrone, COC, progesterone only pill, MPA injection (286[b])	Mirena (285)	41.8–42.1 (5.0–5.5)	29.1–29.3 (6.1–6.7)	NR	NR
Shaaban et al, 2011[95]	Microvlar low-dose COC (56)	Mirena (56)	38.7–39.3 (5.2–6.7)	29.6–31.1 (5.7–5.9)	3 (1-6)	PBAC score: 306–323 (97.3–131) 274–300 mL (142–150)

Abbreviations: BMI, body mass index; COC, combined oral contraceptive; LNG-IUS, levonorgestrel-releasing intrauterine system; MD, median; MPA, medroxyprogesterone acetate; NR, not reported; PBAC, pictorial blood loss assessment chart; SD, standard deviation.

[a]Number of participants randomized to each study arm.

[b]Proportions of intended prescriptions within the medical therapy arm were as follows: 47% mefenamic and tranexamic acid, 17% tranexamic acid alone, 11% mefenamic acid alone, 7% norethindrone, 6% COC, 5% MPA injection, 3% mefenamic acid and tranexamic acid and COC, 4% other combination.[93]

The ECLIPSE trial permitted participants to change treatments during the trial.[93] At 2 years, 64% of women allocated to the LNG-IUS group had not changed treatments, compared with 38% of those assigned to the usual medical therapy group ($P < .001$). Retention rates of assigned therapy at 5-year follow-up were 47% for LNG-IUS and 15% for usual medical therapy. Of the 228 treatment changes over the duration of the trial, 43% in the medical therapy group switched to LNG-IUS and 39% in the LNG-IUS group changed to usual medical therapy.[93]

Table 13 summarizes the quality of life findings of the two trials that compared LNG-IUS and usual medical therapy.

Table 13: Quality of Life Results in Women After LNG-IUS or Usual Medical Therapy

Author, Year	QOL Measure	Follow-Up	QOL Results	*P*
Gupta et al, 2013[93]	MMAS	6 mo 1 y[a] 2 y[a]	**LNG > UMT** • Practical difficulties • Social life during cycle • Psychological health during cycle • Physical health/well-being during cycle • Work/daily routine during cycle • Family life/relationships during cycle	< .001 for all
	SF-36	2 y	**LNG > UMT** • Physical functioning • Physical role • Emotional role • Social functioning • Energy and vitality • Pain • General health perception	.05 < .001 .007 .001 < .001 < .001 .03
	EQ-5D descriptive	2 y	**No difference**	.38
	EQ-VAS		**No difference**	.12
	MMAS	5 y	**No difference**	.90
	SF-36	5 y	**LNG > UMT** • General health perception	.02
	EQ-5D descriptive	5 y	**No difference**	.40
	EQ-5D VAS		**No difference**	.80
Shaaban et al, 2011[95]	HRQOL-4	1 y	COC > LNG • Fewer mentally unhealthy days[b] **LNG > COC** • Fewer activity limitation days (lost days)[c]	.003 < .001

Abbreviations: COC, combined oral contraceptive; EQ-5D, EuroQol 5-dimensions; HRQOL-4, 4-item health-related quality of life survey; LNG, levonorgestrel-releasing intrauterine system; MMAS, menorraghia multi-attribute scale; mo, month; QOL, quality of life; SF-36, 36-item short-form survey; UMT, usual medical therapy; VAS, visual analogue scale; y, year.

[a]Results are the same at each time point.

[b]Mean in COC group of 4.4 +/– 1.7 days compared with mean in the LNG-IUS group of 6.7 +/– 3.1 days, *P* = .003.

[c]Mean in LNG-IUS group of 1.6 +/– 2.4 days compared with mean in the COC group of 6.7 +/– 2.2 days, *P* < .001.

In each RCT comparing the LNG-IUS and usual medical therapy, quality of life improved significantly from baseline within each study group. Gupta et al[93] found that women receiving the LNG-IUS had better quality of life for 2 years, compared with women receiving usual medical therapies, in all domains of the MMAS (*P* < .001 for all comparisons) and in all domains of the SF-36 (*P* < .05 for all comparisons), with the exception of mental health, for which there was no difference (*P* = .23) at 2 years. At 5 years, the differences favouring the LNG-IUS were no longer statistically significant, save for the general health perception dimension of the SF-36.[93] In contrast, Shaaban et al[95] found significant differences in only two of the four HRQOL-4 domains; women taking combined oral contraceptives had fewer mentally unhealthy days than those treated with the LNG-IUS (mean 4.4 +/- 1.7 days vs. 6.7 +/- 3.1 days, *P* = .003), but women using the LNG-IUS had significantly fewer activity limitation days than women treated with oral contraceptives (mean 1.6 +/- 2.4 days vs. 6.7 +/- 2.2 days, *P* < .001). No difference between study groups was found in the number of physically unhealthy days or self-rated health.[95] Because only two RCTs comparing LNG-IUS and usual medical therapy studied

quality of life, we could not stratify their results by risk of bias. Table 14 shows the overall study findings for quality of life, by follow-up time.

Table 14: Quality of Life Improvement by Follow-Up Time: LNG-IUS vs. Usual Medical Therapy

Author, Year	Follow-Up	QOL Improvement: LNG vs Usual Medical Therapy	*P*
Gupta et al, 2013[93]	6 mo	**LNG better**	
		• All MMAS dimensions	< .001
Gupta et al, 2013[93]	1 y	**LNG better**	
		• All MMAS dimensions	< .001
Shaaban et al 2011[95]		**LNG better**	
		• Fewer activity limitation days on HRQOL-4	< .001
		COC better	
		• Fewer mentally unhealthy days on HRQOL-4	.003
		No difference	
		• Both other HRQOL-4 dimensions	
Gupta et al, 2013[93]	2 y	**LNG better**	
		• All MMAS dimensions	< .001
		• All SF-36 dimensions	< .05
Gupta et al, 2013[93]	5 y	**LNG better**	
		• 1[a] of 8 SF-36 dimensions	.02
		No difference	
		• 7 of 8 SF-36 dimensions	
		• All MMAS domains	
		• EQ-5D VAS	
		• EQ-5D descriptive	

Abbreviations: COC, combined oral contraceptive; EQ-5D, EuroQol 5-dimensions; HRQOL-4, 4-item health-related quality of life assessment tool; LNG, levonorgestrel-releasing intrauterine system; MMAS, menorrhagia multi-attribute scale; mo, month; QOL, quality of life; SF-36, 36-item short-form survey; VAS, visual analogue scale; y, year.
[a]General health perception dimension of SF-36.

Overall, the LNG-IUS improved quality of life significantly more than usual medical therapy in the first years of use, although with some variation in the dimensions that improved at various time points. By 5 years, however, there was no evidence of a significant difference in the improvement in quality of life between usual medical therapy and the LNG-IUS.

Summary of Results for Quality of Life

Of the nine RCTs that offer evidence on the impact of the LNG-IUS on quality of life, two did not find improvement from baseline,[82,85] and one did not evaluate change from baseline.[92] The lack of change within treatment groups may be due to using a measure of quality of life that had no assessment of physical well-being[82] and due to inadequate power to detect a difference.[85] Of the eight RCTs that evaluated change in quality of life from baseline, the majority (75%) found significant improvement within each treatment group.

Compared with hysterectomy, the LNG-IUS offered superior or similar (i.e., not significantly different) benefit for women's quality of life (GRADE: Moderate). Compared with endometrial ablation, the LNG-IUS offered similar benefit for quality of life (GRADE: Low). Compared with usual medical therapy, the LNG-IUS offered superior or similar benefit for quality of life (GRADE: Low) (Table 15).

Table 15: GRADE Evidence Profile for Quality of Life Change with LNG-IUS

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared with hysterectomy							
2 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Compared with endometrial ablation							
5 (RCTs)	Serious limitations (–1)[b]	No serious limitations	No serious limitations	Serious limitations (–1)[c]	Undetected	None	⊕⊕ Low
Compared with usual medical therapy							
2 (RCTs)	Serious limitations (–1)[a]	Serious limitations (–1)[d]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.

[a]Lack of blinding. See Appendix 2, Tables A4 to A6, for full risk of bias assessments.

[b]Inadequate allocation concealment, lack of blinding, intention-to-treat analysis was not conducted, and loss to follow-up. See Appendix 2, Tables A4 to A6, for full risk of bias assessment.

[c]Very small sample sizes; loss to follow-up compromised power in most studies.

[d]Results varied from favouring LNG-IUS to no difference depending on quality of life tool used and time point assessed.

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Results for Menstrual Blood Loss

Thirteen studies evaluated menstrual blood loss between study groups, and these results are presented by comparator on the following pages.[77,81,82,84,86-88,90,92,95,97-99] Of the 12 RCTs that reported change from baseline, all found significant improvement in menstrual bleeding, within each study group, after treatment.[77,81,82,84,87,88,90,92,95,97-99] The measures and metrics were heterogeneous, precluding quantitative synthesis; thus, we summarize the results narratively.

LNG-IUS Versus Hysterectomy

The study by Sesti et al[77] compared menstrual blood loss, measured by PBAC scores, between the LNG-IUS and laparoscopic supracervical hysterectomy groups at baseline and at 3 months, 6 months, 1 year, and 2 years after treatment. Table 16 summarizes these findings (see Table 6 for characteristics of this RCT).

Table 16: Menstrual Blood Loss Results for Women Treated with LNG-IUS or Hysterectomy

Author, Year	Follow-Up	MBL LSH, PBAC Score, Mean (SD)	MBL LNG, PBAC Score, Mean (SD)	*P*
Sesti et al, 2012[77]	Baseline	937 (334)	911 (330)	ns[a]
	3 mo	52.9 (22.9)	37.0 (20.1)	.004
	6 mo	19.7 (11.6)	50.4 (13.9)	< .0001
	1 y	3.70 (3.0)	3.50 (16.0)	ns[a]
	2 y	3.74 (3.05)	56.4 (72.8)	< .0001

Abbreviations: LNG, levonorgestrel-releasing intrauterine system; LSH, laparoscopic supracervical hysterectomy; MBL, menstrual blood loss; mo, month; ns, not statistically significant; PBAC, pictorial blood loss assessment chart; SD, standard deviation; y, year.
[a]*P* value not reported.

Both groups experienced a significant decrease in menstrual blood loss compared with pre-treatment (baseline PBAC scores were all greater than 100; *P* not reported). Bleeding generally tapered to within normal range (PBAC 50–100) and then to spotting (PBAC 0–50) over the 24-month study period. There was no difference between the treatment groups in their baseline menstrual blood loss or at the 1-year assessment (*P* not reported).[77]

At 3 months post-treatment, the women treated with the LNG-IUS had significantly less menstrual bleeding compared with those who had received a hysterectomy; however, this significant difference reversed at both 6 months and 2 years post-treatment. At 2 years, there was an apparent but not significant increase in menstrual blood loss in the LNG-IUS group, compared with previous time points.[63] The authors could not explain this finding, but speculated that perhaps the local effect of levonorgestrel on the uterus decreased over time.[77] At 1 year, no women had amenorrhea, nor did any meet the PBAC criteria for amenorrhea (score of 0) during the study period.[77] Although the results varied depending on follow-up time, unsurprisingly the hysterectomy group experienced a significantly greater reduction in menstrual blood loss.

LNG-IUS Versus Endometrial Ablation

Eight studies comparing the LNG-IUS and endometrial ablation reported on the outcome of menstrual blood loss (Table 17).[81,82,84,86-88,90,92] The studies reported various metrics of blood loss, with a few reporting comparisons between final mean PBAC scores,[81,86,88,92] median change from baseline,[84,90] or the difference in proportions of women with increased or decreased menstrual blood loss at differing time points.[82]

Table 17: Menstrual Blood Loss Studies of Women Receiving LNG-IUS or Endometrial Ablation

Author, Year	Ablation Technique (n[a])	LNG-IUS (n[a])	Age, Years, Mean (SD)	BMI, Mean (SD)	Parity, Mean (SD)	Baseline PBAC Score
Ghazizadeh et al, 2011[81]	Transcervical endometrial resection (52)	Mirena (52)	40.2–41.5 (4.3–4.4)	26.7–28.3 (3.3–4.2)	NR	M 595-596 (SD 165–185)
de Souza et al, 2010[82]	ThermaChoice TBEA (30)	Mirena (28)	42–43.4 (0.7)	NR	2.4–2.6 (0.2–0.4)	M 492–522 (SD 56.8–90.3)
Shaw et al, 2007[84]	MenoTreat TBEA (33)	Mirena (33)	MD 42–43 (range 30–49)	MD 27–28 (range 19–41)	MD 3 (range 1–3)	MD 410–450 (range 126–1800)
Busfield et al, 2006[86]	ThermaChoice TBEA (41)	Mirena (42)	NR (range 40–49)	28.9–29.7 (5.4–8.0)	NR	M 490–502 (SD 419-422)
Malak and Shawki, 2006[87]	Endometrial resection (30)	Mirena (30)	46.3–47.7 (1.3–1.4)	NR	1.9–2.4 (0.3–1.9)	M 316–346 (SD 143–152)
Barrington et al, 2003[88]	ThermaChoice TBEA[b] (25)	Mirena (25)	NR	NR	NR	M 107–122 (SD 74–95)
Kittelsen et al, 1998[90]	Transcervical endometrial resection (30)	Mirena (30)	41.4–42.1 (3.6–3.8)	NR	MD 2 (range 2–5)	M 404–420 (352–480)
Crosignani et al, 1997[92]	Endometrial resection (35)	Mirena (35)	43.8–45.4 (3.8)	24.0–25.3 (3.0–4.4)	1.6–1.8 (0.9–1.1)	M 181–204 (SD 59.4–82.9)

Abbreviations: BMI, body mass index; LNG-IUS, levonorgestrel-releasing intrauterine system; M, mean; MD, median; NR, not reported; PBAC, pictorial blood loss assessment chart; SD, standard deviation; TBEA, thermal balloon endometrial ablation.
[a]Number of participants randomized to each study arm.
[b]Preoperative thinning of the endometrium was performed with 3.6 mg goserelin.

Barrington et al[88] reported a difference in baseline menstrual bleeding between the LNG-IUS and endometrial ablation groups (P = .025), but at 6 months follow-up there was no difference (P = .6896). Malak and Shawki[87] reported a binary blood loss outcome called “treatment success,” defined as a PBAC score greater than 75 at 12 months follow-up (not shown in Table 18). They found that the two treatment groups achieved comparable treatment success: 77% with LNG-IUS and 83% with endometrial ablation (P = .747).[87] Results for Malak and Shawki’s amenorrhea rates and for amenorrhea and menstrual blood loss as reported by the other seven studies are in Table 18.

Table 18: Menstrual Blood Loss Results for Women Treated with LNG-IUS or Endometrial Ablation

Author, Year	Follow-Up	Amenorrhea,% LNG-IUS vs. EA	Menstrual Blood Loss, EA	Menstrual Blood Loss, LNG-IUS	*P*
Ghazizadeh et al, 2011[81]	1 y	11 vs. 45[a]	M final PBAC 526.8 (SD 148)	M final PBAC 560.2 (SD 177.9)	ns
de Souza et al, 2010[82]	6 mo	NR	Increased MBL in 10%[b]	Decreased MBL or amenorrhea in 80%[b]	.035
	1 y	NR	Increased MBL in 10%[b]	Decreased MBL or amenorrhea in 95%[b]	.048
	5 y	35.3 vs. 0[a]	Increased MBL in 45.5%	Increased MBL in 0.0%	< .001
Shaw et al, 2007[84]	3 mo	NR	MD[c] 184 (range 5 to 610)	MD[c] −172 (range 0 to 729)	ns
	6 mo	NR	MD[c] −81 (range 0 to 440)	MD[c] −124 (range 0 to 610)	< .05
	9 mo	NR	MD[c] −75 (range 0 to 286)	MD[c] −32 (range 0 to 114)	< .001
	1 y	26 vs. 3[a]	MD[c] −62 (range 0 to 142)	MD[c] −26 (range 0 to 68)	< .001
Malak andShawki, 2006[87]	12 mo	54 vs. 43	NR	NR	
Busfield et al, 2006[86]	3 mo	6 vs. 16	M final PBAC 220.8 (SD 438.5)	M final PBAC 125 (SD 198)	.452
	6 mo	9 vs. 3	M final PBAC 107.5 (SD 135.4)	M final PBAC 72.1 (SD 118.6)	.080
	1 y	20 vs. 7	M final PBAC 94.7 (SD 112)	M final PBAC 41.1 (SD 86.5)	.002
	2 y	35 vs. 5[a]	M final PBAC 75.4 (SD 91.1)	M final PBAC 20.6 (SD 28.8)	.002
Barrington et al, 2003[88]	6 mo	14 vs 9	M final PBAC 61	M final PBAC 31	.6896
Kittelsen et al, 1998[90]	1 y	12.5 vs. 25[b,d]	Diff in MD[c] −249.5 (range 164 to 261.5)	Diff in MD[c] −302.5 (range 156 to 311)	.68
	2 y	25 vs. 33[b]	Diff in MD[c] −253 (range 133.5 to 261.5)	Diff in MD[c] −301 (range 136 to 311)	.34
	3 y	32 vs. 41[b,d]	Diff in MD[c] −2545 (range 160.5 to 261.5)	Diff in MD[c] −307 (range 129 to 311)	.86
Crosignani et al, 1997[92]	1 y	18 vs. 26	M final PBAC 23.5 (SD 32.6)	M final PBAC 38.8 (SD 37.1)	.015[e]

Abbreviations: Diff, difference; EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; M, mean; MBL, menstrual blood loss; MD, median; mo, month; NR, not reported; ns, not statistically significant; PBAC, pictorial blood loss assessment chart; SD, standard deviation; y, year.

[a]Statistical significance at $P < .05$.

[b]Proportions not reported by authors so are estimated from Figure 4 in de Souza et al 2010.[82]

[c]Change from baseline (M or MD).

[d]Proportions calculated using data reported in article.

[e]*P* value pertains to comparison of between-group difference in monthly bleeding score at final assessment with PBAC.

Three studies reported a statistically significant difference in the proportion of women who no longer menstruated; two studies found significantly more women with the LNG-IUS reported amenorrhea,[84,86] whereas Ghazizadeh and colleagues[81] found the opposite: a significantly greater proportion of women treated with endometrial ablation reported amenorrhea. Four studies did not report *P* values for amenorrhea results.[82,88,90,92] Shaw et al[84] reported that continued or prolonged spotting was the main reason women discontinued the allocated treatment (low willingness to tolerate side effects). In that study, by 2 years 20.7% of participants who withdrew from using the LNG-IUS and 13.3% who withdrew from endometrial ablation chose hysterectomy.[84]

Crosignani and his group[92] reported a significantly larger reduction in menstrual blood loss from baseline for women treated with endometrial ablation compared with LNG-IUS (89% vs. 79%). Busfield et al[86] found no difference at 3 and 6 months but a significantly lower final mean PBAC score in the LNG-IUS group compared with endometrial ablation at both 1 and 2 years follow-up. Similarly, Shaw et al[84] found no difference at 3 months; at 6 months women treated with endometrial ablation had a significantly lower PBAC score than women treated with the LNG-IUS; but the opposite was true at 9 months and 1 year (*P* < .001 for both follow-up points). Three studies found no difference between groups in the change from baseline or in their final PBAC scores (*P* > .05), though each of these studies reported significant reductions from baseline within each group.[81,88,90] Results for the studies' menstrual blood loss comparisons by follow-up time are outlined in Table 19.

