

What's the gist of a new FDA label for the LNG-IUS?

➡ Important changes for practice affect insertion and use of the Mirena device, selection of candidates, contraindications, and adverse effects

IN THIS ARTICLE

New label sets out 12 contraindications
page 39

No evidence of increased risk of breast cancer
page 39

How to time LNG-IUS insertion during a patient's cycle
page 40

Since the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena, Bayer Health Care Pharmaceuticals) (FIGURE 1) was introduced in the United States in 2001, more than 2 million devices have been used by women here. This use has contributed to a cumulative experience of 14 million women (36 million woman-years of experience) in 120 countries over the last 18 years.

Recent Food and Drug Administration (FDA)-approved labeling changes for the LNG-IUS¹ expand the pool of women who are candidates for this convenient, reversible method of contraception. This article summarizes those labeling changes and answers questions that are often asked by clinicians who, more and more, insert the LNG-IUS for their patients.

What changes have been made to labeling?

Patient profile. The so-called recommended patient profile has been streamlined. The label now indicates only that the LNG-IUS is recommended for women who have given birth to at least one child. A more detailed description of women who were included in the phase-II US clinical trial is included in that section of the labeling. Clinicians should recognize that neither nulliparity nor nulligravida is listed in labeling as a contraindication to the LNG-IUS.

Depth of cavity. Another important change in the new labeling is that the LNG-IUS can be used in women whose uterine cavity sounds to a depth of 6 to 10 cm (no longer only 6 to 9 cm). This will permit more multiparous wom-

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Dr. Nelson has received research grants from, and participated in a speaker's bureau and an advisory council for, Bayer Health Care Pharmaceuticals for the LNG-IUS (Mirena) and derivative products. Dr. Arias has participated in a speaker's bureau and an advisory board for Bayer Health Care Pharmaceuticals for the LNG-IUS (Mirena).

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en, who may have a larger cavity, to use the LNG-IUS.

Pregnancy risk and consequences. The risk of pregnancy is rare when the LNG-IUS is used; pregnancy with the device in situ does not appear to be associated with an increased risk of birth defects. As of September 2006, there had been only 390 live births among an estimated cumulative 9.9 million LNG-IUS users worldwide. Of those births, congenital anomalies have been infrequent; no clear trend was seen toward an increased risk of any specific anomaly after exposure to the LNG-IUS.

Adverse events. As worldwide experience with the LNG-IUS has expanded since the last labeling, the number of reported cases of relatively rare adverse events has also been updated:

- Only nine cases of infection with group A *Streptococcus* have been reported in 9.9 million users, constituting a risk of approximately one infection for every 1 million users

- Based on postmarketing experience, new wording has been added about the possibility of 1) device breakage (before insertion) and 2) angioedema—a rare allergic reaction that is not specific to levonorgestrel (or the IUS)

- Wording has been added to the labeling that provides reassurance, based on observational studies, that there is no evidence of an increase in the risk of breast cancer risk with use of the LNG-IUS

- Similarly, the new labeling declares that, in general, no adverse effects have been found with use of the LNG-IUS on breastfeeding performance in regard to the health, growth, or development of an infant—even though isolated cases of a decrease in milk production have been reported.

Contraindications. The roster of contraindications (**TABLE**) has been significantly modified to reflect scientific evidence. Removed from that list are 1) a history of ectopic pregnancy and 2) risk factors for ectopic pregnancy. 📌

Reference

1. Mirena (levonorgestrel-releasing intrauterine system) [package insert]. Wayne, NJ: Bayer Health Care Pharmaceuticals; 2008.

FIGURE 1 LNG-IUS, arms open



The LNG-IUS device is readily visible on radiographs. Visualization by ultrasonography is more challenging.

SOURCE: BAYER HEALTH CARE PHARMACEUTICALS. USED WITH PERMISSION.

