

What we've learned from 2 decades' experience with the LNG-IUS

➔ The latest data on long-term use, benefits, and risks of the levonorgestrel-releasing intrauterine system— to fine-tune and amplify its use in your practice

Q&A with Oskari Heikinheimo, MD, PhD

With the total fertility rate in the United States at just over two children for every woman, one thing seems obvious: The “average” woman needs several decades of effective contraception during her fertile life span.¹ The situation is even more compelling in Europe, where several countries are experiencing a *decline* in population. Clearly, women are choosing to have smaller families, or none at all, or are postponing childbearing longer than ever before.

In the past, many women opted for sterilization once childbearing was completed. Today, however, the sterilization rate is declining, in part because of the emerging use of long-acting, reversible contraception.² The levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena) is one of these long-acting contraceptives. It also offers benefits besides contraception: It reduces the severity of heavy menstrual bleeding, requires no daily or monthly attention,

and, when priced over its full 5-year lifetime, is economical. Because of its effect on heavy menstrual bleeding, for which it was FDA-approved in 2009, the LNG-IUS also is emerging as an alternative to endometrial ablation and hysterectomy.³⁻⁵

To elucidate the benefits and risks of the LNG-IUS and explore its ultra-long-term use, we contacted Oskari Heikinheimo, MD, PhD, an expert on the subject. Dr. Heikinheimo is adjunct professor of obstetrics and gynecology at Helsinki University Central Hospital in Helsinki, Finland, and an integral figure in early use of the LNG-IUS. In this interview, he discusses the LNG-IUS overall and offers insight from Scandinavia, which has a long history of LNG-IUS use.

Does the LNG-IUS provide effective contraception?

OBG MANAGEMENT: Let's begin by focusing on the primary indication for the LNG-IUS—as a contraceptive. The device was approved as a contraceptive in the United States in 2001. That means we have a decade of experience. What have we learned?

Dr. Heikinheimo: We have considerably more than 10 years of experience with the LNG-IUS, as it was first approved in Finland in 1990 and in Sweden in 1992. We know that the system is safe and highly effective, with a 5-year cumulative pregnancy rate of 0.1%–0.5%.

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Dr. Heikinheimo is Adjunct Professor of Obstetrics and Gynecology at Helsinki University Central Hospital in Helsinki, Finland.

Dr. Heikinheimo has designed educational events and been a paid lecturer for Bayer Schering Pharma AG, and he belongs to its international advisory board.

OBG MANAGEMENT: Where does that statistic originate?

Dr. Heikinheimo: The safety and efficacy of the LNG-IUS were first established in a Finnish as well as a large European multicenter trial of more than 2,000 women. The women were 18 to 38 years old at the time of enrollment, of proven fertility, and used the system for as long as 5 years, providing 110,000 woman-months of exposure.^{6,7} These results were confirmed in several later studies, most recently in a large post-marketing study of more than 17,000 women and 58,000 woman-years.⁸

OBG MANAGEMENT: Were you involved in development of the LNG-IUS?

Dr. Heikinheimo: No, development of the LNG-IUS began in the 1970s—at that time I was attending elementary school. However, I do have the privilege of knowing the masterminds behind the LNG-IUS, most importantly Professor Tapani Luukkainen.

OBG MANAGEMENT: What amount of levonorgestrel is released by the LNG-IUS?

Dr. Heikinheimo: The progestin is released at a rate of approximately 20 µg daily when the LNG-IUS is first inserted, although that rate gradually declines, decreasing by approximately 50% after 5 years of use, when the system should be replaced.⁹

A stable serum concentration of levonorgestrel of 150 to 200 pg/mL is found within a few weeks of insertion. After 12, 24, and 60 months, that level is 180 ± 66 pg/mL, 192 ± 140 pg/mL, and 159 ± 59 pg/mL, respectively.¹⁰

OBG MANAGEMENT: What is the mechanism of action of the LNG-IUS as a contraceptive?

Dr. Heikinheimo: It isn't completely clear. It is thought that the system thickens the cervical mucus, preventing passage of sperm into the uterus. It may also inhibit sperm capacitation or survival, or alter the endometrium, or all of these things. A recent study from Los Angeles showed convincingly that sperm penetration through samples of mid-cycle cervical mucus, collected from women using the LNG-IUS, is zero.¹¹ Thickening of cervical mucus plays an important role in the contraceptive efficacy of the LNG-IUS.

The main mechanism of action is prevention of fertilization.

OBG MANAGEMENT: Can a woman who has used the LNG-IUS readily conceive once it is removed?

Dr. Heikinheimo: Yes. Approximately 80% of women who wish to become pregnant do so within 12 months after the device is removed.⁹ That figure is similar in women who have not used the LNG-IUS.

What is the effect on bleeding patterns?