Table 19: Menstrual Blood Loss Improvement by Follow-Up Time: LNG-IUS vs. Endometrial Ablation

Author, Year	Follow-Up	MBL Comparison: EA vs. LNG	*P*
Shaw et al, 2007[84]	3 mo	**No difference[a]**	ns
Busfield et al, 2006[86]	.	**No difference[b]**	.452
de Souza et al, 2010[82]	6 mo	**LNG better[c]**	.035
Shaw et al, 2007[84]		EA better[a]	< .05
Busfield et al, 2006[86]		**No difference[b]**	.080
Barrington et al, 2003[88]		**No difference[b]**	.6896
Shaw et al, 2007[84]	9 mo	**LNG better[a]**	< .001
Ghazizadeh et al, 2011[81]	1 y	**No difference[b]**	ns
de Souza et al, 2010[82]		**LNG better[c]**	.048
Shaw et al, 2007[84]		**LNG better[a]**	< .001
Busfield et al, 2006[86]		**LNG better[b]**	.002
Kittelsen et al, 1998[90]		**No difference[a]**	.68
Crosignani et al, 1997[92]		EA better[d]	.015
Busfield et al, 2006[86]	2 y	**LNG better[b]**	.002
Kittelsen et al, 1998[90]		**No difference[a]**	.34
Kittelsen et al, 1998[90]	3 y	**No difference[a]**	.86
de Souza et al, 2010[82]	5 y	**LNG better[c]**	< .001

Abbreviations: EA, endometrial ablation; LNG, levonorgestrel-releasing intrauterine system; MBL, menstrual blood loss; mo, month; ns, not statistically significant; PBAC, pictorial blood loss assessment chart; y, year.
[a]Difference between groups in median change in MBL from baseline.
[b]Difference between groups in final PBAC score (mean or median).
[c]Difference in percentage with increased MBL.
[d]Difference in percent reduction in MBL from baseline.

Among the 17 comparisons listed in Table 19, eight showed no difference in the reduction of menstrual blood loss; in seven comparisons, LNG-IUS produced superior reduction in menstrual blood loss; and in two, endometrial ablation was superior. Significant reductions from baseline within both arms were reported, and at most assessments in seven of the eight RCTs, LNG-IUS was either superior or not significantly different in improving menstrual blood loss compared with endometrial ablation.

LNG-IUS Versus Usual Medical Therapy

Four studies compared menstrual blood loss among women treated with either the LNG-IUS or usual medical therapy (Table 20).[95,97-99]

Table 20: Menstrual Blood Loss Studies of Women Receiving LNG-IUS or Usual Medical Therapy

Author, Year	Medication (n[a])	LNG-IUS (n[a])	Age, Years, Mean (SD)	BMI, Mean (SD)	Parity, Mean (SD)	Baseline MBL
Shaaban et al, 2011[95]	Microvlar low-dose COC (56)	Mirena (56)	38.7–39.3 (5.2–6.7)	29.6–31.1 (5.7–5.9)	3 (1-6)	M PBAC score 306–323 (SD 97.3–131)
Kaunitz et al, 2010[97]	MPA[b] (83)	Mirena (82)	38.3–39.3 (5.2–5.4)	27.2–27.4 (3.9–4.6)	2.5–2.6 (range 1–7)	MD 148–154.2 mL (range 63.4–456)
Reid and Virtanen-Kari, 2005[98]	Mefenamic acid[c] (26)	Mirena (25)	38.5–39.4 (4.2–4.4)	NR	NR	MD 121-122 mL (range 81–389)
Irvine et al, 1998[99]	Norethisterone[d] (22)	Mirena (22)	MD 38.5–39 (range 30-45)	27.8–28.1[e]	MD 2 (range 1–5)	MD 105–120 mL (range 82–780)

Abbreviations: BMI, body mass index; COC, combination oral contraceptive; LNG-IUS, levonorgestrel-releasing intrauterine system; M, mean; MBL, menstrual blood loss; MD, median; MPA, medroxyprogesterone acetate; NR, not reported; PBAC, pictorial blood loss assessment chart; SD, standard deviation.

[a]Number of participants randomized to each study arm.

[b]Oral dose of 10 mg daily for 10 days per cycle, beginning on day 16 of menstrual cycle.

[c]Oral dose 500 mg taken 3 times daily oral for the first 4 days of menstrual cycle.

[d]Oral dose of 5 mg taken 3 times daily for days 5–26 of menstrual cycle.

[e]Calculated based on raw data on height and weight presented in the article.

Only one study investigated the effect of a nonhormonal medical therapy[98]; thus, we could not compare results between hormonal and nonhormonal medication. The baseline characteristics of the study populations were similar among the studies and within treatment groups in each study. Results for each study's evaluations of menstrual blood loss are in Table 21.

Table 21: Menstrual Blood Loss Results for Women Treated with LNG-IUS or Usual Medical Therapy

Author, Year	Follow-Up	Amenorrhea, % LNG-IUS vs. UMT	MBL UMT	MBL LNG-IUS	*P*
Shaaban et al, 2011[95]	1 y	12 vs. 0[a]	M PBAC 118.2 (SD 75)	M PBAC 44.4 (SD 34.9)	< .001
Kaunitz et al, 2010[97]	3 cyc	NR	MD[b] −3.2 mL (range +146.7 to −270.9) MD[b] 2.2%	MD[b] −115.1 mL (range +54.4 to −405.8) MD[a] 83.2%	< .001 < .001
	6 cyc	NR	MD[b] −17.8 mL (range +78.6 to −271.5) MD[b] 13.1%	MD[b] −128.8 mL (range +1,242.2[c] to −393.6) MD[b] 94.5%	< .001 < .001
Reid and Virtanen-Kari, 2005[98]	3 cyc	NR	MD 94 mL (range 29–219 mL)	MD 12 mL (range 0–240 mL)	< .001
	6 cyc	NR	MD 100 mL (range 46–148)	MD 5 mL (range 0–45)	< .001
Irvine et al, 1998[99]	1 mo	NR	MD 46 mL (range 0–213)	MD 16 mL (range 0–62)	.02
	3 mo	32 vs. 0[a]	MD 20 mL (range 4–137)	MD 6 mL (range 0–284)	.03

Abbreviations: cyc, cycle; LNG-IUS, levonorgestrel-releasing intrauterine system; M, mean; MBL, menstrual blood loss; MD, median; mo, month; NR, not reported; PBAC, pictorial blood loss assessment chart; SD, standard deviation; UMT, usual medical therapy; y, year.

[a]Indicates statistical significance at $P < .05$.

[b]Change from baseline (M or MD).

[c]One woman had very heavy menstrual blood loss suspected by the authors to have resulted from LNG expulsion.

As with the previous comparisons, the metrics reported for menstrual blood loss in this group of studies were varied and posed a challenge for quantitative synthesis. Two studies reported median change from baseline;[97,99] one reported median final blood loss;[98] and another, final mean PBAC score.[95] The findings are summarized below.

The 1998 study by Irvine and colleagues[99] reported a 94% reduction in menstrual blood loss within the LNG-IUS group from baseline (both intention-to-treat and per-protocol analysis) and an 87% reduction in the usual medical therapy (norethisterone) group; these reductions from baseline were not significantly different between groups ($P = .56$). More recently, Reid and Virtanen-Kari[98] reported that PBAC scores decreased by 79% from baseline (at 6 cycles). Shaaban et al[95] reported that mean reduction in menstrual blood loss between baseline and 12 months was significantly greater in the LNG-IUS group than in the group taking combined oral contraceptives (86.6% vs. 2.5%, $P < .001$). The RCT conducted by Kaunitz et al[97] found superior relative and absolute reductions from baseline in the LNG-IUS group at both 3 and 6 months ($P < .001$ for all).

All studies found that the LNG-IUS was superior to usual medical therapy, regardless of follow-up time or medication (Table 22).

Table 22: Menstrual Blood Loss Improvement by Follow-Up Time: LNG-IUS vs. Usual Medical Therapy

Author, Year	Follow-Up	MBL Comparison: UMT vs. LNG	*P*
Irvine et al, 1998[99]	1 mo	**LNG better**[a]	.02
Kaunitz et al, 2010[97]	3 mo	**LNG better**[b]	< .001
Reid and Virtanen-Kari, 2005[98]		**LNG better**[a]	< .001
Irvine et al, 1998[99]		**LNG better**[a]	.03
Kaunitz et al, 2010[97]	6 mo	**LNG better**[b]	< .001
Reid and Virtanen-Kari, 2005[98]		**LNG better**[a]	< .001
Shaaban et al, 2011[95]	1 y	**LNG better**[a]	< .001

Abbreviations: LNG, levonorgestrel-releasing intrauterine system; MBL, menstrual blood loss; mo, month; PBAC, pictorial blood loss assessment chart; UMT, usual medical therapy; y, year.
[a]Difference between groups in final PBAC score or mL (mean or median).
[b]Difference between groups in median change in MBL from baseline.

Collectively, these RCTs consistently illustrated that up to 1 year, compared with various usual medical therapies, the LNG-IUS provided superior improvement in menstrual blood loss.

Summary of Results for Menstrual Blood Loss

Of the 13 RCTs that demonstrated evidence on menstrual blood loss, only one did not report data on change from baseline.[85] Compared with laparoscopic supracervical hysterectomy, the LNG-IUS provided a similar (not significantly different) or inferior improvement in menstrual blood loss (GRADE: Moderate). Compared with endometrial ablation, the LNG-IUS provided a not significantly different or a superior improvement in menstrual blood loss (GRADE: Very low). Compared with usual medical therapy, the LNG-IUS provided superior improvement in menstrual blood loss (GRADE: Low) (Table 23).

Table 23: GRADE Evidence Profile for Menstrual Blood Loss Change with LNG-IUS

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared with hysterectomy							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations[b]	Undetected	None	⊕⊕⊕ Moderate
Compared with endometrial ablation							
8 (RCTs)	Serious limitations (–1)[c]	Serious limitations (–1)[d]	No serious limitations	Serious limitations (–1)[e]	Undetected	None	⊕ Very low
Compared with usual medical therapy							
4 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	Serious limitations (–1)[e]	Undetected	None	⊕⊕ Low

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.

[a]Lack of blinding. See Appendix 2, Tables A4 to A6, for full risk of bias assessments.

[b]Single small study but achieved 100% completion for full 2-year study period.

[c]Inadequate allocation concealment, lack of blinding, and some concerns about loss to follow-up. See Appendix 2, Tables A4 to A6, for full risk of bias assessments.

[d]Inconsistent findings between studies and within them at various follow-up points with regards to superior benefit or lack of significant difference in menstrual blood loss.

[e]Very small sample sizes; loss to follow-up compromised power in most studies.

Results for Satisfaction and Acceptability

Only six studies evaluated satisfaction with treatment between study groups.[80-82,84,92,99] These studies are summarized below, by comparator. Table 24 shows the GRADE evidence profile for this outcome.

LNG-IUS Versus Hysterectomy

The Hurskainen et al study[80] reported women's satisfaction with the LNG-IUS and with hysterectomy. Satisfaction was assessed via a 5-point Likert scale (from very unsatisfied to very satisfied) by 115 LNG-IUS patients and 114 hysterectomy patients. At 5 years after randomization, 94% of women in the LNG-IUS group and 93% of women in the hysterectomy group were satisfied or very satisfied with their treatments.[80] The authors did not report a statistical comparison of these proportions.

LNG-IUS Versus Endometrial Ablation

Satisfaction with endometrial ablation or LNG-IUS was reported in four studies. Ghazizadeh and colleagues[81] asked patients to rate their satisfaction with the treatment on a scale from 1 (least satisfied) to 5 (most satisfied). The mean score in the LNG group was 3.08 (standard deviation 1.6) compared with a mean of 2.5 (standard deviation 1.59) in the endometrial ablation group; the difference in these scores was not statistically significant (P = .43).[81]

Crosignani et al[92] assessed patients' satisfaction with their treatment by asking if they were very satisfied, satisfied, uncertain, or dissatisfied. At 1-year follow-up, the proportion who were satisfied or very satisfied in both groups was high and did not differ by intervention (85% of LNG-IUS and 94% of endometrial ablation (P = .26, odds ratio 0.35, 95% confidence interval 0.60–1.95).[92]

De Souza et al[83] evaluated acceptability and satisfaction in terms of whether patients felt better after treatment, were satisfied with the treatment, would hypothetically choose the treatment again, and noticed great improvements in their physical and emotional well-being after treatment. At 5 years, acceptability and satisfaction with LNG-IUS was superior compared with thermal balloon endometrial ablation (P < .05 for all aspects).[83]

A fourth RCT asked patients to evaluate their satisfaction with either the LNG-IUS or thermal balloon endometrial ablation. More LNG-IUS patients were dissatisfied at 3 and 6 months, but satisfaction in both groups was similar at 12 and 24 months.[84] The authors did not report a statistical comparison of the proportions rating "good" or "very good" perceived treatment effect.

LNG-IUS Versus Usual Medical Therapy

Irvine and colleagues[99] asked women who completed the treatment to report if they were well satisfied, moderately well satisfied, moderately satisfied, or poorly satisfied after 3 months. In the LNG-IUS group, 64% were well or moderately well satisfied, while the same was true for 44% in the norethisterone group.[99] No statistical comparison of these proportions was reported.

Table 24: GRADE Evidence Profile for Satisfaction with LNG-IUS

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Compared with hysterectomy							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Compared with endometrial ablation							
4 (RCTs)	Serious limitations (–1)[b]	Serious limitations (–1)[c]	No serious limitations	Serious limitations (–1) [d]	Undetected	None	⊕ Very low
Compared with usual medical therapy							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations[e]	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕ Low

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.
[a]Lack of blinding in the study. See Appendix 2, Tables A4 to A6, for full risk of bias assessment.
[b]Inadequate allocation concealment, lack of blinding in all, intention-to-treat analysis not conducted, and substantial loss to follow-up. See Appendix 2, Tables A4 to A6, for full risk of bias assessment.
[c]Mixed findings between studies and within them at various follow-up points with regards to superior benefit or lack of significant difference.
[d]Very small sample sizes and substantial loss to follow-up compromised power in most studies.
[e]Only 1 small study providing evidence could not assess inconsistency.

Results for Complications, Side Effects, and Adverse Events

Most of the 16 studies reported some data on complications, side effects, or adverse events; four studies did not.[82,85,88,95] These occurrences during the study periods (ranging from 3 months to 10 years) are summarized below, by treatment option.

Complications and Side Effects

No study reported any occurrence of uterine perforation during insertion of the LNG-IUS. No pregnancies were reported during treatment with the LNG-IUS in any of the studies. Total or partial expulsion of the device occurred in 3% to 16% of cases, across the RCTs. Among the four studies reporting device expulsion, 50% to 100% of the women involved successfully had a new LNG-IUS inserted and thus continued treatment.[79,85,90,97]

Most studies provided only descriptive information about side effects related to the use of LNG-IUS. Although it is unclear exactly how many women experience them, side effects associated with LNG-IUS treatment appeared to occur in as many as 40% of study participants across all RCTs. Side effects were described in the studies as mild, and the LNG-IUS was well tolerated overall.[81,87,90]

Across all studies, the most common side effects were related to menstrual bleeding (irregular, persistent, heavy, or prolonged in less than 1% to 53% of participants).[81,84,85,87,90,94,95,99] Spotting (intermenstrual bleeding) affected the largest proportion of women (10%[87] to 53%) across RCTs; the largest percentage (53%) occurred at 3 months follow-up in one study.[99] Hormonal side effects were common, experienced by up to two-thirds of participants (e.g., bloating, weight gain, mood changes, breast tenderness).[81,87,90,92,98] Genitourinary infections occurred in up to 9 participants in the RCTs[97] and pelvic inflammatory disease in 2 participants,[90] and all cases were resolved. Pelvic pain occurred in 2% to 10% of study participants[87,92,93,97] and abdominal pain in 4% to 32%.[81,87,90,97,98] Benign ovarian cysts were reported as mild and uneventful in three studies[81,97,98] in 2% to 24% of women treated with LNG-IUS. One study noted that one woman had her LNG-IUS device removed because of a cyst.[80]

Of the few available comparisons of this outcome by intervention, Crosignani and his group[92] found significantly more side effects reported by participants in the LNG-IUS group compared with endometrial ablation (55.9% vs. 25.7%, $P = .02$), but provided no detail on the type or severity of side effects. In another study, compared with women taking oral norethisterone, women with an LNG-IUS were more likely to experience breast tenderness ($P = .0008$) and spotting in the first 3 months (statistics not reported).[99] However, the two groups showed no difference in pain, headache, acne, nausea, edema, weight gain, decreased libido, sweating, hair loss or greasy hair, or hirsutism (increased body hair).[99] Both groups experienced a small but statistically significant weight gain from baseline that was unnoticed by participants (1.1 kg in norethisterone group, 0.6 kg in the LNG-IUS group; no difference between groups).[99]

Spotting or continued menorrhagia were the primary reasons that women discontinued treatment.[81,84,85,93,95,99] One study reported that side effects were more commonly reported in the LNG-IUS group than in the endometrial ablation group, but this was not statistically significant nor cited as a reason for discontinuing treatment.[87] In two RCTs, continuation rates were reportedly higher in the LNG-IUS groups compared with usual medical therapy.[93,99]

Adverse Events

A minority of RCTs reported the occurrence of serious adverse events during the study periods. Several studies reported that no serious adverse events occurred in either group.[77,86,97,99]

Reid and Virtanen-Kari[98] compared the LNG-IUS to mefenamic acid and reported two serious adverse events in the LNG-IUS group that were successfully resolved. The first event involved numbness in the arm, light-headedness, and pelvic pain that were due to pre-existing hypertension and resolved with treatment of the hypertension. In the same woman, the device was found in the endocervical canal and was subsequently removed. The second adverse event in the LNG-IUS group was the development of chlamydial endometritis, which was successfully treated, but the LNG-IUS was still ultimately expelled.[98] As reported by Gupta et al[93] in another study comparing the LNG-IUS to multiple medications, the rate of serious adverse events among women treated with the LNG-IUS was not significantly different from the usual medical therapy group (49 events in 46 of 285 women vs. 58 in 51 of 286 women, respectively; $P = .59$).

Kittelsen et al[90] reported a number of significant adverse events in their study comparing the LNG-IUS and endometrial ablation. In the LNG-IUS group, there were three diagnoses of endometritis and two of pelvic inflammatory disease. In the endometrial ablation group, the diagnoses included one woman with hypertension who developed a stroke (considered unrelated), three cases of pelvic inflammatory disease, one woman with adenomyosis, one with myometritis, and two with abnormal Pap tests. No other details were provided.[90]

The studies comparing hysterectomy and the LNG-IUS provided little information on adverse events or complications. Sesti et al[77] reported no early post-operative complications requiring readmission, blood transfusion, or repeat surgery in either group. Hurksainen and colleagues[79] reported that the complication rate from hysterectomy was high in their study compared with other registry studies, but similar to cohort studies.

Discussion

The evidence in this review supports the 52-mg LNG-IUS as an effective treatment option for idiopathic heavy menstrual bleeding. The majority of RCTs that we included found significant improvement in quality of life and menstrual blood loss from baseline within the LNG-IUS group and the comparator treatment groups (medical therapy, endometrial ablation, and hysterectomy), irrespective of which treatments were being compared. Essentially, these studies often showed no significant differences in benefit between treatment options.

Our results are consistent with previous reviews comparing these treatment options (Table 4). Though our review focused on women with idiopathic heavy menstrual bleeding, our findings were similar to other systematic reviews that included this population along with women whose menorrhagia was related to uterine fibroids, adenomyosis, endometriosis, endometrial hyperplasia, or treatment for other conditions. Thus, our findings are likely generalizable to other populations with heavy menstrual bleeding from a variety of causes.

Also consistent with previous reviews, we were unable to perform quantitative synthesis of this body of evidence due to the significant methodological and data heterogeneity among the studies. Challenges included variation in measuring quality of life outcomes: different approaches to measurement, unknown or undefined minimum clinically important differences in scores, issues with interpretability of dimension-specific and aggregate scores, and different

metrics reported. Measurement challenges across studies were also present for the outcome of menstrual blood loss.

Sample sizes tended to be small overall, and a priori power calculations were not consistently reported. Most studies sought menstrual blood loss as the primary outcome, whereas only three studies were designed and oriented to evaluate quality of life as a primary or secondary endpoint.[79,82,93] An advantage was that the follow-up horizons for many studies extended into 2, 3, 5, or even 10 years. This allowed us to see effects beyond the first three to six cycles where spotting and side effects are known to occur, and to better understand treatment effects over the 5-year lifespan of the device, and beyond.