TABLE A new label lists 12 contraindications to the LNG-IUS

The LNG-IUS is contraindicated in the presence of one or more of the following:

Pregnancy or suspicion of pregnancy

Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity

Acute pelvic inflammatory disease or a history of pelvic inflammatory disease, unless there has been a subsequent intrauterine pregnancy

Postpartum endometritis or infected abortion in the past 3 months

Known or suspected uterine or cervical neoplasia or unresolved, abnormal Pap smear

Genital bleeding of unknown cause

Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infection, until infection is controlled

Acute liver disease or liver tumor (benign or malignant)

Conditions associated with an increased susceptibility to pelvic infection

Previously inserted intrauterine device that has not been removed

Hypersensitivity to any device component

Known or suspected carcinoma of the breast

FAST TRACK

The new label downplays concerns over group A strep infection and the risk of pregnancy while using the LNG-IUS

CONTINUED ON PAGE 40

Clinicians' FAQs about the LNG-IUS

When should I place the LNG-IUS?

Labeling recommends that, in a cycling woman, the LNG-IUS be placed sometime during the first 7 days of menses. A woman who has it placed at any other time in the cycle needs to be screened for pregnancy and needs to use back-up contraception for 7 days after the LNG-IUS is placed.

How should I place the device?

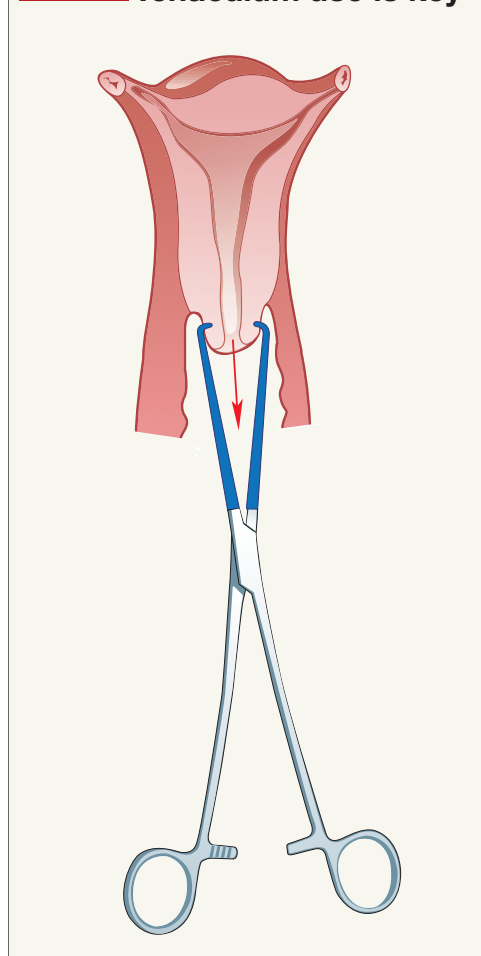
Complete instructions on insertion are provided in the package insert for the LNG-IUS. A few points about placement highlighted in the new labeling should be noted:

- The need to use a tenaculum to stabilize the cervix and to straighten the uterine axis has been reinforced in the new labeling (FIGURE 2)
- Careful uterine sounding (FIGURE 3) is needed to evaluate the uterine cavity to rule out any significant distortion of the cavity and to ensure appropriate uterine size before the LNG-IUS package is opened
- Uterine perforation is rare with the LNG-IUS, but to achieve that low risk you must wait at least 10 seconds for the arms of the device to open within the uterine cavity before it is advanced to the fundus
- The procedure-related expulsion rate can be reduced if the clinician moves the slider to the end of the handle (Position 3) carefully and waits for the tail strings to be released from the cleft (FIGURE 4) before trying to withdraw the insertion device.

What should I do if the LNG-IUS isn't at the fundus?

Studies have shown there can be significant migration of the LNG-IUS within the uterine cavity. Fundal placement insures that the tail strings will be long enough to remove the device regardless of where it settles. **A device that settles within the lower uterine segment is still effective.** Removal of the device is necessary only if 1) a portion of it protrudes from the cervix or 2) the woman has excessive cramping with a low-lying device.