OBG MANAGEMENT: In the United States, in 2009, the LNG-IUS was approved for a second indication—to reduce heavy menstrual bleeding. What do we know about its efficacy in that regard?

Dr. Heikinheimo: A marked reduction in uterine bleeding is a hallmark of LNG-IUS use. The typical bleeding pattern during its use is oligomenorrhea or amenorrhea, with minor occasional bleeding.

OBG MANAGEMENT: What data do we have on the effect of the LNG-IUS on heavy menstrual bleeding?

Dr. Heikinheimo: This effect was explored in a randomized, open-label, active-control, parallel-group trial of 79 women who used the LNG-IUS and 81 women who were given medroxyprogesterone acetate (MPA) over six menstrual cycles.⁴ When the trial began, all of these women experienced menstrual blood loss of 80 mL or more. By trial's end, the LNG-IUS had caused a significantly greater reduction in menstrual blood loss than MPA had, and more women using the LNG-IUS had successful treatment. Success was defined as menstrual blood loss below 80 mL and a reduction in menstrual blood loss of 50% or more from baseline.

Women who had organic or systemic conditions that may cause heavy uterine bleeding were excluded, except for women who had small fibroids that did not exceed 5 mL in volume.

OBG MANAGEMENT: What is the mechanism of action for the LNG-IUS in the reduction of heavy menstrual bleeding?



The typical bleeding pattern during use of the LNG-IUS is oligomenorrhea or amenorrhea, with minor occasional bleeding

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Dr. Heikinheimo: The high local concentration of levonorgestrel causes marked suppression of the endometrium. This suppression is associated with several biochemical events, such as reduced expression of steroid receptors, altered expression of steroid-metabolizing enzymes, and inhibition of insulin-like growth factor activity.¹² These alterations render the endometrium insensitive to growth-promoting entities, such as estradiol. The result is thin endometrium and uterine bleeding that is either minor or nonexistent.

How does the LNG-IUS compare with endometrial ablation and hysterectomy?

OBG MANAGEMENT: How does the LNG-IUS compare with endometrial ablation and hysterectomy in the treatment of heavy menstrual bleeding?

Dr. Heikinheimo: The LNG-IUS is increasingly used in the treatment of heavy menstrual bleeding. In the Finnish VUOKKO study, women who were referred to a gynecologic outpatient clinic because of heavy menstrual bleeding were randomized to hysterectomy or to treatment with the LNG-IUS. At 5 years, approximately half of the women randomized to the LNG-IUS were still using the device.⁵ Also, quality of life and psychological well-being were similar between the groups. Although 40% of the women randomized to the LNG-IUS eventually underwent hysterectomy, the cost of the treatment was significantly lower in the LNG-IUS group than in the hysterectomy group (\$2,820 versus \$4,660).⁵

Endometrial resection is less commonly used to treat heavy menstrual bleeding in Scandinavia. However, in research studies, the efficacy of the LNG-IUS has been comparable to that of endometrial resection.³

Is the LNG-IUS completely benign?

OBG MANAGEMENT: What adverse reactions are associated with the LNG-IUS?

Dr. Heikinheimo: The main effect is an altered bleeding pattern. The device can cause spotting and irregular bleeding, oligomenorrhea, amenorrhea, or even heavy bleeding. Most of these changes occur during the first 3 to 6 months after insertion. Altered bleeding is seen in approximately 30% of women using the LNG-IUS. Proper patient information, provided before and at insertion, is the key element in guiding these women through these initial inconveniences.¹³ After the first months, the number of bleeding and spotting days commonly decreases, although bleeding may remain irregular. Amenorrhea develops in about 20% of users by the end of the first year of use.⁹

In most women who experience heavy menstrual bleeding, the number of bleeding and spotting days may increase during the first months of therapy but declines with continued use, as does the volume of blood loss each month.

A potential concern with irregular bleeding is that it may mask the signs and symptoms of endometrial polyps or malignancy. For this reason, abnormal uterine bleeding should be evaluated before insertion of the LNG-IUS. Similarly, any woman who develops unexplained bleeding during prolonged use of the device should also be evaluated.

Does the LNG-IUS raise the risk of breast cancer?

OBG MANAGEMENT: Because the LNG-IUS is hormonal contraception, some women may worry about their risk of breast cancer when using it. What do we know about that risk?

Dr. Heikinheimo: A large post-marketing study in Finland revealed that the risk of breast cancer among users of the LNG-IUS is similar to that among the general population.¹⁴ The results are clear: When used for contraception, the LNG-IUS is not associated with an increased risk of breast cancer.

Is patient satisfaction high?

OBG MANAGEMENT: Here's a critical question—are women happy with the LNG-IUS?