According to local experts, the populations captured in this review are generally representative of those seen in Ontario practice. A possible difference is that some Ontario patients (e.g., rural residents[110]) may have a higher body mass index than patients in the included RCTs. We had planned to examine results by obesity status, but these subanalyses could not be conducted, so there is no evidence to support or refute a difference in benefits or side effects in using the LNG-IUS in a population with higher BMI.

In the clinical management of heavy menstrual bleeding, it is essential to understand patients' individual values and preferences, as they will invariably drive the selection of treatment. Similarly, it is important to recognize that the perceived effectiveness of treatment partly depends on a patient's tolerance for side effects and the magnitude of improvement she will accept. These factors in turn may be reflected in a patient's preference for a more invasive or less invasive treatment option. These factors also likely play a role in a paradoxical result sometimes observed with the LNG-IUS: objective outcomes varied (e.g., some women saw less improvement in menstrual blood loss) while at the same time most participants were generally satisfied with this treatment option.

In addition to the influence of patient preference, treatment selection is also qualified by each patient's eligibility for the various treatment options, although subpopulations with differing eligibility were not represented in the RCTs included in this review. For instance, women under 40 years of age, smokers aged 35 or older, and morbidly obese women (BMI > 40) are typically ineligible, respectively, for endometrial ablation, combined oral contraceptives, and hysterectomy. Such relative and absolute contraindications further emphasize the importance of the LNG-IUS as a treatment option for heavy menstrual bleeding.

Conclusions

- Based on very low to moderate quality of evidence from 16 randomized controlled trials, the 52-mg LNG-IUS appears to be an effective treatment option for heavy menstrual bleeding of unknown cause (idiopathic menorrhagia) to improve quality of life and menstrual blood loss, and is well tolerated compared with endometrial ablation, hysterectomy, or usual medical therapies.
- We found limited evidence of a significant difference in quality of life outcomes for women treated with the LNG-IUS compared with endometrial ablation techniques or hysterectomy. The vast majority of quality of life scores were superior among women treated with the LNG-IUS compared with usual medical therapies.
- The improvement in menstrual blood loss was not significantly different between the LNG-IUS and surgical treatments (endometrial ablation or hysterectomy), but there was evidence

that the LNG-IUS was superior in improving menstrual blood loss compared with usual medical therapy.

- The most common side effects of the LNG-IUS were mild hormonal effects related to taking progestogens.

ECONOMIC EVIDENCE REVIEW

Objectives

The primary objective of this study was to review the published literature on the cost-effectiveness of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) compared with endometrial ablation, hysterectomy, or nonsurgical intervention in patients with heavy menstrual bleeding.

Methods

Sources

We performed an economic literature search on August 18, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database, for studies published from 1946 to August 18, 2015. We also reviewed reference lists of included economic literature for any additional relevant studies not identified through the systematic search. Appendix 3 provides details of the search strategy.

Literature Screening

We based our search terms on those used in the clinical evidence review of this report and applied economic filters to the search results. A single reviewer reviewed titles and abstracts and, for those studies meeting the inclusion and exclusion criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Studies published between 1946 and August 18, 2015
- Studies in patients with heavy menstrual bleeding
- Studies reporting on LNG-IUS compared with endometrial ablation, hysterectomy, nonsteroidal anti-inflammatory drugs, oral contraceptive pills, progestin therapy, gonadotropin-releasing hormone agonists, danazol, and/or tranexamic acid
- Cost-utility, cost-effectiveness, or cost-benefit analyses

Exclusion Criteria

- Menopausal women or those seeking treatment for perimenopausal menstrual bleeding, or menorrhagia due to structural or pathological causes (e.g., fibroids, cancer, polyps, adenomyosis, endometriosis, systemic bleeding disorders)
- Intrauterine systems releasing different doses of levonorgestrel, other progestogens, or other medications, or other 52-mg levonorgestrel products with differing guidance on indications or administration

Outcomes of Interest

- Costs, cost per quality-adjusted life-year, cost per clinical effect

Data Extraction

We extracted relevant data on the following:

- source (i.e., name, location, year)
- population and comparator
- interventions
- outcomes (i.e., health outcomes, costs, cost-effectiveness)

We contacted authors of the studies to provide unpublished data where required.

Study Applicability Appraisal

We determined the usefulness of each identified study for decision-making by applying a modified methodology checklist for economic evaluations developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform development of clinical guidelines by NICE.[111] An example of the modified methodology checklist can be found in Appendix 4. We modified the wording of the questions to remove references to guidelines and to make it Ontario specific. The original NICE checklist was separated into two sections: an applicability section and a methodological quality section. We used only the first section for our review. From this checklist, studies are deemed directly applicable, partially applicable, or not applicable to the research question.

Limitations

The literature review was limited to a single reviewer.

Results

Literature Search

The database search yielded 373 citations published between 1946 and August 18, 2015 (with duplicates removed). We excluded a total of 359 articles based on information in the title and abstract. We then obtained the full texts of 14 potentially relevant articles for further assessment. Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

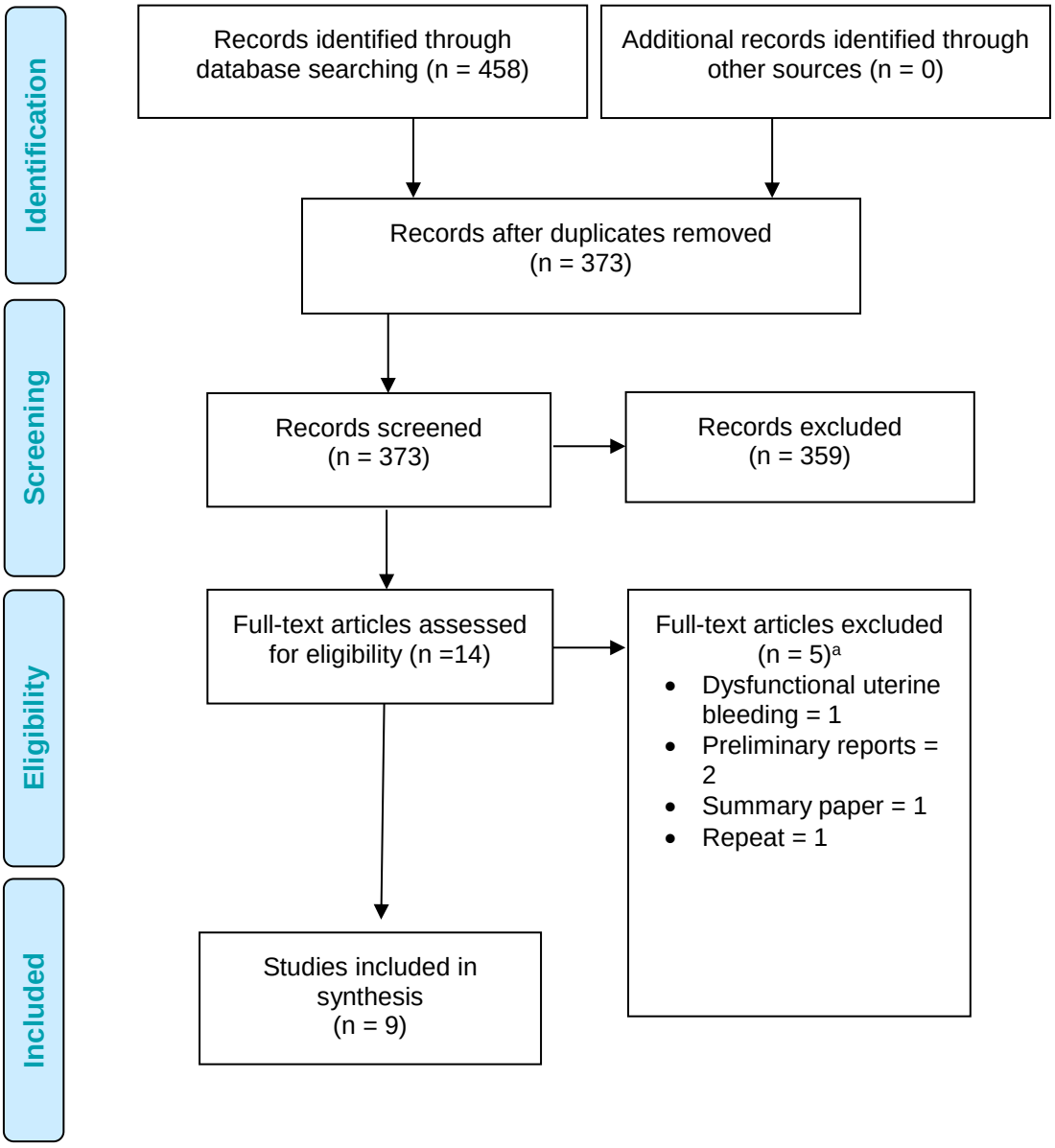

Figure 2: PRISMA Flow Diagram for Economic Evidence Review

[a]Dysfunctional uterine bleeding = Blumenthal 2006[112]; preliminary reports = Hurskaienen 2001, 2004[79,80]; summary paper = Hurskaienen 2001[113]; repeat = Roberts 2011.[114]

Source: Adapted from Moher et al, 2009.[70]

Fourteen studies met the inclusion criteria. We hand-searched the reference lists of the included studies but did not find any more studies. After a full-text review of all articles, five studies were excluded, resulting in a total of nine studies included in the critical review.

Study Applicability

After review of the nine studies using the quality appraisal checklist, we found that none of the studies evaluated the LNG-IUS from the perspective of the Ontario or Canadian public health care payer. As a result, all studies were deemed partially applicable. The complete results of the quality appraisal checklist applied to all of the included full-text articles can be found in Appendix 5, Table A7.

Two studies evaluated the LNG-IUS against both surgical and nonsurgical treatments,[115,116] four had surgical treatments as comparators,[78,117-119] and three used nonsurgical comparators.[120-122] Table 25 presents a summary of the study characteristics and results for articles comparing the LNG-IUS to both surgical and nonsurgical treatments. Studies comparing the LNG-IUS to surgical treatments are summarized in Table 26, and Table 27 describes articles on the LNG-IUS versus nonsurgical comparators.

Methodological Quality of the Included Studies

Most of the studies limited the model timeline to 5 years,[115,116,118,120,122] while four had a timeline that was longer (10 years)[78,117] or shorter (2 years).[119,121] Seven studies used Markov models to determine the cost-effectiveness of the LNG-IUS.[115-118,120-122] The remaining two studies were economic evaluations piggy-backed to a randomized controlled trial (RCT).[78,119] All studies included almost all important outcomes related to treatment and heavy menstrual bleeding. Four of the studies were either sponsored by an LNG-IUS manufacturer or had manufacturer employees as study co-authors.[115,118,120,122]

Table 25: Results of Economic Literature Review—Summary, LNG-IUS vs. Surgical and Nonsurgical Comparators (Cost-Utility Analyses)

Name, Year, Location	Study Design and Perspective	Population	Interventions	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Ganz et al, 2013, United States[115]	Markov model United States public health care payer perspective 5-year model	30-year-old women with menorrhagia also seeking contraception	• LNG-IUS • Combined oral contraceptive • Oral progestin • Tranexamic acid • Endometrial ablation • Hysterectomy	LNG-IUS = 3.78 QALYs per person Combined oral contraceptive = 3.71 QALYs per person Oral progestin = 3.67 QALYs per person Tranexamic acid = 3.72 QALYs per person EA = 3.79 QALYs per person Hysterectomy = 3.88 QALYs per person 3% discount rate	LNG-IUS = $1,137 per person Combined oral contraceptive = $1,804 (branded); $1,196 (generic) per person Oral progestin = $1,583 per person Tranexamic acid = $3,065 per person EA = $2,612 per person Hysterectomy = $6,250 per person 3% discount rate	LNG-IUS dominated all nonsurgical treatments Hysterectomy = $49,614/QALY compared with LNG-IUS EA = $122,278/QALY compared with LNG-IUS
You et al, 2006, China[116]	Markov model Chinese public health care payer perspective 5-year model	Women of reproductive age (≤ 40 years) with menorrhagia	• LNG-IUS • Endometrial ablation • Hysterectomy • Oral medical therapy	LNG-IUS = 4.625 QALYs per person EA = 4.624 QALYs per person Hysterectomy = 4.725 QALYs per person Oral medical therapy = 4.575 QALYs per person	LNG-IUS = $4,528 per person EA = $6,185 per person Hysterectomy = $6,878 per person Oral medial therapy = $5,508 per person 3% discount rate	LNG-IUS dominated EA and oral medical treatment Hysterectomy = $23,500/QALY

Abbreviations: EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life-year.

Table 26: Results of Economic Literature Review—Summary, LNG-IUS vs. Surgical Comparators (Cost-Utility Analyses)

Name, Year, Location	Study Design and Perspective	Population	Interventions	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Bhattacharya et al, 2011, United Kingdom[117]	Markov model UK National Health Service perspective 10-year model	42-year-old women with menorrhagia	• LNG-IUS • First-generation EA techniques • Second-generation EA techniques • Hysterectomy (primary comparator)	LNG-IUS = 68,566 QALYs (total cohort) First-generation EA = 63,745 QALYs (total cohort) Second-generation EA = 69,678 QALYs (total cohort) Hysterectomy = 73,332 QALYs (total cohort) 3.5% discount rate	LNG-IUS = £16 million (total cohort) First-generation EA = £24 million (total cohort) Second-generation EA = £19 million (total cohort) Hysterectomy = £23 million (total cohort) UK pounds, 2008 rate 3.5% discount rate	LNG-IUS = 1,440/QALY First-generation EA = Dominated Second-generation EA = 970/QALY (Hysterectomy comparator)
Heliovaara-Peippo et al, 2013, Finland[78]	RCT piggy-back Finland hospital and patient perspective 10-year follow-up	Women aged 35–49 years with menorrhagia, had completed childbearing	• LNG-IUS • Hysterectomy	LNG-IUS = 0.45 QALYs per person; mean −0.02 change in utility at 10 years compared with baseline Hysterectomy = 0.51 QALYs; per person mean −0.01 change in utility at 10 years compared with baseline	LNG-IUS = $2,291 direct costs over 10 years per person ($1,133 indirect costs) Hysterectomy = $3,036 direct costs over 10 years per person ($1,900 indirect costs) 3% discount rate	LNG-IUS = $7,607/QALY Hysterectomy = $9,680/QALY (as reported by author)
Clegg et al, 2007, United Kingdom[118]	Markov model UK National Health Service perspective 5-year model	43-year-old women with menorrhagia	• LNG-IUS • Microwave EA • Thermal balloon EA • Hysterectomy	LNG-IUS followed by EA = 4.14 QALYs per person LNG-IUS followed by hysterectomy = 4.12 QALYs per person Thermal balloon EA = 4.13 QALYs per person Microwave EA = 4.13 QALYs per person Hysterectomy = 4.01 QALYs per person 3.5% discount rate	LNG-IUS followed by EA = £828 per person LNG-IUS followed by hysterectomy = £1,355 per person Thermal balloon EA = £1,679 per person Microwave EA = £1,812 per person Hysterectomy = £2,983 per person 3.5% discount rate	LNG-IUS followed by EA dominated LNG-IUS followed by hysterectomy, microwave EA, thermal balloon EA, and hysterectomy EA dominated hysterectomy Microwave EA = £66,800/QALY vs. LNG-IUS Thermal balloon EA = £47,500/QALY vs. LNG-IUS
Brown et al, 2006, New Zealand[119]	Decision model Uncertain perspective (possibly societal) 2-year model	Women with menorrhagia	• LNG-IUS • Thermal balloon EA	LNG-IUS = 15-point increase in SF-36 score per person Thermal balloon EA = 12-point increase in SF-36 score per person	LNG-IUS = $1,242 over 2 years per person Thermal balloon EA = $2,419 over 2 years per person	Results suggest that LNG-IUS results in slight increase in quality of life and is less costly compared with EA

Abbreviations: EA, endometrial ablation; LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life-year; SF 36, 36-item short form survey.

Table 27: Results of Economic Literature Review—Summary, LNG-IUS vs. Nonsurgical Comparators (Cost-Utility Analyses)

Name, Year, Location	Study Design and Perspective	Population	Interventions	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Calaf et al, 2015, Spain[120]	Markov model Spanish national health system perspective 5-year model	Women of reproductive age with menorrhagia, wishing to retain fertility	• LNG-IUS • Estradiol valerate/ dienogest multiphase oral contraceptive • Combined oral contraceptives • Progestins	LNG-IUS = 49.57 QALMs per person Estradiol valerate/ dienogest multiphase oral contraceptive = 47.83 QALMs per person Combined oral contraceptives = 46.24 QALMs per person Progestins = 44.18 QALMs per person	LNG-IUS = €205 over 6 months per person Estradiol valerate/ dienogest multiphase oral contraceptive = €325 over 6 months per person Combined oral contraceptives = €416 over 6 months per person Progestins = €796 over 6 months per person	LNG-IUS dominates all other treatment options
Sanghera et al, 2014, United Kingdom[121]	Markov model UK National Health Services perspective 2-year model	Women aged 25 to 50 years with menorrhagia	• LNG-IUS • Usual treatment (mefenamic acid, tranexamic acid, norethisterone, combination oral contraceptive, progestogen only contraceptive or methoxyprogesterone acetate injection)	LNG-IUS = 1.580 QALYs per person Usual medical treatment = 1.513 QALYs per person 3.5% discount rate	LNG-IUS = £430 per person Usual medical treatment = £330 per person 3.5% discount rate	LNG-IUS = £1,600/QALY
Lete et al, 2011, Spain[122]	Markov model Spanish national health system perspective 5-year model	Women of reproductive age with menorrhagia, wishing to retain fertility	• LNG-IUS • Combination oral contraceptive • Progestogens	LNG-IUS = 50.53 QALMs per person Combination oral contraceptive = 47.86 QALMs per person Progestogens = 45.59 QALMs per person 3% discount rate	LNG-IUS = €3,099 per person Combination oral contraceptive = €3,409 per person Progestogens = €3,677 per person 3% discount rate	LNG-IUS dominated both combination oral contraceptive and progestogens

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year.

Discussion

In terms of surgical comparators, the LNG-IUS was consistently less costly, but the results for quality-adjusted life-years (QALYs) were mixed. When the LNG-IUS was compared with hysterectomy, LNG-IUS was less costly than hysterectomy in all studies.[78,115-119] In three of the studies, the LNG-IUS resulted in lower total QALYs than hysterectomy.[115-117] One study showed more total QALYs for LNG-IUS than hysterectomy.[118] Another study showed no statistical differences in the change in QALYs for treatment with the LNG-IUS versus hysterectomy over 10 years of follow-up.[78] Of the four studies that compared the LNG-IUS to endometrial ablation, all studies observed that the LNG-IUS was less costly.[115-118] In one study, the LNG-IUS had more total QALYs compared with first-generation endometrial ablation techniques but lower total QALYs compared with second-generation endometrial ablation.[117] In one study that compared the LNG-IUS to thermal balloon and microwave ablation, LNG-IUS had greater total QALYs.[118] Another study with thermal balloon ablation as comparator found that the LNG-IUS resulted in a greater increase in quality of life, based on Short Form-36 scores.[119]

For studies that compared the LNG-IUS to medical therapy, LNG-IUS was less costly and had better total QALYs or quality-adjusted life-months in three of the four studies.[115,116,120,122] In one study, LNG-IUS had better total QALYs but was more costly.[121] The incremental cost-effectiveness ratio observed in this study was £1,600 per QALY.

Conclusions

Overall, the results of published economic evaluations comparing the LNG-IUS to medical therapy suggest that the LNG-IUS is cost-effective: LNG-IUS is either less costly and has better outcomes or it has a lower cost per QALY. Based on studies comparing the LNG-IUS to surgical treatment options, LNG-IUS is less costly. However, the evidence is mixed as to whether the LNG-IUS results in lower or higher QALYs compared with surgical options. Given this uncertainty in the evidence, we conducted an economic evaluation comparing the LNG-IUS to endometrial ablation and hysterectomy.