FIGURE 2 Tenaculum use is key



How can I visualize an LNG-IUS?

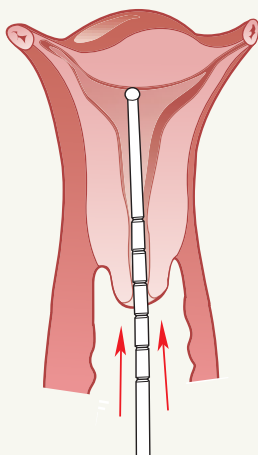
The LNG-IUS is visible on a radiograph. It is more challenging to image the device by ultrasonography; visualization of the shadowing beneath the device can help localize the unit. It is important to know that the tail strings are more echogenic than the device. Failure to recognize this allows the false impression that the IUD is lower than it actually is.

A woman can safely have a magnetic resonance imaging study without disrupting the position of the LNG-IUS device. It will not set off alarms in security systems—such as those used at an airport.

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Optimally, a cycling woman should have the LNG-IUS placed during the first 7 days of menses

FIGURE 3 Sound the uterus



I place only a few LNG-IUS devices each year. What should I do to remain competent and confident at performing this procedure?

Many teaching aids are available to refresh your skills. Options include instructional CD-ROMs and manuals and hands-on

practice with a representative of the manufacturer of the device. As noted, the LNG-IUS package insert offers step-by-step instructions on the procedure for placing the device.

What about concerns over cost that some patients express to me?

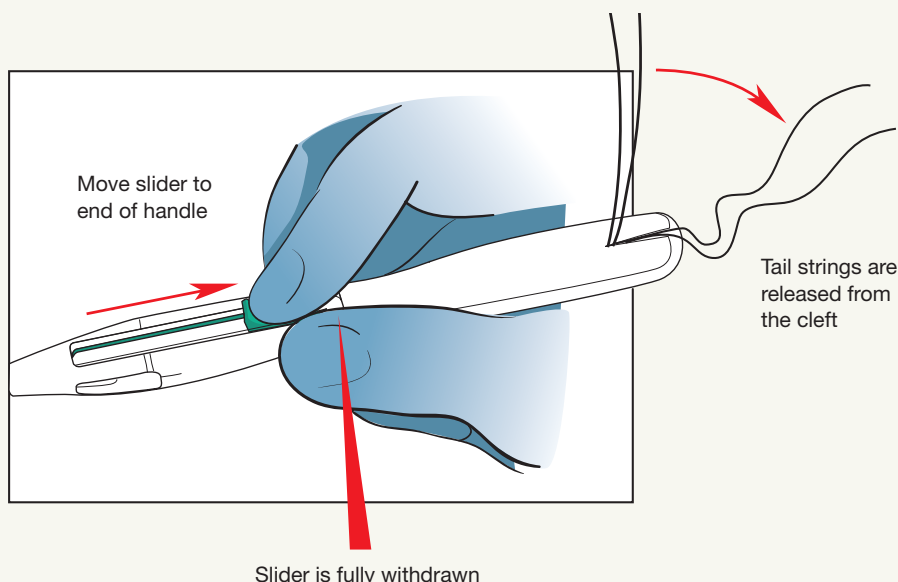
Women can charge the cost of the device to a credit card if their health insurance does not cover it, or its insertion. Payment plans are also available from the manufacturer.

If you attempt to assist your patients by finding less expensive LNG-IUS units (that is, from a source other than the manufacturer), be aware that the device must be stored under controlled conditions in transit, similar to the way other delicate devices are (e.g., NuvaRing, Implanon). LNG-IUS devices that are shipped under less-than-optimal controlled conditions may not maintain their stability or provide the appropriate rate of release of the contraceptive hormone.

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TRACK**

An LNG-IUS device that settles in the lower uterine segment still maintains its effectiveness

FIGURE 4 Release tail strings before withdrawing insertion device



FIGURES 2-4: ROB FLEWELL FOR OBG MANAGEMENT