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The LNG-IUS is not associated with an increased risk of breast cancer

Dr. Heikinheimo: They certainly appear to be. Continuation rates in large post-marketing trials have been high, in the range of 65% at 5 years.¹³ I often tell my patients and students that, as a gynecologist, I see lots of happy women; many of them are using the LNG-IUS. That means that many women are likely to use more than one LNG-IUS during their fertile years.

OBG MANAGEMENT: You were coauthor of a study on consecutive use of the system, were you not? What did you find?

Dr. Heikinheimo: We enrolled 204 women 23 to 45 years old who had used an LNG-IUS for 4 years and 3 to 9 months and who opted to have a second system inserted at the time the first one was removed. Overall, we found the LNG-IUS to be well tolerated and highly acceptable among the women. In addition, the pattern of reduced menstrual bleeding that had developed during use of the first LNG-IUS continued after it was replaced; in some cases, it was even further reduced.¹⁵

Removal of the previous system and insertion of a new one at the same visit ensures that the initial irregular spotting period, which is typical of the first months after LNG-IUS insertion, does not recur in consecutive use. The rate of overall satisfaction with the system, assessed at the end of the first year after insertion of the second LNG-IUS, was high—93%. The women who were amenorrheic were most satisfied (100%).

The view from Scandinavia

OBG MANAGEMENT: As you noted earlier, the LNG-IUS has been widely used in Finland and Sweden for 20 years now. What else have we learned about the benefits and risks of the system from that long experience?

Dr. Heikinheimo: More and more women are asking for a bleeding-free contraceptive method! Also, the widespread use of the LNG-IUS has had an important impact on the entire specialty of obstetrics and gynecology. Because women are happy with the high contraceptive efficacy and reduced uterine bleeding, there has been a marked reduction in female sterilization. Similarly,

the number of hysterectomies performed for benign causes has decreased by 40% over the past 10 years. These figures also translate into effective use of the surgical ward.

OBG MANAGEMENT: What other features of the LNG-IUS are worth mentioning here?

Dr. Heikinheimo: Besides the conventional users of intrauterine contraception—married parous women—nulliparous women are increasingly using the LNG-IUS.¹⁶ Young, highly fertile women need effective contraception that does not need to be remembered on a daily basis.

There is also an increasing number of publications describing the use of the LNG-IUS in women with various pre-existing conditions, such as insulin-dependent diabetes, HIV infection, and inherited bleeding disorders, as well as in institutionalized women. It is reassuring to see that the benefits of the LNG-IUS—safety, high contraceptive efficacy, and markedly reduced uterine bleeding—are also apparent in these women. I'm convinced that there are still several additional subgroups of women who will benefit from use of the LNG-IUS. ☺

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In Scandinavia, widespread use of the LNG-IUS has had an important impact on the ObGyn specialty: a marked decrease in sterilization and hysterectomy rates over the past 10 years

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Comment & Controversy

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Thanks for the great article!

Thanks to Dr. Goldstein for continuing to write rather than retire (as I have urged him to do). Dr. Timor-Tritsch and he have produced a truly great article!

Regards from a resting ultrasonographer, now in Florida.

Donald Meek, MD
Bonita Springs, Fla

“THE DIFFICULT VAGINAL HYSTERECTOMY: 5 KEYS TO SUCCESS”

JOHN A. OCCHINO, MD, AND
JOHN B. GEBHART, MD, MS
(NOVEMBER 2010)

We need more minimally invasive hysterectomies!

I would agree with Dr. Occhino and Dr. Gebhart that we need to perform more minimally invasive hysterectomies. Over the past year, we have been able to perform laparoscopic and supracervical hysterectomies in more than 90% of cases, including

those involving a uterus as large as 16 to 18 weeks' gestational size.

We use both myomectomy and hysterectomy technique during laparoscopy, as well as in patients who have a partially obliterated cul-de-sac.

We use retroperitoneal uterine artery ligation in cases involving a large uterus, and this strategy has helped us keep blood loss to an average of 100 to 150 cc.

Chauncey Stokes, MD
Leesburg, Va

“HOW STEEP IS THE LEARNING CURVE FOR ROBOTIC-ASSISTED SACROCOLPOPEXY?”

CINDY L. AMUNDSEN, MD, AND
AMIE KAWASAKI, MD
(UPDATE ON PELVIC FLOOR DYSFUNCTION; OCTOBER 2010)

Easier surgeries mean a steep learning curve

The slope of the learning curve is frequently misunderstood. A procedure that is difficult requires many cases

to achieve competency. As such, the learning curve would be flat, not steep. In contrast, a procedure that can be mastered in a relatively few number of cases would be represented by a steep learning curve. Unfortunately, innumerable scientific papers equate difficult procedures with steep learning curves when it is exactly the contrary. Fortunately, Akl and coworkers got it right in their featured paper on robotic-assisted sacrocolpopexy.

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Please send it to us for a future installment of Comment & Controversy

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