PRIMARY ECONOMIC EVALUATION

Published economic evaluations identified in our literature review have compared the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) with surgical and medical therapy for heavy menstrual bleeding (menorrhagia). Studies comparing the LNG-IUS with medical therapy have consistently shown LNG-IUS to be the more cost-effective option. Results for LNG-IUS versus surgical treatments have been inconsistent: while the LNG-IUS is invariably shown to be the least costly intervention, the quality of life outcomes have been mixed. As a result, we conducted an economic evaluation comparing the LNG-IUS with surgical treatments.

Objectives

The objective of this study was to assess the cost-effectiveness, from the perspective of the Ontario Ministry of Health and Long-Term Care, of the LNG-IUS compared with hysterectomy and endometrial ablation in patients with heavy menstrual bleeding.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[123]

Type of Analysis

Given the availability of utilities (measures of patients' preferences) related to treatment options for heavy menstrual bleeding and the uncertainty regarding the total quality-adjusted life-years (QALYs) associated with the LNG-IUS compared with surgical options, we developed a cost-utility analysis.

Target Population

The model population was women with heavy menstrual bleeding who were eligible for all three treatments being evaluated: LNG-IUS, endometrial ablation, or hysterectomy. The age of the women in the model cohort was 42 years, similar to the age in three economic evaluations studying the same interventions.[78,117,118]

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We evaluated the LNG-IUS compared with endometrial ablation and with hysterectomy.

Discounting and Time Horizon

We applied an annual discount rate of 5% to both costs and QALYs. With 51 years being the mean age of menopause in Canada, the total time horizon for our base case was 9 years.

Model Structure

For this analysis, we constructed a health-state transition model that followed a cohort of women with heavy menstrual bleeding (Figures 3 to 5). The components of the model were based on the health states commonly observed in prior studies. The model begins when a woman is cleared by a physician for initial treatment with either the LNG-IUS, endometrial ablation, or hysterectomy. Women receiving hysterectomy (Figure 5) or endometrial ablation (Figure 4) treatment will experience a wait time just prior to surgery. After receiving treatment, women can transition between the following states: well, menorrhagia, pregnant, and adverse event.

Women whose initial treatment with the LNG-IUS fails can switch to endometrial ablation (Figure 4) or hysterectomy (Figure 5). For those who switch to endometrial ablation, another failure would lead to hysterectomy. Where endometrial ablation is the initial treatment but fails, women can switch to a repeat endometrial ablation or to hysterectomy. After a second failed endometrial ablation, the only other treatment option is hysterectomy. The cycle length for this model is one month, to adequately capture all important events that a woman may experience.

The different health states in the model are described below.

Well: Women in this state are free of menorrhagia symptoms and are content with their current treatment. They may experience treatment-related adverse events. Women currently on the LNG-IUS or endometrial ablation may experience treatment failure (recurrent menorrhagia) that will result in a treatment switch and proceed to the endometrial ablation or hysterectomy model.

Pregnant: For women being treated with the LNG-IUS or endometrial ablation, there is a small probability of pregnancy. The model assumes that women will not be able to carry a pregnancy to full term and will abort after the first trimester. It is also assumed that after pregnancy the woman will continue to experience menorrhagia and will seek an alternative treatment.

Menorrhagia resolved; no further treatment: Some women initially treated with the LNG-IUS will discontinue treatment and no longer experience menorrhagia.

Menorrhagia; endometrial ablation wait time: Wait times for endometrial ablation in Ontario are approximately 69 days.[124] Women will experience menorrhagia while in this state, where they will remain for two cycles.

Menorrhagia; hysterectomy wait time: Current wait times for hysterectomy in Ontario are approximately 86 days, according to public reporting by the Ministry of Health and Long-Term Care.[124] In our analysis, women receiving hysterectomy enter the hysterectomy wait-time state for three cycles, during which time they continue to experience menorrhagia symptoms.

Hysterectomy convalescence: For women receiving a hysterectomy, the model assumes a one-month convalescence after surgery. This length of time falls between expected recovery times for laparoscopic, vaginal, and abdominal hysterectomy.[125,126]

Adverse events: Women may experience adverse events related to their current treatment and transition to the adverse event state for one cycle. We assumed that adverse events will last up to one month and that the woman will return to the same treatment afterwards. The adverse events included in this model were identified in our clinical evidence review (Table 28).

Death: At any point during the model timeline, a woman has a probability of death.

Table 28: Treatment-Related Adverse Events Included in the Economic Model

Treatment	Adverse Event
LNG-IUS	Device reinsertion
	Gastrointestinal obstruction
	Lower abdominal pain
	Pelvic pain
	Pelvic inflammatory disease
Endometrial ablation	Hematometra
	Pelvic pain
Hysterectomy	Gastrointestinal obstruction
	Lower abdominal pain
	Secondary hemorrhage
	Urinary retention
	Surgical infection

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

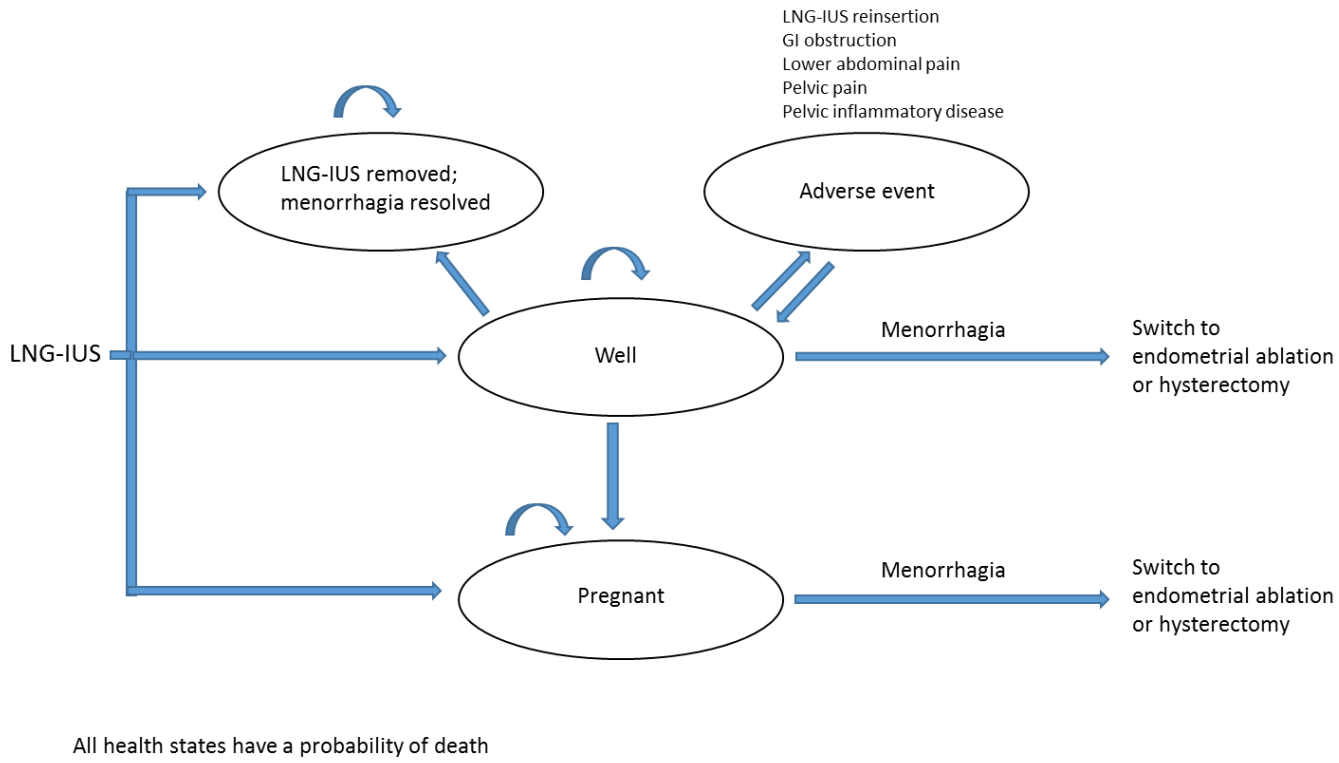

Figure 3: Model Structure (LNG-IUS)

Abbreviations: GI, gastrointestinal; LNG-IUS, levonorgestrel-releasing intrauterine system.

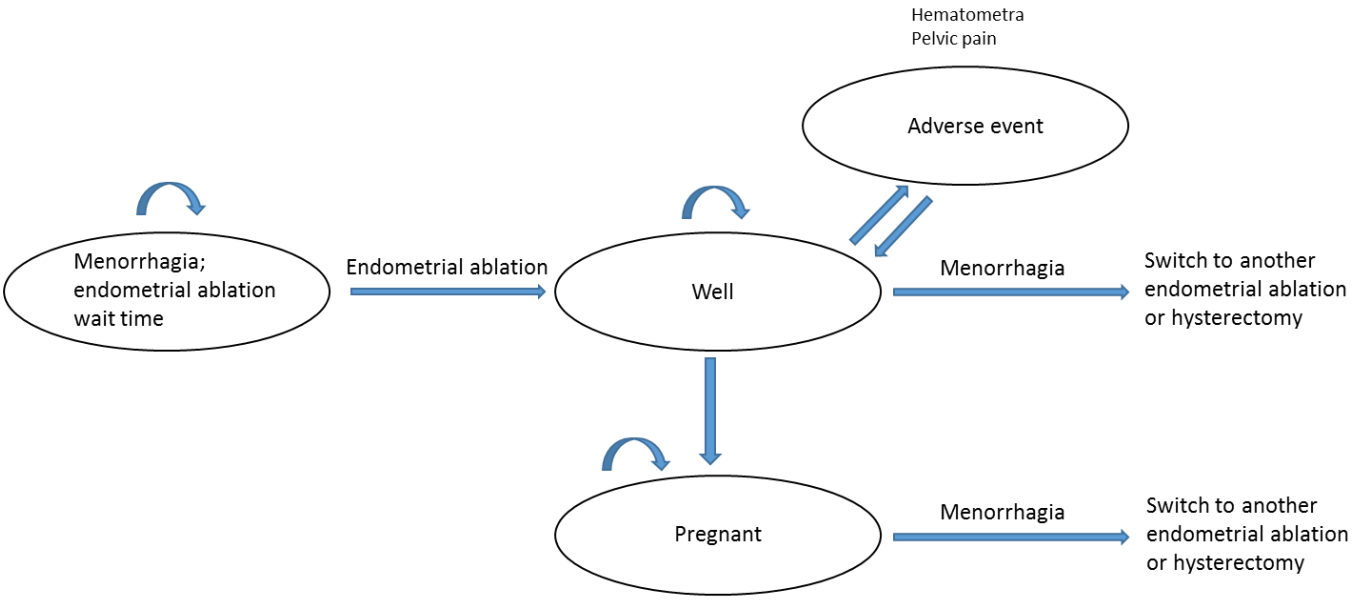

Figure 4: Model Structure (Endometrial Ablation)

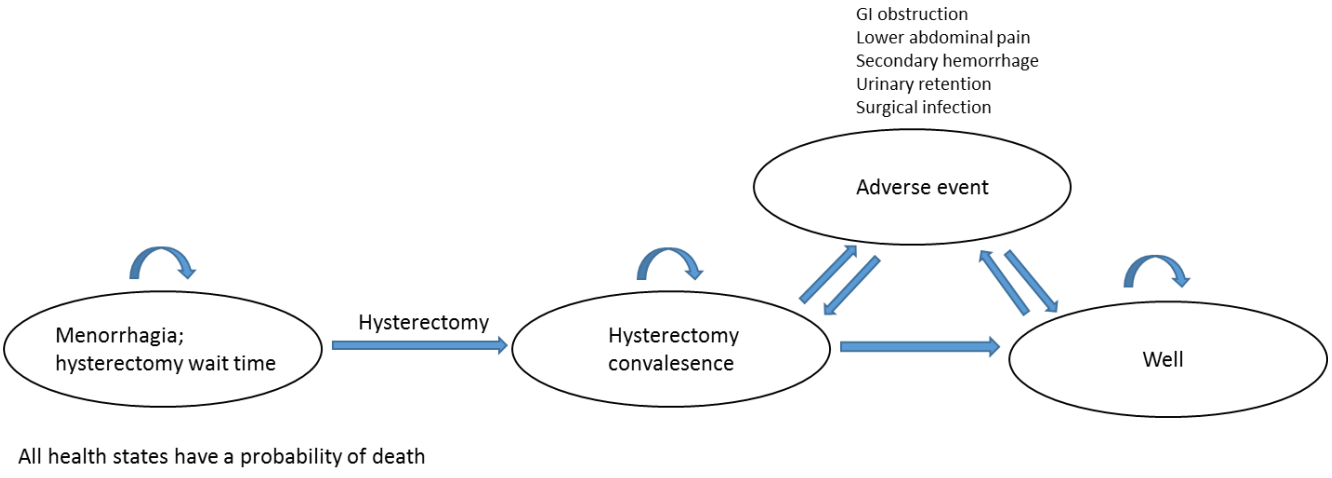

Figure 5: Model Structure (Hysterectomy)

Abbreviations: GI, gastrointestinal.

Model Parameters

We used a number of input parameters to populate the model. These inputs—clinical outcomes, utilities, and costs—are explained below.

Clinical Outcomes

Adverse Events

The probability of experiencing a treatment-related adverse event over time was extracted from the studies identified in our clinical evidence review. Because all extracted data reflected a time frame greater than the cycle length of our model, we converted these data to monthly probabilities (Table 29). Full calculations for our conversion of study data to monthly probabilities are presented in Appendix 6, Tables A8.

Table 29: Adverse Event Inputs Used in the Economic Model

Model Parameters	Monthly Probability	Duration of Risk in the Model	Reference
LNG-IUS			
Device reinsertion	0.0037	1 year	Hurskainen et al, 2001[79]
Gastrointestinal obstruction	0.0009	9 years	Heliovaara-Peippo et al, 2013[78]
Lower abdominal pain	0.0015	9 years	Malak and Shawki, 2006[87]
Pelvic pain	0.0009	9 years	Malak and Shawki, 2006[87]
Pelvic inflammatory disease	0.0004 (0.0003)	Year 1 (Years 2–9)	Hurskainen et al, 2001[79]
Endometrial ablation			
Hematometra	0.0003	9 years	Malak and Shawki, 2006[87]
Pelvic pain	0.0012	9 years	Malak and Shawki, 2006[87]
Hysterectomy			
Gastrointestinal obstruction	0.0014	9 years	Heliovaara-Peippo et al, 2013[78]
Lower abdominal pain	0.00007	9 years	Heliovaara-Peippo et al, 2013[78]
Secondary hemorrhage	0.0002	9 years	Heliovaara-Peippo et al, 2013[78]
Urinary retention	0.0002	9 years	Heliovaara-Peippo et al, 2013[78]
Surgical infection	0.0031	1 year	Hurskainen et al, 2001[79]

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Treatment Switch

The probability of switching treatment over time was extracted from the studies identified in the clinical review, and data were converted to monthly probability. Calculations are presented in Appendix 6, Tables A9 and A10. Model inputs are presented in Table 30.

Table 30: Treatment Switch Inputs Used in the Economic Model

Model Parameters	Monthly Probability	Reference
LNG-IUS to endometrial ablation		
0–6 months	0.0053[a]	Heliovaara-Peippo et al, 2013[78]
7–12 months	0.0112[a]	Heliovaara-Peippo et al, 2013[78]
2–5 years	0.0031[a]	Heliovaara-Peippo et al, 2013[78]
6–10 years	0.0007[a]	Heliovaara-Peippo et al, 2013[78]
LNG-IUS to hysterectomy		
0–6 months	0.0080[a]	Heliovaara-Peippo et al, 2013[78]
7–12 months	0.0168[a]	Heliovaara-Peippo et al, 2013[78]
2–5 years	0.0047[a]	Heliovaara-Peippo et al, 2013[78]
6–10 years	0.0011[a]	Heliovaara-Peippo et al, 2013[78]
Endometrial ablation to hysterectomy		
Year 1	0.0087	Silva-Filho et al, 2013[83]
Year 2	0.0031	Silva-Filho et al, 2013[83]
Year 3	0.0066	Silva-Filho et al, 2013[83]
Year 4	0	Silva-Filho et al, 2013[83]
Year 5	0	Silva-Filho et al, 2013[83]
Years 6–10	0	Assumption

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Assuming that 40% of women switching from LNG-IUS will receive endometrial ablation and 60% will receive hysterectomy.

Physician Follow-Up After Intervention

A randomized controlled trial comparing the LNG-IUS and endometrial ablation over 2 years included data on the total number of family physician or general practitioner visits related to each treatment for menorrhagia.[119] For our analysis, we assumed that hysterectomy requires 0.56 times as many general practitioner visits as the LNG-IUS, corresponding to the difference in physician-related costs observed in US administrative data.[115] During the waiting period for hysterectomy and endometrial ablation, when women would continue to experience menorrhagia, our model assumed that physician visits were twice the number observed for women successfully treated with the LNG-IUS.

Table 31: Physician Post-Treatment Follow-Up Inputs Used in the Economic Model

Model Parameters	Monthly Visits,[a] n	Reference
LNG-IUS	0.05	Brown et al, 2006[119]
Endometrial ablation	0.08	Brown et al, 2006[119]
Hysterectomy	0.028	Ganz et al, 2013[115]
Menorrhagia	0.10	Assumption

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Visits to a general practitioner or family physician after treatment for menorraghia.

Pregnancy

The risk of pregnancy with LNG-IUS treatment was extracted from a published literature review of contraceptive methods.[127] In that study, the observed rate of pregnancy among women using

the LNG-IUS was 0.006 per year (monthly probability 0.0005). Likewise, the risk of pregnancy after endometrial ablation was observed to be 0.007 per year, or 0.0006 per month.[128]

The distribution of pregnancy outcomes during treatment with the LNG-IUS and following endometrial ablation was based on observations from Blumenthal and colleagues[1] and Yin,[112,129] respectively. We assumed that half of the reported spontaneous abortions were complete and half were incomplete. In the literature, a proportion of women carried the pregnancy to term, but those studies were based on younger cohorts. Our model uses an older cohort so we assumed that women who did not have a spontaneous abortion or ectopic pregnancy had an induced abortion. The distribution of pregnancy outcomes in our model is presented in Appendix 6, Table A11, and calculations for the monthly probabilities are shown in Table A12.

Other Clinical Outcomes

We incorporated into the model the probability that menorrhagia would resolve after a woman discontinued the LNG-IUS, using data from Heliovaara-Peippo and colleagues.[78] We included mortality (10-year risk of death) using age-adjusted data from Ontario life tables.[130] These model inputs are presented in Table 32. Full calculations are presented in Appendix 6, Table A12.

Table 32: Other Clinical Outcome Inputs Used in the Economic Model

Model Parameters	Monthly Probability	Duration of Risk in the Model, years	Reference
Menorrhagia resolved; no further treatment	0.0014	10	Heliovaara-Peippo et al, 2013[78]
LNG-IUS risk for pregnancy	0.0005	10	Mansour 2010[127]
Mortality	0.00008–0.00022	10	Life tables 2009–2011[130]

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Intervention Utilities

Utility values were based on a study in the United Kingdom that used time trade-off methodology to elicit preferences in a cohort of 60 women with menorrhagia.[130] The utility values extracted from that study included menorrhagia, perimenopause following recovery after abdominal hysterectomy, and the convalescence period after abdominal hysterectomy. For our model, we assumed that the utility values after recovery from hysterectomy observed in the literature were similar to the utilities experienced in the well state in our model, regardless of the intervention. Utility values for women experiencing a treatment-related adverse event were not available in the literature, and we assumed that utility values for these women would fall between the values for the well and menorrhagia states. We tested this assumption in a sensitivity analysis. Table 33 shows the utility values incorporated in the model.

Table 33: Utilities Used in the Economic Model

Health State	Mean Utility (Standard Error)	Reference
Well	0.86 (0.03)	Sculpher, 1998[131]
Intervention adverse event	0.68 (0.03)	Assumption
Pregnant	0.86 (0.03)	Sculpher, 1998[131]
Menorrhagia resolved; no further treatment	0.86 (0.03)	Sculpher, 1998[131]
Well; hysterectomy convalescence	0.74 (0.05)	Sculpher, 1998[131]
Menorrhagia; hysterectomy wait time	0.5 (0.04)	Sculpher, 1998[131]
Menorrhagia; one month transition between treatments	0.5 (0.04)	Sculpher, 1998[131]

Cost Parameters

All costs included in our study originated from the Ontario Schedule of Benefits for Physician Services,[132] the Ontario Drug Benefit Formulary,[133] and Ontario administrative data. A cohort of women who received the LNG-IUS was identified through the provincial physician billing database. The number of women receiving endometrial ablation or hysterectomy for heavy menstrual bleeding was calculated through the inpatient and outpatient hospital care databases. Treatment-related adverse events were likewise identified through inpatient hospital care databases. The diagnosis and procedure codes used to search the administrative data are presented in Appendix 6, Tables A13 and A14.

LNG-IUS

Initial treatment. Cost of initial treatment includes physician services for the procedure as well as the cost of the technology. According to Ontario administrative data, approximately 88% of LNG-IUS insertions were administered by a gynecologist for menorrhagia. Therefore, our model included a consult with a gynecologist in 88% of treatments. The model repeated this cost at 5 years, the lifespan of this technology.[134] Unit cost inputs for initial LNG-IUS treatment are presented in Table 34.

Table 34: LNG-IUS Treatment Costs Used in the Economic Model

Variable	Unit Cost, $	Reference
Gynecologist consultation	101.70	Ontario Schedule of Benefits for Physician Services[132] (code A205)
LNG-IUS initial procedure	337.90	Ontario Drug Benefit Formulary[133]
LNG-IUS procedure physician services	36.65	Ontario Schedule of Benefits for Physician Services[132] (code G378)

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Physician follow-up. Physician follow-up costs were calculated by multiplying the mean number of visits per month by the cost per physician service. In our analysis, we assumed that all physician visits were to a family physician. Table 35 shows the unit cost.

Table 35: Physician Follow-Up Costs Used in the Economic Model

Variable	Unit Cost, $	Reference
Family physician	38.35	Ontario Schedule of Benefits for Physician Services[132] (code A004)

Endometrial Ablation

Initial treatment. The cost of initial treatment with endometrial ablation includes a concurrent tubal occlusion procedure assumed to occur in 30% of all women receiving this treatment for heavy menstrual bleeding. This was estimated assuming 35% sterilization rates, with 5% coming from vasectomies (Expert opinion, written communication, November 17, 2015). The cost for physician services includes the surgeon, assistant surgeon, and anesthesiologist. If the woman receiving endometrial ablation is switching from the LNG-IUS to endometrial ablation, the model included an additional cost for the removal of the device. Table 36 shows the costs for initial treatment with endometrial ablation.

Physician follow-up. For endometrial ablation, these costs were the same as described for LNG-IUS treatment (Table 35).

Table 36: Endometrial Ablation Treatment Costs Used in the Economic Model

Variable	Unit Cost, $ (Standard Deviation)	Reference
Gynecologist consultation	101.70	Ontario Schedule of Benefits for Physician Services[132] (code A205)
Endometrial ablation initial procedure	1,137.00[a] (425)	Administrative data[b]
Endometrial ablation procedure physician services	309.71	Ontario Schedule of Benefits for Physician Services[132] (code S772)
Concurrent tubal occlusion procedure	1,110.00[a] (114)	Administrative data[b]
Tubal occlusion procedure physician services	318.00	Ontario Schedule of Benefits for Physician Services[132] (code S741)
LNG-IUS removal physician services (only if switching from LNG-IUS)	47.45	Ontario Schedule of Benefits for Physician Services[132] (code A203)

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Mean cost.
[b]Data provided by Ontario IntelliHEALTH.

Hysterectomy

Initial treatment. The cost of initial treatment for hysterectomy includes hospital and physician procedure costs. Physician costs include the fees of the surgeon, assistant surgeon, and anesthesiologist. For women receiving hysterectomy after failure of previous treatment with either LNG-IUS or endometrial ablation, the model included an additional cost for a preoperative physician visit.

Physician follow-up. For hysterectomy, these costs were the same as described for LNG-IUS treatment (Table 35).

Table 37: Hysterectomy Treatment Costs Used in the Economic Model

Variable	Unit Cost, $ (Standard Deviation)	Reference
Gynecologist consultation	101.70	Ontario Schedule of Benefits for Physician Services[132] (code A205)
Hysterectomy initial procedure	4,573.00[a] (1,575)	Administrative data[b]
Hysterectomy procedure physician services	640.31	Ontario Schedule of Benefits for Physician Services[132] (code S757 or S816)
Hysterectomy preoperative physician services (only if switching from another treatment)	101.70	Ontario Schedule of Benefits for Physician Services[132] (code A205)

[a]Mean cost.
[b]Data provided by Ontario IntelliHEALTH.

Treatment-Related Adverse Events

Costs for adverse events were based on the mean inpatient or outpatient hospital length of stay observed in administrative data. Costs included the hospital stay and physician services. These costs are summarized in Table 38, and a further breakdown is provided in Appendix 6, Table A14.

Table 38: Treatment-Related Adverse Event Costs Used in the Economic Model

Variable	Unit Cost, $ (Standard Deviation)	Reference
LNG-IUS–related adverse events		
Reinsertion		
Procedure	338	Ontario Drug Benefit Formulary[133]
Physician	36.65	Ontario Schedule of Benefits for Physician Services[132] (code G378 and E542)
Gastrointestinal obstruction		
Hospital	4,156 (2,615)	Administrative data[a]
Physician	249	Ontario Schedule of Benefits for Physician Services[132]
Lower abdominal pain		
Hospital	385 (222)	Administrative data[a]
Physician	77.20	Ontario Schedule of Benefits for Physician Services[132]
Pelvic pain		
Hospital	4,211 (1,063)	Administrative data[a]
Physician	218	Ontario Schedule of Benefits for Physician Services[132]
Pelvic inflammatory disease		
Hospital	503 (704)	Administrative data[b]
Physician	77	Ontario Schedule of Benefits for Physician Services[132]
Endometrial ablation–related adverse events		
Hematometra		
Hospital	2,450 (1,638)	Administrative data[a]
Physician	308	Ontario Schedule of Benefits for Physician Services[132]
Pelvic pain		
Hospital	1,372 (1,814)	Administrative data[a]
Physician	159	Ontario Schedule of Benefits for Physician Services[132]

Variable	Unit Cost, $ (Standard Deviation)	Reference
Hysterectomy-related adverse events		
Gastrointestinal obstruction		
Hospital	3,823 (2,269)	Administrative data[a]
Physician	367	Ontario Schedule of Benefits for Physician Services[132]
Lower abdominal pain		
Hospital	424 (374)	Administrative data[a]
Physician	77.20	Ontario Schedule of Benefits for Physician Services[132]
Secondary hemorrhage		
Hospital	1,878 (646)	Administrative data[a]
Physician	159	Ontario Schedule of Benefits for Physician Services[132]
Urinary retention		
Hospital	510 (706)	Administrative data[a]
Physician	77.20	Ontario Schedule of Benefits for Physician Services[132]
Surgical infection		
Hospital	1,195 (3,331)	Administrative data[a]
Physician	77.20	Ontario Schedule of Benefits for Physician Services[132]

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Data provided by Ontario IntelliHEALTH.

Pregnancy-related costs

Pregnancy costs consist of physician services. No additional costs were included in our analysis. Unit costs are presented in Table 39.

Table 39: Physician Costs Related to Pregnancy Outcomes Used in the Economic Model

Variable	Unit Cost, $	Reference
Spontaneous complete abortion	161.15	Ontario Schedule of Benefits for Physician Services[132] (code A004)
Spontaneous incomplete abortion	183.06	Ontario Schedule of Benefits for Physician Services[132] (code A206)
Induced abortion	202.46	Ontario Schedule of Benefits for Physician Services[132] (code A004)
Ectopic abortion	207.80	Ontario Schedule of Benefits for Physician Services[132] (code A004)

Analysis

In the base case analysis, we applied actual values or mean values as the model inputs. This method provides the best estimate of the cost-effectiveness of the LNG-IUS, but it does not consider the uncertainty of various inputs to the model or the possibility of other clinical scenarios. We present the results as the incremental costs (the difference in costs) and incremental QALYs of LNG-IUS compared with hysterectomy and endometrial ablation.

While the base case analysis provided the best estimates of the cost-effectiveness of the LNG-IUS, we performed sensitivity analyses to address the uncertainty of model inputs and clinical scenarios. We assessed variability and uncertainty in the model through one-way and probabilistic sensitivity analyses. To determine the impact of simultaneously varying numerous variables within the assigned distributions, we conducted a probabilistic sensitivity analysis by

running 1,000 simulations of the model. Results of the probabilistic sensitivity analysis are presented on a cost-effectiveness plane and, if necessary, a cost-effectiveness acceptability curve. We assigned a beta distribution for utility values. For cost inputs where standard deviation or confidence intervals were presented, a gamma distribution was assigned. We conducted one-way sensitivity analyses by varying specific model variables and examining the impact on the results. The variables and ranges are presented in Table 40.

Table 40: Variables Varied in One-Way Sensitivity Analyses

Variable	Range	Reference
Adverse events and switch rates	Clinical inputs from administrative data	Administrative data[a]
Mean age when initial treatment in administered	38 to 46 years	Assumption
Pregnancy	Exclude from model	Assumption
Frequency of physician follow-up after endometrial ablation	0.028 to 0.05	Same as LNG-IUS to hysterectomy
Women experiencing repeat LNG-IUS	All switch to hysterectomy	Assumption
Women experiencing repeat endometrial ablation	All switch to hysterectomy	Assumption
Women experiencing repeat LNG-IUS or endometrial ablation	All switch to hysterectomy	Assumption
Treatment-related adverse event health state	0.5 to 0.86	Sculpher, 1998[131]
Menorrhagia utility	0.76	Heliovaara-Peippo et al, 2013[78]
Physician follow-up	Exclude from model	Assumption
Discount rate	3%	Assumption
Hysterectomy wait time	Exclude prior to initial treatment	Assumption

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Data provided by Ontario IntelliHEALTH.

Main Assumptions

The major assumptions for this model are:

- A woman's quality of life after successful treatment is the same regardless of treatment
- Quality of life after treatment-related adverse events is worse than with successful treatment but better than with continued menorrhagia
- Treatment-related adverse events do not last more than a month
- Women who become pregnant do not carry the pregnancy to term
- First-generation and second-generation endometrial ablation are combined into one treatment arm
- Women who initially receive LNG-IUS and switch to endometrial ablation will only be offered hysterectomy if endometrial ablation fails
- Women who initially receive endometrial ablation may receive a second endometrial ablation if treatment fails, but not a third.
- There are no post-hysterectomy complications that require a repeat procedure

Generalizability

The findings of this economic analysis cannot be generalized to all patients with heavy menstrual bleeding. They may, however, be used to guide decision-making about the specific patient populations in Ontario addressed in the studies evaluated by Health Quality Ontario.

Expert Consultation

Throughout the development of this model, we solicited expert consultation from physicians in the specialty areas of obstetrics and gynecology. The role of the expert advisors was to review the structure and inputs of the economic model to confirm that the information we used reasonably reflects the clinical setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Base Case Analysis

The base case results for our analysis are presented in Table 41. The LNG-IUS costs less and has higher quality-adjusted life-years (QALYs) than both endometrial ablation and hysterectomy.

Table 41: Base Case Analysis Results

Strategy	Average Total Costs, $	Incremental Cost, $	Average Total QALYs	Incremental QALYs	Incremental Cost-Effectiveness Ratio
LNG-IUS	3,142		6.32		
Hysterectomy	6,280	−3,138[a]	6.28	0.04[b]	LNG-IUS dominates
Endometrial ablation	3,514	−372[c]	6.27	0.05[d]	LNG-IUS dominates

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life-year.
[a]Incremental costs = average costs of LNG-IUS – average costs of hysterectomy.
[b]Incremental effects = average effects of LNG-IUS − average effects of hysterectomy.
[c]Incremental costs = average costs of LNG-IUS − average costs of endometrial ablation.
[d]Incremental effects = average effects of LNG-IUS − average effects of endometrial ablation.

Sensitivity Analysis

The incremental cost and incremental QALYs calculated for each simulation of the probabilistic sensitivity analysis for LNG-IUS versus hysterectomy and LNG-IUS versus endometrial ablation are illustrated in Figures 6 and 7, respectively. In the comparison of the LNG-IUS and hysterectomy, incremental costs ranged from −$14,008 to $1,609, while incremental QALYs ranged from 0.05 to 0.15. When LNG-IUS was compared with endometrial ablation, incremental cost ranged from −$2,630 to $1,524 and incremental QALYs ranged from 0.03 to 0.07. We did not develop cost-effectiveness acceptability curves because almost all simulations in the probabilistic sensitivity analysis resulted in a dominant situation for LNG-IUS (lower incremental cost and higher incremental QALYs). The results of the one-way sensitivity analysis are presented in Tables 42 and 43.

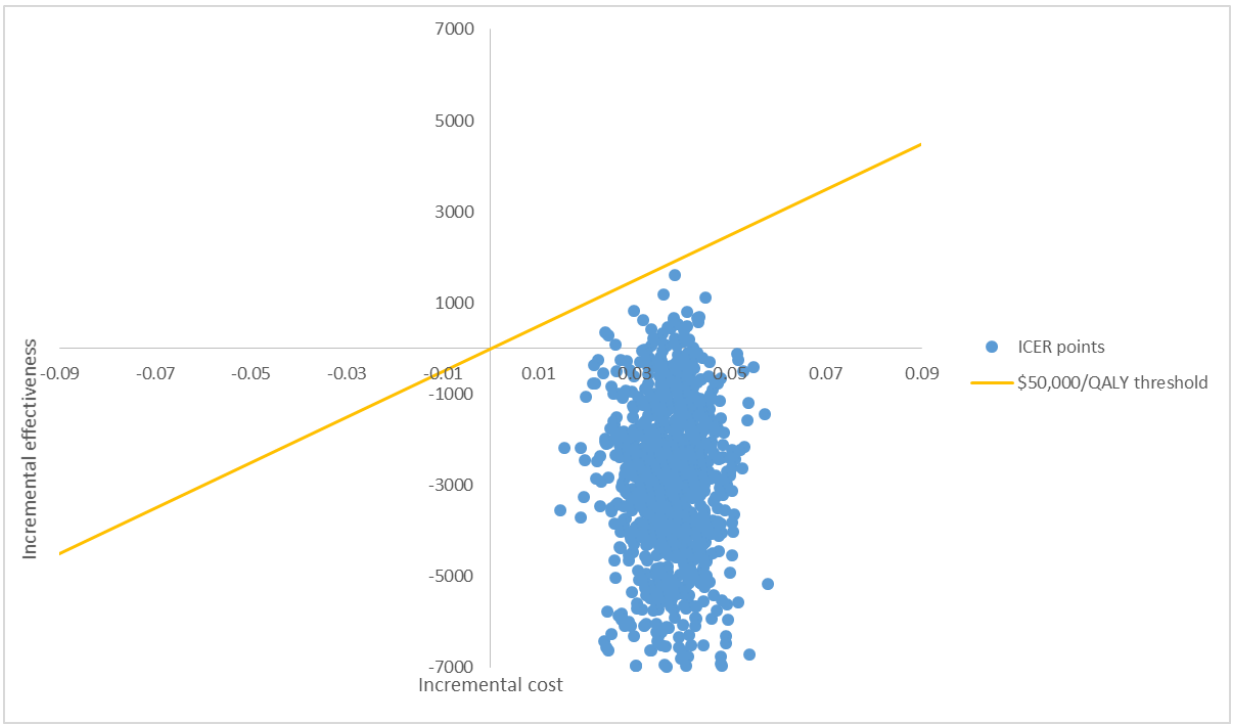

Figure 6: Incremental Cost and QALYs of LNG-IUS Compared With Hysterectomy

Abbreviations: ICER, incremental cost-effectiveness ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life-year.

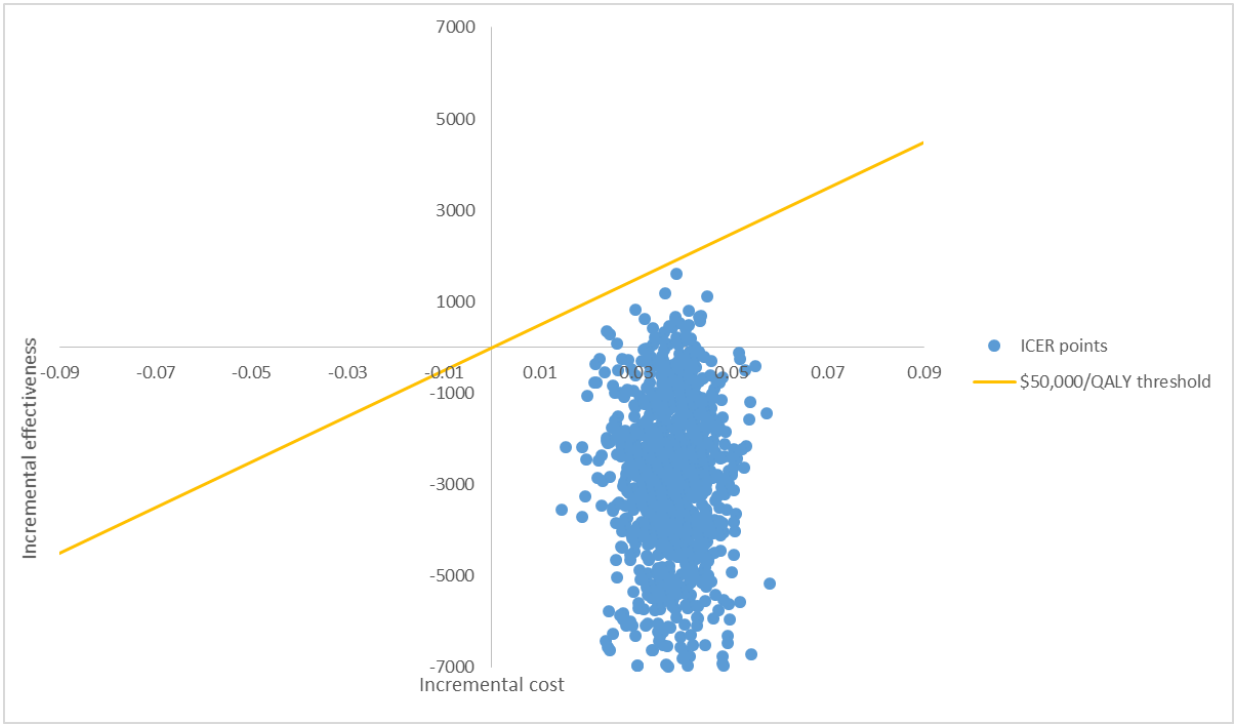

Figure 7: Incremental Cost and QALYs of LNG-IUS Compared With Endometrial Ablation

Abbreviations: : ICER, incremental cost-effectiveness ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life-year.

Table 42: One-Way Sensitivity Analysis Results, LNG-IUS vs. Hysterectomy

Scenario	Incremental Cost, $[a]	Incremental Effect[b]	Result
Administrative data inputs for adverse events and switch rates	−4,004	0.056	LNG-IUS dominates
Model excludes pregnancy	−3,237	0.041	LNG-IUS dominates
5-year model	−3,367	0.041	LNG-IUS dominates
13-year model	−3,036	0.037	LNG-IUS dominates
Endometrial ablation physician follow-up same as hysterectomy	−3,153	0.038	LNG-IUS dominates
Endometrial ablation physician follow-up same as LNG-IUS	−3,138	0.038	LNG-IUS dominates
All LNG-IUS switches to hysterectomy with recurrence of menorrhagia	−2,792	0.037	LNG-IUS dominates
All endometrial ablation switches to hysterectomy with recurrence of menorrhagia	−3,138	0.038	LNG-IUS dominates
All LNG-IUS and endometrial ablation switches to hysterectomy with recurrence of menorrhagia	−2,792	0.038	LNG-IUS dominates
Treatment-related adverse event quality of life is the same as menorrhagia state	−3,138	0.039	LNG-IUS dominates
Treatment-related adverse event quality of life is the same as well state	−3,126	0.037	LNG-IUS dominates
Menorrhagia utilities at 0.76	−3,138	0.076	LNG-IUS dominates
Exclude physician follow-up	−3,213	0.038	LNG-IUS dominates
3% discount rate	−3,052	0.036	LNG-IUS dominates
Exclude initial hysterectomy wait time	−3,161	−0.052	Lower cost and lower QALYs for LNG-IUS

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; QALY, quality-adjusted life year
[a]Incremental costs = average costs of LNG-IUS – average costs of hysterectomy.
[b]Incremental effects = average effects of LNG-IUS – average effects of hysterectomy.

Table 43: One-Way Sensitivity Analysis Results, LNG-IUS vs. Endometrial Ablation

Scenario	Incremental Cost, $[a]	Incremental Effect[b]	Result
Administrative data inputs for adverse events and switch rates	−1,067	0.056	LNG-IUS dominates
Model excludes pregnancy	−318	0.045	LNG-IUS dominates
5-year model	−574	0.049	LNG-IUS dominates
13-year model	−136	0.045	LNG-IUS dominates
Endometrial ablation physician follow-up same as hysterectomy	−244	0.046	LNG-IUS dominates
Endometrial ablation physician follow-up same as LNG-IUS	−372	0.046	LNG-IUS dominates
All LNG-IUS switches to hysterectomy with recurrence of menorrhagia	−46	0.045	LNG-IUS dominates
All endometrial ablation switches to hysterectomy with recurrence of menorrhagia	−496	0.046	LNG-IUS dominates
All LNG-IUS and endometrial ablation switches to hysterectomy with recurrence of menorrhagia	−42	0.043	LNG-IUS dominates
Treatment-related adverse event quality of life is the same as menorrhagia state	−364	0.042	LNG-IUS dominates
Treatment-related adverse event quality of life is the same as well state	−372	0.050	LNG-IUS dominates
Menorrhagia utilities at 0.76	−365	0.049	LNG-IUS dominates
Exclude physician follow-up	−302	0.046	LNG-IUS dominates
3% discount rate	−279	0.045	LNG-IUS dominates

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Incremental costs = average costs of LNG-IUS – average costs of endometrial ablation.
[b]Incremental effects = average effects of LNG-IUS – average effects of endometrial ablation.

Discussion

In our primary economic evaluation comparing the LNG-IUS with hysterectomy for treatment of heavy menstrual bleeding, we observed that LNG-IUS was less costly and had better QALYs. This observation remained consistent in the one-way sensitivity analyses except when surgical wait time was excluded from the model. In that case, the LNG-IUS was still less costly but had lower QALYs than hysterectomy. The probabilistic sensitivity analysis confirmed that the overall results remained consistent (lower cost and higher QALYs for LNG-IUS) even when the uncertainty in the model inputs was considered.

Compared with endometrial ablation and hysterectomy, the LNG-IUS was less costly and had higher QALYs, and this was consistently observed in more than 99% of all simulation results in the sensitivity analyses. In some cases, costs were higher for LNG-IUS, but all simulations resulted in LNG-IUS costs below the commonly used threshold of $50,000 per QALY.

The results of our analysis are within range of past economic evaluations comparing LNG-IUS and hysterectomy for treatment of heavy menstrual bleeding. The incremental cost savings of LNG-IUS fall between the findings of past studies, where the cost difference ranged between −$745 and −$5,113.[78,115] The lower QALYs for LNG-IUS versus hysterectomy when we excluded the wait time for surgery were similar to most previous studies. This is to be expected given that past studies did not consider surgical wait times in their analyses.

Our base case comparing the LNG-IUS and endometrial ablation resulted in incremental cost savings for LNG-IUS that were lower than past studies (−$1,475 to −$1,657).[115,116] This may be because the model duration in prior studies was only 5 years, whereas we used a 9-year time horizon. When we limited our model to 5 years, the incremental cost savings for LNG-IUS were closer to past studies. Unlike the mixed results on the incremental QALYs of LNG-IUS versus endometrial ablation from past studies, our results showed an increase in total QALYs for LNG-IUS compared with endometrial ablation.

Our analysis has numerous strengths. The longer timeline allowed our analysis to include all clinical impacts that women with heavy menstrual bleeding typically experience, across the duration of the condition. Using monthly cycles allowed us to model changes in treatment and in rates of treatment-related adverse events that were similar to changes experienced by patients. The probabilities of treatment-related adverse events included in our model were based on an extensive clinical review of the published literature. Where model inputs were not available from published studies, we used Ontario administrative data. This minimized the use of assumptions in the analysis and allowed us to incorporate Ontario-specific data, another strength.

There were also several limitations in our analysis. First, no data were available to provide values for the utility of adverse events related to treatment for heavy menstrual bleeding. As a result, we assumed that this utility was between the values for the well state and the heavy menstrual bleeding state. However, given the small probability of adverse events related to the treatments we modelled, changes to this utility would only result in small changes to the total QALYs for any of the treatments. Second, utility values were based on data collected more than 20 years ago and quality of life data were for women receiving hysterectomy to treat heavy menstrual bleeding. We assumed that these utility values would be similar for women receiving the LNG-IUS or endometrial ablation today. Third, no published studies have compared physician follow-up times for all three treatment options. Our study relied on data from two different studies with the assumption that the two study cohorts were similar to each other and to our population. Fourth, there was no information on the average wait time for receiving the

LNG-IUS. For our analysis, we assumed that the wait would be less than a month. A longer wait would reduce the total QALYs for LNG-IUS and shrink the incremental QALYs of that treatment versus hysterectomy or endometrial ablation. Fifth, no information was available on the possibility that some women might discontinue using the LNG-IUS and not switch to another treatment, even though their heavy menstrual bleeding continued. If a proportion of women would make that choice, this would mean our total QALYs for LNG-IUS are an overestimate, as we assumed that all women experiencing treatment failure with LNG-IUS would opt for endometrial ablation or hysterectomy. Sixth, we used a generic diagnosis code of "menstrual problem" to search the administrative data for women receiving the LNG-IUS for heavy menstrual bleeding. We assumed that approximately 50% of this cohort had menorrhagia but the actual size of the cohort could be different. Further, many women who received the LNG-IUS did not have a reported diagnosis code. As a result, we may have underestimated the size of our cohort. Finally, this economic evaluation does not consider patient preference for initial treatment. The underlying assumption with our model was that women were cleared for all treatment options and did not have a preference for any specific treatment.

Conclusions

The results of our analysis show that the LNG-IUS is less costly and has better QALY outcomes compared with both hysterectomy and endometrial ablation. These observations were consistent even when uncertainty in model inputs and parameters was considered.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden over the next 5 years of funding the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) for the treatment of heavy menstrual bleeding (menorrhagia). All costs are reported in 2015 Canadian dollars. A 5-year time frame was selected because it corresponds to the lifetime of the LNG-IUS device.

Objectives

The objective of this study was to assess the budget impact, within the context of the Ontario Ministry of Health and Long-Term Care, of publicly funding the LNG-IUS compared with hysterectomy and endometrial ablation for treatment of heavy menstrual bleeding,

Methods

Target Population

Three distinct hypothetical populations were incorporated into this analysis. The first group consists of women who are prescribed the LNG-IUS for heavy menstrual bleeding and would pay for the device out-of-pocket or be reimbursed by private health insurance if LNG-IUS were not publicly funded. (If LNG-IUS were to be publicly funded, the only additional cost from the public health care payer perspective would be the cost to reimburse the device.) We estimated the number of new cases each year by extrapolating from the volume of new LNG-IUS cases between 2006 and 2012 identified through administrative data.

The second group in the analysis is women seeking a replacement LNG-IUS when the device has reached the end of its lifetime (approximately 5 years). We approximated the size of this group by identifying women who received an initial treatment of LNG-IUS for heavy menstrual bleeding 5 years prior to the most recent administrative data. To exclude women who switch to an alternative treatment or stop treatment altogether, we calculated that 70% of women will continue with LNG-IUS at 5 years, based on the primary economic evaluation in this report. We then multiplied the number of new cases of LNG-IUS treatment by 70% to estimate the number of women requiring an LNG-IUS replacement.

The third group is women who are prescribed LNG-IUS for menorrhagia but would instead receive hysterectomy or endometrial ablation if LNG-IUS were not publicly funded. In this cohort, we considered both the cost of the device and downstream costs in six scenarios: four comparing LNG-IUS and hysterectomy and two comparing LNG-IUS and endometrial ablation.

For the first (upper limit) hysterectomy scenario, we assumed that all women who had a hysterectomy for heavy menstrual bleeding will instead receive LNG-IUS as their initial treatment. In a second scenario, we assumed that 88% of those who would have had a hysterectomy if LNG-IUS were not publicly funded will accept LNG-IUS if it is offered. This assumption corresponded to an observation that 12% of women who had a hysterectomy chose that treatment over LNG-IUS.[29] A third scenario considered women who will have a hysterectomy because they do not have private health insurance covering LNG-IUS and cannot afford the cost of the device. In this scenario, we assumed that all women with unsupportive pathology for hysterectomy (meaning they may not have needed the surgery as their initial treatment for heavy menstrual bleeding) did not have private health insurance. The proportion of women with unsupportive pathology was 12%, as reported in a US cohort.[135] For a fourth (lower

limit) scenario, we assumed that 50% of the cohort with unsupportive pathology will be treated by hysterectomy instead of LNG-IUS because they could not afford the LNG-IUS device if they had to pay for it.

In our analyses comparing LNG-IUS and endometrial ablation, in the first (upper limit) scenario we assumed that all women who would have been treated with endometrial ablation will receive LNG-IUS instead. As a second (lower limit) scenario, we assumed that 78% of women who would have received endometrial ablation will choose LNG-IUS if it is offered initially. This assumption is based on a study finding that about 22% of women receiving endometrial ablation for heavy menstrual bleeding preferred that treatment over LNG-IUS.[29]

Table 44 presents the total estimated volumes of treatment procedures over 5 years for all scenarios. The total volumes were calculated by summing the volumes for the three treatment groups in each scenario (see Appendix 8, Tables A18 to 22 for more detail).

Table 44: Target Population Scenarios to Compare LNG-IUS and Surgical Treatments

	Number of Women Receiving LNG-IUS				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
LNG-IUS compared with hysterectomy					
Scenario 1 (upper limit): Women who would have received hysterectomy if LNG-IUS were not publicly funded (includes all women receiving hysterectomy for heavy menstrual bleeding)	6,503	6,493	6,487	6,514	6,493
Scenario 2: Women who would have received hysterectomy if LNG-IUS were not publicly funded (assumes 12% of women offered LNG-IUS prefer hysterectomy)	5,479	5,516	5,559	5,633	5,660
Scenario 3: Women who would have received hysterectomy if LNG-IUS were not publicly funded (assumes all with unsupportive pathology for hysterectomy did not have private health insurance)	1,860	2,023	2,191	2,392	2,543
Scenario 4 (lower limit): Women who would have received hysterectomy if LNG-IUS were not publicly funded (assumes 50% with unsupportive pathology for hysterectomy did not have private health insurance)	1,574	1,747	1,925	2,135	2,297
LNG-IUS compared with endometrial ablation					
Scenario 1 (upper limit): Women who have received endometrial ablation if LNG-IUS were not publicly funded (includes all women receiving endometrial ablation)	7,469	7,693	7,922	8,184	8,397
Scenario 2 (lower limit): Women who would have received endometrial ablation if LNG-IUS were not publicly funded (assumes 22% of women offered LNG-IUS prefer endometrial ablation)	6,109	6,324	6,544	6,797	7,001

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Resource and Costs

The cost of the LNG-IUS for women who will privately cover the cost of the device if it is not publicly funded is the cost of the device as reported in the Ontario Drug Benefit Formulary ($338).[133] Costs for women who will have a hysterectomy or endometrial ablation if LNG-IUS is not publicly funded are based on the annual incremental cost and cost savings associated with the LNG-IUS compared with the surgical treatments for the first 5 years, as reported in our primary economic evaluation. These costs include the initial treatment, physician follow-up, and costs of treatment-related adverse events. Total annual costs for each treatment group are presented in Table 45.

Table 45: Estimated Per-Patient Costs for Calculating Budget Impact of Publicly Funding LNG-IUS

	Cost to Publicly Fund LNG-IUS, $				
Strategy	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
For women who will privately pay for the device if LNG-IUS is not publicly funded	338	0	0	0	0
For women who will receive hysterectomy if LNG-IUS is not publicly funded[a]	−4,507	389	213	355	326
For women who will receive endometrial ablation if LNG-IUS is not publicly funded[b]	−1,449	104	−33	260	376

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a] Cost of LNG-IUS relative to cost of hysterectomy.
[b] Cost of LNG-IUS relative to cost of endometrial ablation.

Analysis

To obtain the total cost of providing the LNG-IUS to women who will choose this option whether or not it is publicly funded, we multiplied the unit cost of LNG-IUS by the estimated number of women who will either pay for the device out-of-pocket or have it reimbursed by private insurance.

For the total cost of new cases (i.e., for women who can be expected to choose the LNG-IUS over surgical options if it is publicly funded), we multiplied the annual incremental cost of the LNG-IUS compared with hysterectomy by the volumes for each of the four scenarios described above, resulting in four separate analyses. Likewise, the annual incremental cost of the LNG-IUS compared with endometrial ablation was multiplied by the total volumes for each the two endometrial ablation scenarios.

Finally, the total budget impact was calculated by summing the total cost of providing the LNG-IUS to women who will choose that option regardless of public funding and the total cost of treating the additional women who will newly choose the LNG-IUS over surgical treatment (i.e. hysterectomy and endometrial ablation) as a result of public funding.

In a supplementary analysis, we calculated the new cost to government of the estimated increase in use of the LNG-IUS to treat heavy menstrual bleeding if this treatment becomes publicly funded. In this analysis, only the cost of the LNG-IUS device was included; we multiplied the total annual volumes for all scenarios by the cost of the device, as reported in the Ontario Drug Benefit Formulary.[133]

Results

Table 46 presents the results of the budget impact analysis for all of the scenarios comparing the cost of the LNG-IUS versus hysterectomy and endometrial ablation. Detailed calculations for each scenario are presented in Appendix 8, Tables A23 to A28. Results show a general trend towards cost savings each year for LNG-IUS versus hysterectomy and endometrial ablation.

Table 46: Results of Budget Impact Analysis of Publicly Funding LNG-IUS vs. Surgical Treatments for Heavy Menstrual Bleeding

	$ million				
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
LNG-IUS vs. hysterectomy					
Scenario 1 (upper limit)	−23.1	−20.1	−18.1	−15.4	−13.0
Scenario 2	−18.5	−16.1	−14.5	−12.4	−10.5
Scenario 3	−2.1	−1.8	−1.5	−1.1	−0.8
Scenario 4 (lower limit)	−0.8	−0.6	0.5	0.2	−0.1
LNG-IUS vs. endometrial ablation					
Scenario 1 (upper limit)	−8.5	−7.9	−8.1	−6.5	−4.2
Scenario 2 (lower limit)	−6.6	−6.0	−6.2	−5.0	−3.2

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

The annual costs of funding the estimated increase in demand for LNG-IUS devices, for all scenarios, are presented in Table 47. This includes only the additional cost of publicly funding the devices and does not account for the potential cost-savings from decreased use of other types of treatment. Detailed calculations behind these costs are shown in Appendix 8, Tables A29 to A34. Results show a cost between $0.7 to $4.2 million per year.

Table 47: New Annual Cost of Publicly Funding LNG-IUS Treatment

	$ million				
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
LNG-IUS vs. hysterectomy					
Scenario 1 (upper limit)	2.2	2.2	2.2	2.2	3.4
Scenario 2	1.9	1.8	1.7	1.5	2.0
Scenario 3	0.6	0.7	0.7	0.8	1.0
Scenario 4 (lower limit)	0.5	0.6	0.7	0.7	0.8
LNG-IUS vs. endometrial ablation					
Scenario 1 (upper limit)	2.5	2.6	2.6	2.7	4.2
Scenario 2 (lower limit)	2.1	2.1	2.2	2.2	3.4

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Discussion

This budget impact analysis revealed that, in the first 5 years, publicly funding the LNG-IUS for heavy menstrual bleeding as an alternative to surgical interventions could result in savings of between $3 million and $30 million per year. This includes potential savings of $0.1 million to

$23 million per year by replacing hysterectomies and $3.2 million to $8.5 million per year by replacing endometrial ablation procedures. Cost savings are expected to decrease over time as more women begin treatment with the LNG-IUS and the number of women currently on this treatment rises. This trend would likely stabilize at approximately year 10 as women who have used an LNG-IUS for close to a decade approach menopause.

In a supplementary analysis, we estimated the total new cost of publicly funding LNG-IUS treatment for heavy menstrual bleeding; this involves only the cost of providing the devices because physician fees related to the procedure are already covered. The total new cost for the first 5 years would be about $3 million to $8 million per year. This includes between $0.5 million and $3.4 million per year as LNG-IUS replaces some hysterectomies, and between $2.1 and $4.2 million per year as LNG-IUS replaces some endometrial ablations.

To our knowledge, no other budget impact analysis has been published on the use of the LNG-IUS to treat heavy menstrual bleeding. Our evaluation has several strengths. We included incremental cost data from our primary economic evaluation, which encompassed all downstream costs in the first 5 years. Calculating the 5-year budget impact allowed us to include costs for a complete lifetime of the LNG-IUS device. Further, our analysis considered three groups of potential users of LNG-IUS: women who would choose the LNG-IUS without public funding (they have private insurance or would pay out-of-pocket); women who would have chosen hysterectomy or endometrial ablation if LNG-IUS were not publicly funded; and women who need a repeat LNG-IUS procedure because their device has reached the end of its 5-year lifetime.

Our analysis also had two key limitations. First, our estimates of cohort size were based on volumes of procedures from administrative data. Due to limitations in reporting, the cohort sizes used in our calculations are likely an underestimation. The actual volumes are currently unknown. Second, and arguably the most important limitation, was the uncertainty regarding the number of women who would receive the LNG-IUS instead of hysterectomy or endometrial ablation if this treatment were publicly funded. We addressed this uncertainty by developing a variety of scenarios based on different assumptions. Comparing the LNG-IUS with hysterectomy, for the upper limit we included all women who would be expected to receive a hysterectomy for heavy menstrual bleeding; this is likely an overestimate since it does not consider that some patients may prefer hysterectomy. For the lower limit, we only included women who received an unnecessary hysterectomy; this is likely an underestimate since it does not consider women who may be appropriate for hysterectomy but would prefer the LNG-IUS. However, by exploring different volume estimates, we calculated the upper and lower boundaries between which the true budget impact is expected to fall.

Our study estimated the budget impact of publicly funding the LNG-IUS for heavy menstrual bleeding and does not include the cost of funding the LNG-IUS for contraception. The budget impact of the LNG-IUS for all indications would be much higher than the results in our analysis.

Conclusions

Overall, our analysis suggests that if the LNG-IUS were publicly funded as an alternative to surgical treatment for heavy menstrual bleeding, it would result in cost savings in the first 5 years. The amount of cost savings is uncertain but could be up to $23 million per year compared with hysterectomy and up to $9 million per year compared with endometrial ablation.

ABBREVIATIONS

BMI	Body mass index
EQ-5D	EuroQol five-dimension, a quality of life assessment tool
EQ-VAS	EuroQol visual analogue scale, a quality assessment tool
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HRQOL-4	Four-item health-related quality of life assessment tool; also called the Healthy Days Measure
LNG-IUS	Levonorgestrel-releasing intrauterine system
MMAS	Menorrhagia multi-attribute scale
PBAC	Pictorial blood loss assessment chart
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
SF-36	Short Form 36, a 36-item quality of life assessment tool

GLOSSARY

Cost-effective	The technique or intervention has been determined to provide results sufficiently positive to justify the cost.
Incremental cost	The extra cost associated with using one test or treatment instead of another.
Parity	The number of pregnancies a person has had in which the fetus reached the point of viability, even if not carried to full term or successfully delivered.
Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). One QALY is expressed as a number between zero (no benefit) and one (perfect health). The QALY is commonly used as an outcome measure in cost–utility analyses.
Randomized controlled trial	A type of study in which subjects are assigned randomly into different groups, with one group receiving the intervention or treatment under study and the other group(s) receiving a different intervention or treatment (or a placebo or no treatment) in order to determine the effectiveness of one approach over another.
Sensitivity analysis	Every evaluation contains some degree of uncertainty. Study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact on study results. There are various types of sensitivity analyses. Examples include deterministic, probabilistic, and scenario.
Systematic review	A process to answer a research question by methodically identifying and assessing all available studies that evaluate the specified research question. The systematic review process is designed to be transparent and objective and is aimed at reducing bias in determining the answers to research questions.
Utility	The perceived benefit (value) placed on a treatment by a person or society.

APPENDICES

Appendix 1: Clinical Literature Search Strategies

Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, EMBASE <1980 to 2015 Week 33>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Menorrhagia/ (11505)
2 (menorrhag* or hypermenorrh*).tw. (8019)
3 (((abnormal* or heavy or excessive* or irregular* or dysfunction* or prolonged or frequent) adj2 (menstrua* or period* or uter* bleeding or uter* blood or vaginal bleeding or vaginal blood)) or AUB or DUB or HMB).tw. (55064)
4 or/1-3 (66531)
5 exp Intrauterine Devices, Medicated/ (17410)
6 (((intrauterine or intra-uterine) adj2 (device* or system*)) or IUD or IUDs or IUS or IUSs).tw. (24149)
7 Levonorgestrel/ (13820)
8 exp Progestins/ (205021)
9 exp Progesterone/ (140496)
10 (levonorgestrel* or LNG).tw. (9767)
11 mirena.tw. (1564)
12 or/5-11 (244698)
13 4 and 12 (5953)
14 Meta Analysis.pt. (59760)
15 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (211030)
16 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (439892)
17 (meta analy* or metaanaly* or health technolog* assess*).mp. (310716)
18 or/14-17 (626281)
19 13 and 18 (409)
20 limit 19 to english language [Limit not valid in CDSR,DARE; records were retained] (400)
21 20 use pmoz (105)
22 20 use cctr (7)
23 Menorrhagia/ (11505)
24 (menorrhag* or hypermenorrh*).tw. (8019)

25 (((abnormal* or heavy or excessive* or irregular* or dysfunction* or prolonged or frequent) adj2 (menstrua* or period* or uter* bleeding or uter* blood or vaginal bleeding or vaginal blood)) or AUB or DUB or HMB).tw. (55064)
26 or/1-3 (66531)
27 exp Intrauterine Contraceptive Device/ (24926)
28 (((intrauterine or intra-uterine) adj2 (device* or system*)) or IUD or IUDs or IUS or IUSs).tw. (24149)
29 Levonorgestrel/ (13820)
30 exp Gestagen/ (140678)
31 Progesterone/ (127671)
32 (levonorgestrel* or LNG).tw. (9767)
33 mirena.mp. (1719)
34 or/27-33 (226375)
35 26 and 34 (5583)
36 Meta Analysis.pt. (59760)
37 Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (195987)
38 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (439892)
39 (meta analy* or metaanaly* or health technolog* assess*).mp. (310716)
40 or/36-39 (625180)
41 35 and 40 (395)
42 limit 41 to english language [Limit not valid in CDSR,DARE; records were retained] (387)
43 42 use emez (211)
44 13 use coch (56)
45 13 use dare (17)
46 13 use clhta (7)
47 13 use cleed (17)
48 or/21-22,43-47 (420)

Appendix 2: Clinical Evidence Quality Assessment

Our first consideration was study design; we started with the assumption that randomized controlled trials are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[56] For more detailed information, please refer to the latest series of GRADE articles.[56]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	We are very confident that the true prognosis (probability of future events) lies close to that of the estimate
Moderate	We are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different
Low	Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate
Very Low	We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate

Table A1: GRADE Evidence Profile for Conclusions Related to the Comparison of LNG-IUS and Hysterectomy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Quality of life							
2 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Menstrual bleeding							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations[b]	Undetected	None	⊕⊕⊕ Moderate
Satisfaction							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.
[a]Lack of blinding. See Table A4 for full risk of bias assessment.
[b]Single small study but achieved 100% completion for full 2-year study period.

Table A2: GRADE Evidence Profile for Conclusions Related to the Comparison of LNG-IUS and Endometrial Ablation

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Quality of life							
5 (RCTs)	Serious limitations (–1)a	No serious limitations	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕ Low
Menstrual bleeding							
8 (RCTs)	Serious limitations (–1)[a]	Serious limitations (–1)[c]	No serious limitations	Serious limitations (–1)	Undetected	None	⊕ Very low
Satisfaction							
4 (RCTs)	Serious limitations (–1)[a]	Serious limitations (–1)[c]	No serious limitations	Serious limitations (–1) [b]	Undetected	None	⊕ Very low

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.
[a]Inadequate allocation concealment, lack of blinding in all, intention-to-treat analysis was not conducted, and loss to follow-up. See Table A5 for full risk of bias assessment.
[b]Very small sample sizes; loss to follow-up compromised power in most studies.
[c]Mixed findings between studies and within them at various follow-up points with regards to superior benefit or lack of significant difference.

Table A3: GRADE Evidence Profile for Conclusions Related to the Comparison of LNG-IUS and Usual Medical Therapy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Quality of life							
2 (RCTs)	Serious limitations (–1)[a]	Serious limitations (–1)[b]	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Menstrual bleeding							
4 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	Serious limitations (–1)[c]	Undetected	None	⊕⊕ Low
Satisfaction							
1 (RCT)	Serious limitations (–1)[a]	No Serious Limitations[d]	No serious limitations	Serious limitations (–1)[c]	Undetected	None	⊕⊕ Low

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; RCT, randomized controlled trial.
[a]Lack of blinding. See Table A6 for full risk of bias assessment.
[b]Results varied from favouring LNG-IUS to no difference depending on quality of life tool used and time point assessed.
[c]Small samples and loss to follow-up, posing issues with adequate power.
[d]Only 1 small study providing evidence.

Table A4: Risk of Bias Among Randomized Controlled Trials for the Comparison of LNG-IUS and Hysterectomy

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Sesti et al, 2012[77]	No limitations	Limitations[a]	No limitations	No limitations	No limitations
Hurskainen et al, 2001[79]	No limitations	Limitations[b]	No limitations	No limitations	No limitations

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Only outcome assessors were blinded to treatment allocation.
[b]No blinding was reported.

Table A5: Risk of Bias Among Randomized Controlled Trials for the Comparison of LNG-IUS and Endometrial Ablation

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Ghazizadeh et al, 2011[81]	No limitations	Limitations[a]	Limitations[b]	No limitations	No limitations
de Souza et al, 2010[82]	Limitations[c]	Limitations[a]	Limitations[b]	Limitations[d]	No limitations
Shaw et al, 2007[84]	Limitations[c]	Limitations[a]	Limitations[b,e]	No limitations	No limitations
Tam et al, 2006[85]	Limitations[c]	Limitations[a]	Limitations[b,f]	No limitations	No limitations
Busfield et al, 2006[86]	No limitations	Limitations[a]	Limitations[b]	No limitations	No limitations
Malak and Shawki, 2006[87]	No limitations	Limitations[a]	Limitations[b]	No limitations	No limitations
Barrington et al, 2003[88]	Limitations[c]	Limitations[a]	Limitations[b]	No limitations	No limitations
Kittelsen and Istre, 1998[90]	No limitations	Limitations[a]	Limitations[b,g]	No limitations	No limitations
Crosignani et al, 1997[92]	Limitations[a]	Limitations[a]	Limitations[b]	No limitations	No limitations

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]RCTs were not blinded due to the nature of interventions.
[b]Outcomes were analyzed only for those participants completing treatment, not as intention-to-treat.
[c]Allocation concealment not reported so unclear risk of bias.
[d]Satisfaction outcome not reported at 1 year but only at 5-year follow-up.
[e]Loss to follow-up was 34.8% overall and those lost were excluded from the analysis.
[f]Loss to follow-up was 25% overall.
[g]Loss to follow-up was 30.5% overall.

Table A6: Risk of Bias Among Randomized Controlled Trials for the Comparison of LNG-IUS and Medical Therapy

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Gupta et al, 2013[93]	No limitations	Limitations[a]	No limitations[b]	No limitations	No limitations
Shaaban et al, 2011[95]	No limitations	Limitations[a]	No limitations[c]	No limitations	No limitations
Kaunitz et al, 2010[97]	Limitations[d]	Limitations[a]	Limitations[c,e]	No limitations	No limitations
Reid and Virtanen-Kari, 2005[98]	Limitations[f]	Limitations[a]	No limitations[c]	No limitations	No limitations
Irvine et al, 1998[99]	No limitations	Limitations[a]	Limitations[c,d]	No limitations	No limitations

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]RCTs were not blinded due to the nature of interventions.
[b]Loss to follow-up was 25.8% at 5-year follow-up, 16.3% at 2-year follow-up; however, planned power of the study was 90% and year 5 post hoc power was calculated to be 87%.
[c]Loss to follow-up was less than 20% overall.
[d]Allocation concealment not reported.
[e]Primary analyses adhered to the intention-to-treat principle; however, secondary analyses were analyzed according to treatment received.
[f]Principal investigator personally recruited, consented, randomized, and followed up all participants, and conducted 75% of analyses with known allocation.

Appendix 3: Economic Literature Search Strategies

Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, EMBASE <1980 to 2015 Week 33>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 Menorrhagia/ (11506)
2 (menorrhag* or hypermenorrh*).tw. (8019)
3 (((abnormal* or heavy or excessive* or irregular* or dysfunction* or prolonged or frequent) adj2 (menstrua* or period* or uter* bleeding or uter* blood or vaginal bleeding or vaginal blood)) or AUB or DUB or HMB).tw. (55071)
4 or/1-3 (66539)
5 exp Intrauterine Devices, Medicated/ (17410)
6 (((intrauterine or intra-uterine) adj2 (device* or system*)) or IUD or IUDs or IUS or IUSs).tw. (24150)
7 Levonorgestrel/ (13820)
8 exp Progestins/ (205023)
9 exp Progesterone/ (140498)
10 (levonorgestrel* or LNG).tw. (9767)
11 mirena.tw. (1564)
12 or/5-11 (244701)
13 4 and 12 (5953)
14 economics/ (247515)
15 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (699564)
16 economics.fs. (370014)
17 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (639364)
18 exp "costs and cost analysis"/ (487137)
19 cost*.ti. (219849)
20 cost effective*.tw. (229772)
21 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (143701)
22 models, economic/ (127581)
23 markov chains/ or monte carlo method/ (116576)
24 (decision adj1 (tree* or analy* or model*)).tw. (31175)
25 (markov or markow or monte carlo).tw. (92890)
26 quality-adjusted life years/ (26199)
27 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (44922)
28 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (88425)

29 or/14-28 (2158916)
30 13 and 29 (498)
31 limit 30 to english language [Limit not valid in CDSR,DARE; records were retained] (471)
32 31 use pmoz,cctr,coch,dare,clhta (171)
33 Menorrhagia/ (11506)
34 (menorrhag* or hypermenorrh*).tw. (8019)
35 (((abnormal* or heavy or excessive* or irregular* or dysfunction* or prolonged or frequent) adj2 (menstrua* or period* or uter* bleeding or uter* blood or vaginal bleeding or vaginal blood)) or AUB or DUB or HMB).tw. (55071)
36 or/33-35 (66539)
37 exp Intrauterine Contraceptive Device/ (24926)
38 (((intrauterine or intra-uterine) adj2 (device* or system*)) or IUD or IUDs or IUS or IUSs).tw. (24150)
39 Levonorgestrel/ (13820)
40 exp Gestagen/ (140678)
41 Progesterone/ (127673)
42 (levonorgestrel* or LNG).tw. (9767)
43 mirena.mp. (1719)
44 or/37-43 (226378)
45 36 and 44 (5583)
46 Economics/ (247515)
47 Health Economics/ or exp Pharmacoeconomics/ (209294)
48 Economic Aspect/ or exp Economic Evaluation/ (376085)
49 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (639364)
50 exp "Cost"/ (487137)
51 cost*.ti. (219849)
52 cost effective*.tw. (229772)
53 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (143701)
54 Monte Carlo Method/ (47541)
55 (decision adj1 (tree* or analy* or model*)).tw. (31175)
56 (markov or markow or monte carlo).tw. (92890)
57 Quality-Adjusted Life Years/ (26199)
58 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (44922)
59 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (88425)
60 or/46-59 (1766428)
61 45 and 60 (457)
62 limit 61 to english language [Limit not valid in CDSR,DARE; records were retained] (434)
63 62 use emez (270)
64 13 use cleed (17)
65 or/32,63-64 (458)
66 remove duplicates from 65 (381)

Appendix 4: Modified Methodological Checklist for Economic Evaluations

Question topic:		
Study reference:		
Checklist completed by:		
APPLICABILITY (relevance to question under review)		
Item	**Yes/Partly/ No/Unclear/NA**	**Comments**
Is the study population appropriate to the question?		
Are the interventions appropriate to the question?		
Are all relevant interventions compared?		
What country was this study conducted in?		
Is the health care system in which the study was conducted sufficiently similar to Ontario with respect to this question/topic? Explain the ways in which they differ.		
Are estimates of relative treatment effect the same as those included in the clinical report?		
Are costs measured from a health care payer perspective?		
Are non-direct health effects on individuals excluded?		
Are both costs and health effects discounted at an annual rate of 5%?		
Do the estimates of resource use differ from that which would be expected in an Ontario context?		
Is the value of health expressed in terms of quality-adjusted life-years (QALYs)?		
Are changes in health-related quality of life (HRQOL) obtained directly from patients and/or carers?		
Was the valuation of changes in HRQOL (utilities) obtained from a representative sample of the general public?		
Overall judgment (directly applicable/partially applicable/not applicable): If a study is considered not applicable, there is no need to assess its quality.		

Appendix 5: Applicability of Studies in Economic Evidence Review

Table A7: Applicability of Studies Given Full-Text Review

Objective: To assess the cost-effectiveness of LNG-IUS					
Author, Year	**Is the study population similar to the question?**	**Are the interventions similar to the question?**	**Is the health care system in which the study was conducted sufficiently similar to the current Ontario context?**	**Was/were the perspective(s) clearly stated and what were they?**	**Are estimates of relative treatment effect from the best available source?**
Bhattacharya et al, 2011[63]	Yes	Yes (LNG-IUS vs. surgical treatment)	No (United Kingdom)	Yes (public health care payer in secondary care)	Yes
Heliovaara-Peippo et al, 2013[78]	Yes	Partly (LNG-IUS vs. hysterectomy)	No (Finland)	No (likely societal)	Yes
Calaf et al, 2015[120]	Yes	Yes (LNG-IUS vs. oral treatment)	No (Spain)	Yes (public health care payer)	Yes
You et al, 2006[116]	Yes	Yes	No (Hong Kong)	Yes (public health care payer)	Yes
Sanghera et al, 2014[121]	Yes	Yes (LNG-IUS vs. oral treatment)	No (United Kingdom)	Yes (public health care payer)	Yes
Lete et al, 2011[122]	Yes	Yes (LNG-IUS vs. oral treatment)	No (Spain)	Yes (public health care payer)	Yes
Ganz et al, 2013[115]	Yes	Yes	No (United States)	Yes (public health care payer)	Yes
Clegg et al, 2007[118]	Yes	Yes (LNG-IUS vs. surgical treatment)	No (United Kingdom)	Yes (public health care payer)	Yes
Brown et al, 2006[119]	Yes	Partly (LNG-IUS vs. thermal balloon endometrial ablation)	No (New Zealand)	No (likely societal)	Yes

Table A7 (continued)

Author, Year	Are all future costs and outcomes discounted? (If yes, at what rate?)	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgement (directly applicable/partially applicable/ not applicable)
Bhattacharya et al, 2011[63]	Yes (3.5%)	Yes	No	Partially applicable
Heliovaara-Peippo et al, 2013[78]	Yes (3% base case, 5% sensitivity)	Yes	No	Partially applicable
Calaf et al, 2015[120]	Yes (3%)	Yes	No	Partially applicable
You et al, 2006[116]	Yes (3%)	Yes	No	Partially applicable
Sanghera et al, 2014[121]	Yes (3.5%)	Yes	No	Partially applicable
Lete et al, 2011[122]	Yes (3%)	Yes	No	Partially applicable
Ganz et al, 2013[115]	Yes (3%)	Yes	No	Partially applicable
Clegg et al, 2007[118]	Yes (3.5%)	Yes	No	Partially applicable
Brown et al, 2006[119]	Yes (5%)	No	No	Partially applicable

Appendix 6: Full Economic Model Inputs

Table A8: Adverse Event Inputs Used in the Economic Model

Model Parameters	Probability Reported in Study (Time Frame)	Converted Monthly Rate	Monthly Probability	Duration of Risk in the Model	Reference
LNG-IUS					
Device reinsertion	0.04310 (1 year)	0.0036	0.0037	1 year	Hurskainen et al, 2001[79]
Gastrointestinal obstruction	0.1026 (10 years)	0.0009	0.0009	9 years	Heliovaara-Peippo et al, 2013[78]
Lower abdominal pain	0.1667 (5 years)	0.0015	0.0015	9 years	Malak and Shawki, 2006[87]
Pelvic pain	0.1 (5 years)	0.0009	0.0009	9 years	Malak and Shawki, 2006[87]
Pelvic inflammatory disease	0.0504 /0.0336 (10 years)	0.0004 /0.0003	0.0004 /0.0003	9 years	Heliovaara-Peippo et al, 2013[78]
Endometrial ablation					
Hematometra	0.033 (5 years)	0.0003	0.0003	9 years	Malak and Shawki, 2006[87]
Pelvic pain	0.1333 (5 years)	0.0012	0.0012	9 years	Malak and Shawki, 2006[87]
Hysterectomy					
Gastrointestinal obstruction	0.15179 (10 years)	0.00137	0.0014	10 years	Heliovaara-Peippo et al, 2013[78]
Lower abdominal pain	0.00893 (10 years)	0.00007	0.00007	10 years	Heliovaara-Peippo et al, 2013[78]
Secondary hemorrhage	0.01786 (10 years)	0.00015	0.00015	10 years	Heliovaara-Peippo et al, 2013[78]
Urinary retention	0.02678 (10 years)	0.00023	0.00023	10 years	Heliovaara-Peippo et al, 2013[78]
Surgical infection	0.3125 (1 year)	0.0031	0.0031	1 year	Hurskainen et al, 2001[79]

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A9: Adverse Event Inputs for Secondary Analysis Using Administrative Data

Model Parameters	Monthly Probability	Duration of Risk in the Model
Initial treatment LNG-IUS		
Device reinsertion	0.0020	1 year
Gastrointestinal obstruction	0.00002	9 years
Lower abdominal pain	0.0004	9 years
Pelvic pain	0.00003	9 years
Pelvic inflammatory disease	0.00007	9 years
Switch to endometrial ablation		
Hematometra	0.00003	9 years
Pelvic pain	0.000003	9 years
Switch to hysterectomy		
Gastrointestinal obstruction	0	9 years
Lower abdominal pain	0.00006	9 years
Secondary hemorrhage	0	9 years
Urinary retention	0	9 years
Surgical infection	0.0042	1 year
Initial treatment endometrial ablation		
Hematometra	0.00003	9 years
Pelvic pain	0.0005	9 years
Switch to another endometrial ablation		
Hematometra	0.000003	9 years
Pelvic pain	0.00002	9 years
Switch to hysterectomy		
Gastrointestinal obstruction	0.000004	9 years
Lower abdominal pain	0.00008	9 years
Secondary hemorrhage	0.0000006	9 years
Urinary retention	0.0000006	9 years
Surgical infection	0.0042	1 year
Initial treatment hysterectomy		
Gastrointestinal obstruction	0.00004	9 years
Lower abdominal pain	0.0008	9 years
Secondary hemorrhage	0	9 years
Urinary retention	0.00007	9 years
Surgical infection	0.0042	1 year

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A10: Treatment Switch Inputs Used in the Economic Model

Model Parameters	Probability Reported in Study (Time Frame)	Converted Rate	Monthly Probability	Reference
LNG-IUS to endometrial ablation				
First 6 months	0.0769	0.0133	0.0053	Heliovaara-Peippo et al, 2013[78]
7–12 months	0.1563	0.0283	0.0112	Heliovaara-Peippo et al, 2013[78]
2–5 years	0.3133	0.0078	0.0031	Heliovaara-Peippo et al, 2013[78]
6–10 years	0.1020	0.0018	0.0007	Heliovaara-Peippo et al, 2013[78]
LNG-IUS to hysterectomy				
First 6 months	0.0769	0.0133	0.0080	Heliovaara-Peippo et al,2013[78]
7–12 months	0.1563	0.0283	0.0168	Heliovaara-Peippo et al, 2013[78]
2–5 years	0.3133	0.0078	0.0047	Heliovaara-Peippo et al, 2013[78]
6–10 years	0.1020	0.0018	0.0011	Heliovaara-Peippo et al, 2013[78]
Endometrial ablation to hysterectomy				
1st year	0.1 (1 year)	0.0088	0.0088	Silva-Filho et al, 2013[83]
2nd year	0.0370 (1 year)	0.0031	0.0031	Silva-Filho et al, 2013[83]
3rd year	0.0769 (1 year)	0.0067	0.0066	Silva-Filho et al, 2013[83]
4th year	0	0	0	Silva-Filho et al, 2013[83]
5th year	0	0	0	Silva-Filho et al, 2013[83]
6th –13th years	0	0	0	Extrapolation

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A11: Distribution of Pregnancy Outcomes Used in the Economic Model

Model Parameters	Probability	Reference
Pregnancy post LNG-IUS		
Spontaneous abortion – complete	0.13	Yin, 2010,[129] assuming half of spontaneous abortions are complete
Spontaneous abortion – incomplete	0.13	Yin, 2010,[129] assuming half of spontaneous abortions are incomplete
Ectopic pregnancy	0.07	Yin, 2010[129]
Induced abortion	0.67	Assumption
Pregnancy post endometrial ablation		
Spontaneous abortion – complete	0.0025	Blumenthal et al, 2006,[112] assuming half of spontaneous abortions are complete
Spontaneous abortion – incomplete	0.0025	Blumenthal et al, 2006,[112] assuming half of spontaneous abortions are complete
Ectopic pregnancy	0.60	Blumenthal et al, 2006[112]
Induced abortion	0.39	Assumption

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A12: Other Clinical Outcome Inputs Used in the Economic Model

Model Parameters	Probability Reported in Study (Time Frame)	Converted Rate	Monthly Probability	Duration of Risk in the Model	Reference
Menorrhagia resolved; no further treatment	0.1538 (10 years)	0.0014	0.0014	10 years	Heliovaara-Peippo et al, 2013[78]
LNG-IUS risk for pregnancy	0.006 (1 year)	0.0005	0.0005	10 years	Mansour et al, 2010[127]
Endometrial ablation risk for pregnancy	0.007 (1 year)	0.0006	0.0006	10 years	Lo and Pickersgill, 2006[128]
Mortality (assuming base case initial age of 42)					
1 year	0.00094	0.00008	0.00008		Life table 2006[130]
2 years	0.00102	0.00009	0.00009		Life table 2006[130]
3 years	0.00111	0.00009	0.00009		Life table 2006[130]
4 years	0.00122	0.00010	0.00010		Life table 2006[130]
5 years	0.00133	0.00011	0.00011		Life table 2006[130]
6 years	0.00145	0.00012	0.00012		Life table 2006[130]
7 years	0.00158	0.00013	0.00013		Life table 2006[130]
8 years	0.00173	0.00014	0.00014		Life table 2006[130]
9 years	0.00188	0.00016	0.00016		Life table 2006[130]

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A13: Procedure Costs for Physician Services for LNG-IUS, Endometrial Ablation, and Hysterectomy

Variable	Fee Code	Unit Cost, $	Total Units/ Procedure	Total Cost, $	Reference
LNG-IUS					
Insertion of intrauterine contraceptive device	G378	25.50	NA	25.50	Ontario Schedule of Benefits for Physician Services[132]
When performed outside hospital	E542	11.15	NA	11.15	Ontario Schedule of Benefits for Physician Services[132]
Total				36.65	
Endometrial ablation					
Surgeon	S772	218.65	NA	218.65	Ontario Schedule of Benefits for Physician Services[132]
Anesthesiologist	S772	15.01	6	90.06	Ontario Schedule of Benefits for Physician Services[132]
Total				308.71	
Hysterectomy					
Surgeon	S757	463.00	NA	463.00	Ontario Schedule of Benefits for Physician Services[132]
Assistant surgeon	S757	12.04	6	72.24	Ontario Schedule of Benefits for Physician Services[132]
Anesthesiologist	S757	15.01	7	105.07	Ontario Schedule of Benefits for Physician Services[132]
Total				640.31	

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system; NA not applicable.

Table A14: Treatment-Related Adverse Event Costs for LNG-IUS, Endometrial Ablation, and Hysterectomy

Variable	Unit Cost, $ (Standard Deviation)	Reference
LNG-IUS–related adverse events		
Reinsertion		
Procedure	337.90	Ontario Drug Benefit Formulary[133]
Physician	36.65	Ontario Schedule of Benefits for Physician Services[132] (code G378 and E542)
Gastrointestinal obstruction (assuming 2-day mean length of stay according to administrative data)		
Hospital	4,156.00 (2,615)	Administrative data[a]
Admission assessment	100.36	Ontario Schedule of Benefits for Physician Services[132] (code C003)
General surgery consultation	90.30	Ontario Schedule of Benefits for Physician Services[132] (code A035)
Physician discharge assessment	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C124)
Lower abdominal pain (assuming most are outpatient visits according to administrative data)		
Hospital	492.00 (222)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Pelvic pain (assuming 2-day mean length of stay according to administrative data)		
Hospital	4,211.00 (1,063)	Administrative data[a]
Admission assessment	100.36	Ontario Schedule of Benefits for Physician Services[132] (code C003, E082)
Most responsible physician follow-up assessment – second day	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C122)
Physician discharge assessment	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C124)
Pelvic inflammatory disease (assuming most are outpatient visits according to administrative data)		
Hospital	503.00 (704)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Endometrial ablation–related adverse events		
Hematometra (assuming 3-day mean length of stay according to administrative data)		
Hospital	3,854.00 (3,859)	Administrative data[a]
Admission assessment	100.36	Ontario Schedule of Benefits for Physician Services[132] (code C003)
General surgery consultation	90.30	Ontario Schedule of Benefits for Physician Services[132] (code A035)
Most responsible physician follow-up assessment – second day	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C122)
Physician discharge assessment	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C124)

Variable	Unit Cost, $ (Standard Deviation)	Reference
Pelvic pain (assuming most are outpatient visits according to administrative data)		
Hospital	1,372.00 (1,818)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Hysterectomy-related adverse events		
Gastrointestinal obstruction (assuming 5-day mean length of stay according to administrative data)		
Hospital	3,823.00 (2,269)	Administrative data[a]
Admission assessment	100.36	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Most responsible physician follow-up assessment – second day	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C122)
Most responsible physician follow-up assessment – third day	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C123)
Physician follow-up assessment – subsequent visit	31.00	Ontario Schedule of Benefits for Physician Services[132] (code C002)
General surgery consultation	90.30	Ontario Schedule of Benefits for Physician Services[132] (code A035)
Physician discharge assessment	58.80	Ontario Schedule of Benefits for Physician Services[132] (code C124)
Lower abdominal pain (assuming most are outpatient visits according to administrative data)		
Hospital	390.00 (246)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Secondary hemorrhage (assuming 2-day mean length of stay according to administrative data)		
Hospital	1,878.00 (646)	Administrative data[a]
Admission assessment	100.36	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Physician discharge assessment	$58.80	Ontario Schedule of Benefits for Physician Services[132] (code C124)
Urinary retention		
Hospital	549.00 (683.82)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)
Surgical infection		
Hospital	758.90 (1,093.67)	Administrative data[a]
Physician assessment	77.20	Ontario Schedule of Benefits for Physician Services[132] (code C003)

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Data provided by Ontario IntelliHEALTH.

Appendix 7: Administrative Data Sources for the Economic Model Population and Treatment-Related Adverse Events

The total number of women receiving LNG-IUS for heavy menstrual bleeding in Ontario was calculated from the OHIP physician billing database, using procedure fee code G378.

Women receiving endometrial ablation or hysterectomy were identified from the Discharge Abstract Database and the National Ambulatory Care Reporting System database (Table A15).

Table A15: Administrative Data Codes Used to Identify Endometrial Ablation or Hysterectomy for Heavy Menstrual Bleeding

	Procedure Code	Diagnosis Code
Endometrial ablation for heavy menstrual bleeding	1.RM.59	N920
		N921
		N924
		N925
		N926
		N938
		N939
Hysterectomy for heavy menstrual bleeding	1.RM.87	N920
	1.RM.89	N921
		N924
		N925
		N926
		N938
		N939

To ensure that only women with idiopathic heavy menstrual bleeding were included, we used the diagnosis codes shown in Table A16 to exclude from the Discharge Abstract Database women with a diagnosis of malignant neoplasms, carcinoma, fibroids, endometriosis, prolapse, or polyps of the uterus or cervix.

Table A16: Administrative Data Codes Used to Exclude Non-idiopathic Heavy Menstrual Bleeding

	Diagnosis Code
Malignant neoplasms	All C codes
Carcinoma	D05.9-D07.3
Fibroids	D25
Endometriosis	N80
Prolapse	N81
Polyps of the uterus or cervix	N84.0 and N84.1

Treatment-related adverse events were identified among the LNG-IUS, endometrial ablation, and hysterectomy cohorts by finding inpatient hospitalizations in the Discharge Abstract Database where the most responsible diagnosis was related to the adverse events identified in the clinical review. The specific diagnosis codes are presented in Table A17.

Table A17: Diagnosis Codes Used to Identify Adverse Events Related to LNG-IUS, Endometrial Ablation, and Hysterectomy

	Diagnosis Code
Gastrointestinal obstruction	K56.6
Lower abdominal pain	R10.39
Pelvic pain	R10.2
Pelvic inflammatory disease	N73.8–N73.9
Hematometra	N85.7
Secondary hemorrhage	T81.0
Urinary retention	R33
Surgical infection	T81.4

Appendix 8: Budget Impact Analysis Inputs

The estimated number of women who could be expected to receive LNG-IUS regardless of public funding was calculated from administrative data. We used physician billing data for 2008 to 2012 to extract a cohort of individuals who received an IUD insertion procedure (fee code G378)[132] with a diagnosis code for menstrual dysfunction. Since the proportion of women with menstrual dysfunction who specifically have menorrhagia is unknown, we assumed this to be 25% based on epidemiological data.[136] Cohort projections were calculated using linear extrapolation in Microsoft Excel (Table A18).

Table A18: Projected Incident Volumes of LNG-IUS Without Public Funding

	Volumes from Administrative Data[a]					Projected Volumes				
	2008	2009	2010	2011	2012	Year 1	Year 2	Year 3	Year 4	Year 5
Women receiving LNG-IUS insertion procedure with diagnosis of menstrual dysfunction	1,735	2,083	2,499	3,168	3,443	3,938	4,423	4,880	5,292	5,787
Women receiving LNG-IUS for heavy menstrual bleeding (assuming 25% of menstrual dysfunction cohort)	433	520	625	792	861	984	1,106	1,220	1,323	1,447

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.
[a]Data provided by Ontario IntelliHEALTH.

The estimated number of women who could be expected to need a replacement procedure for the LNG-IUS because the device has reached the end of its life was calculated from the volumes of women receiving LNG-IUS for heavy menstrual bleeding 5 years earlier. We assumed that 70% women would remain on LNG-IUS after 5 years, as calculated in our primary economic model (Table A19).

Table A19: Projected Incident Volumes of LNG-IUS Reinsertions

	Volumes per Year				
	Year 1	Year 2	Year 3	Year 4	Year 5
Women receiving LNG-IUS insertion procedure for heavy menstrual bleeding, 2008–2012	433	520	625	792	861
Women remaining on LNG-IUS 5 years later and requiring a reinsertion	304	365	439	556	605

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

The estimated number of women who could be expected to receive a hysterectomy or endometrial ablation for heavy menstrual bleeding was calculated from administrative data. Cohort projections were calculated using linear extrapolation in Microsoft Excel. The results are presented in Tables A20 and Table A21. Detailed calculations for the different scenarios are shown in Table A22, and Tables A23 to A34 provide detailed results for each scenario in the budget impact analysis.

Table A20: Projected Incident Volumes of Hysterectomy for Heavy Menstrual Bleeding

	Volumes from Administrative Data[a]					Projected Volumes				
	2008	2009	2010	2011	2012	Year 1	Year 2	Year 3	Year 4	Year 5
Women receiving hysterectomy for heavy menstrual bleeding	6,161	5,989	5,835	5,596	5,391	5,215	5,021	4,828	4,635	4,441

[a]Data provided by Ontario IntelliHEALTH.

Table A21: Projected Incident Volumes of Endometrial Ablation for Heavy Menstrual Bleeding

	Volumes from Administrative Data[a]					Projected Volumes				
	2008	2009	2010	2011	2012	Year 1	Year 2	Year 3	Year 4	Year 5
Women receiving endometrial ablation for heavy menstrual bleeding	6,021	5,984	6,002	6,122	6,158	6,181	6,222	6,263	6,305	6,346

[a]Data provided by Ontario IntelliHEALTH.

Table A22: Detailed Calculations of Patient Volumes for Different Scenarios

Strategy	Example Calculation	Incidence, N				
		Year 1	Year 2	Year 3	Year 4	Year 5
Hysterectomy						
Scenario 1 (upper limit): Women who would have received hysterectomy if LNG-IUS were not publicly funded (includes all women receiving hysterectomy for heavy menstrual bleeding)	Projected volumes based on administrative data	5,215	5,021	4,828	4,635	4,441
Scenario 2: Women who would have received hysterectomy if LNG-IUS were not publicly funded (assuming 12% of women offered LNG-IUS would prefer hysterectomy)	4,763 x 0.88 = 4,191 (Scenario 1 volumes multiplied by 88%)	4,191	4,045	3,900	3,754	3,608
Scenario 3: Women who would have received hysterectomy if LNG-IUS were not publicly funded (assuming all with unsupportive pathology for hysterectomy [12%] did not have private health insurance coverage)	4,763 x 0.12 = 572 (Scenario 1 volumes multiplied by 12%)	572	552	532	512	492
Scenario 4 (lower limit): Women who would have received hysterectomy if LNG-IUS were not publicly funded (assuming 50% with unsupportive pathology for hysterectomy did not have private health insurance coverage)	4,763 x 0.12 x 0.5 = 286 (Scenario 1 volumes multiplied by 12% multiplied by 50%)	286	276	266	256	246
Endometrial Ablation						
Scenario 1 (upper limit): Women who would have received endometrial ablation if LNG-IUS were not publicly funded (includes all women receiving endometrial ablation)	Projected volumes based on administrative data	6,181	6,222	6,263	6,305	6,346
Scenario 2 (lower limit): Women who would have received endometrial ablation if LNG-IUS were not publicly funded (assuming 22% of women offered LNG-IUS would prefer endometrial ablation)	6,181 x 0.88 = 4,838 (Scenario 1 volumes multiplied by 88%)	4,821	4,853	4,885	4,918	4,950

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A23: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Hysterectomy, Scenario 1

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−23.1	2.0	1.1	1.8	1.7
Year 2 cohort		−22.1	2.0	1.1	1.8
Year 3 cohort			−21.2	1.9	1.0
Year 4 cohort				−20.2	1.8
Year 5 cohort					−19.3
Total	−23.1	−20.1	−18.1	−15.4	−13.0

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A24: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Hysterectomy, Scenario 2

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−18.4	1.6	0.9	1.5	1.3
Year 2 cohort		−17.7	1.6	0.8	1.4
Year 3 cohort			−17.0	1.5	0.8
Year 4 cohort				−16.3	1.5
Year 5 cohort					−15.6
Total	−18.5	−16.1	−14.5	−12.4	−10.5

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A25: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Hysterectomy, Scenario 3

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−2.1	0.2	0.1	0.2	0.2
Year 2 cohort		−2.0	0.2	0.1	0.2
Year 3 cohort			−1.8	0.2	0.1
Year 4 cohort				−1.7	0.2
Year 5 cohort					−1.5
Total	−2.1	−1.8	−1.5	−1.1	−0.8

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A26: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Hysterectomy, Scenario 4

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−0.8	0.1	0.06	0.1	0.09
Year 2 cohort		−0.7	0.1	0.06	0.1
Year 3 cohort			−0.6	0.1	0.06
Year 4 cohort				−0.5	0.1
Year 5 cohort					−0.4
Total	−0.8	−0.6	−0.5	−0.2	−0.06

Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A27: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Endometrial Ablation, Scenario 1

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−8.5	0.6	−0.2	1.6	2.3
Year 2 cohort		−8.5	0.6	−0.2	1.6
Year 3 cohort			−8.6	0.6	−0.2
Year 4 cohort				−8.6	0.7
Year 5 cohort					−8.6
Total	−8.5	−7.9	−8.1	−6.5	−4.2

Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A28: Detailed Results of Budget Impact Analysis, LNG-IUS vs. Endometrial Ablation, Scenario 2

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	−6.6	0.5	−0.2	1.2	1.8
Year 2 cohort		−6.6	0.5	−0.2	1.2
Year 3 cohort			−6.6	0.5	−0.2
Year 4 cohort				6.6	0.5
Year 5 cohort					−6.6
Total	−6.6	−6.1	−6.2	−5.0	−3.2

Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A29: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Hysterectomy, Scenario 1

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	2.2				1.2
Year 2 cohort		2.2			
Year 3 cohort			2.2		
Year 4 cohort				2.2	
Year 5 cohort					2.2
Total	2.2	2.2	2.2	2.2	3.4

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A30: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Hysterectomy, Scenario 2

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	1.9				1.0
Year 2 cohort		1.8			
Year 3 cohort			1.7		
Year 4 cohort				1.5	
Year 5 cohort					1.0
Total	1.9	1.8	1.7	1.5	2.0

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A31: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Hysterectomy, Scenario 3

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	0.6				0.1
Year 2 cohort		0.7			
Year 3 cohort			0.7		
Year 4 cohort				0.8	
Year 5 cohort					0.8
Total	0.6	0.7	0.7	0.8	0.9

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A32: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Hysterectomy, Scenario 4

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	0.5				0.07
Year 2 cohort		0.6			
Year 3 cohort			0.7		
Year 4 cohort				0.7	
Year 5 cohort					0.8
Total	0.5	$0.6	0.7	0.7	0.8

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A33: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Endometrial Ablation, Scenario 1

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	2.5				1.5
Year 2 cohort		2.1			
Year 3 cohort			2.2		
Year 4 cohort				2.2	
Year 5 cohort					2.3
Total	2.5	2.6	2.6	2.7	4.2

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

Table A34: Detailed Results, New Annual Cost of Funding LNG-IUS vs. Endometrial Ablation, Scenario 2

	$ million				
Year	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Year 1 cohort	2.1				1.1
Year 2 cohort		2.1			
Year 3 cohort			2.2		
Year 4 cohort				2.2	
Year 5 cohort					2.2
Total	2.1	2.1	2.2	2.2	3.4

Abbreviations: LNG-IUS, levonorgestrel-releasing intrauterine system.

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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About OHTAS

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