Learning Objectives

1. Identify four contraceptive methods approved by the FDA in the U.S. since 1999
2. State the five-year cumulative failure rate with levonorgestrel intrauterine contraception (LNG IUS)
3. Describe the bleeding patterns with LNG IUS during the first year of use
4. Name two non-contraceptive benefits of LNG IUS

Why the Need for New Contraceptives

- Endemic rate of unintended pregnancies
- 43% of all U.S. women will have had an induced abortion by age 45
- 20% of women selecting sterilization at age 30 years or younger later express regret

If current rates were to continue, the U.S. would have the highest abortion rate in the developed world. These are by definition unintended pregnancies that could have been prevented with effective contraception. Many of the women who opt for sterilization at a young age do so because they don’t know that equally effective reversible options exist.

Sources
Outline

• Review these new methods
  – Description
  – Advantages/disadvantages
  – Effectiveness
• Emphasis on the LNG IUS

New Methods

Single-rod Implant
LNG IUS
Monthly Injectable
Vaginal Ring
Patch

Reversible Methods of Contraception

• Cervical cap, diaphragm, sponge
• Male and female condom
• DMPA
• Implants
• Intrauterine methods
• Combined and progestin-only OCs
• Spermicides

Future Methods

• Extended regimen oral contraception
• Extended regimen of other hormonal contraceptive delivery systems
• Microbicides
• Male hormonal contraception
• New barrier methods
• Standard Days® natural family planning method

Usage of Different Contraceptive Methods by Age Groups

Source
IUDs are used far less often than sterilization – despite the fact that this method is effective, convenient, allows a rapid return to fertility, and is not adherence-dependent. The legacy of the Dalkon Shield and persistent myths about IUDs have contributed to lack of use, along with patient concerns about safety, mechanism of action, and comfort. Among all contraceptive users in the U.S., IUDs are used far less often than sterilization. The opposite is true in other countries.

Of course, this chart does not include experience with LNG IUS from early clinical trials in the U.S.

Sources


Medroxyprogesterone estradiol cypionate (MPA E₂C) is the first monthly combination contraceptive to be licensed for routine use in the U.S. It is administered intramuscularly and contains 5 mg of estradiol cypionate and 25 mg of medroxyprogesterone acetate.

In dose-ranging studies, the 5 mg/25 mg combination was found to provide the best balance of efficacy and safety. Higher doses of medroxyprogesterone, although no more effective in suppressing ovulation, produced significantly higher rates of amenorrhea. Lower doses of the progesterone produced inadequate ovulation suppression. Higher doses of estrogen were associated with menstrual irregularities.

The greatest advantage of monthly injectables is their high efficacy.
### Monthly Injectable: Efficacy

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>785</td>
</tr>
<tr>
<td>Woman-months of use</td>
<td>8,920</td>
</tr>
<tr>
<td>First-year cumulative pregnancy rate</td>
<td>0.2%</td>
</tr>
</tbody>
</table>


### Subdermal Implant
- Single-rod system with disposable inserter
- Releases etonogestrel (3-ketodesogestrel) for three years
- As of July 2002 not approved by the FDA

The subdermal implant is a new contraceptive implant system consisting of a non-biodegradable, single rod. The product is supplied in a pre-loaded, sterile and disposable applicator which facilitates insertion.

The active component in a single-rod implant is etonogestrel; it does not contain an estrogen.

The core of the implant contains 68 mg of crystalline etonogestrel, dispersed in a matrix of ethylenevinylacetate (EVA) copolymer surrounded by a 0.06 EVA membrane.

### Implant: Characteristics
- High efficacy
- Long-term reversible method
- Hormonal side effects
- Requires insertion/removal
- Irregular bleeding
- Can be felt under skin

### Implant: Efficacy

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>200</td>
</tr>
<tr>
<td>Woman-years of use</td>
<td>645</td>
</tr>
<tr>
<td>2-year cumulative pregnancy rate</td>
<td>0%</td>
</tr>
</tbody>
</table>


### Vaginal Ring
- Steroid release
  - Progestin: Etonogestrel: 120 mcg/day (~1500 pg/ml)
  - Estrogen: Ethinyl estradiol: 15 mcg/day (~20 pg/ml)
- Worn for three weeks out of four
- Approved by the FDA in October 2001

The vaginal ring is a low-dose sustained release contraceptive system.

Daily doses are less than those of OCPs.

The peak serum concentrations reached are much less than with OCPs (less than a fifth of OCPs)

One size of the ring fits everyone.
**Vaginal Ring: Characteristics**

- Self administered
- Insertion every four weeks
- Foreign body in vagina
- Expulsions
- Limited published data on efficacy

**Vaginal Ring: Efficacy**

<table>
<thead>
<tr>
<th>Number of women</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman-cycles of use</td>
<td>16 cycles</td>
</tr>
<tr>
<td>Cumulative pregnancy rate</td>
<td>Limited published data</td>
</tr>
</tbody>
</table>

Source

**Contraceptive Patch**

- Steroid release
  - Progestin: norelgestromin 150 mcg/day
  - Estrogen: ethinyl estradiol 20 mcg/day
- Worn for three weeks out of four
- Approved by the FDA in November 2001

The patch provides daily steroid doses equivalent to the lowest dose OCPs. Maximum serum concentrations are lower with the patch than with OCPs because the patch is a sustained release system. The size of the patch determines daily dose and maximum concentrations.

Source

**Contraceptive Patch: Characteristics**

- Self administered
- Once-a-week administration
- Hormonal side effects
- Efficacy similar to combined oral contraceptives

Source
Audet et al. JAMA 2001;285:2347

**Patch: Efficacy**

<table>
<thead>
<tr>
<th>Number of women</th>
<th>1,417</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman-cycles of use</td>
<td>2,440</td>
</tr>
<tr>
<td>Cumulative pregnancy rate</td>
<td>1%</td>
</tr>
</tbody>
</table>

Source
The product is as wide (32mm) as it is long with its arms fully extended. Small T-shaped frame with a LNG-containing cylinder. Potent progestin found in many combination oral contraceptive, progestin-only pills, and implants. The LNG system releases LNG from the cylinder at 20 mcg per day into the uterine cavity for at least 5 years. Highly effective contraceptive protection. Published studies provide data on 12,000 women years of use. Two million women have used this method world-wide to date.

The picture on the slide is just a schematic, so it is not anatomically proportional. The mechanism of action of the levonorgestrel intrauterine system is similar to that of LNG implants or LNG-containing mini-pills. As with other methods, thickening of the cervical mucus (1) and inhibition of sperm motility and function are the primary role (2). The LNG intrauterine system does not usually inhibit ovulation (3), but the pregnancy rate and the ectopic rate are extremely low, suggesting that a primary endometrial effect as the mechanism of action is unlikely. The endometrial atrophy which is a consequence of the high endometrial levels of LNG leads to the substantial decrease in menstrual flow and absence of bleeding in some women noted in users of this form of intrauterine contraception. A weak foreign-body effect is also noted.

It is important to some patients that the LNG IUS mechanisms of action are all pre-conception. They prevent fertilization rather than disrupt implantation (a common misconception).

**Sources**


According to Luukkanen et al., the 12-month net pregnancy rate with the LNG IUS is 0.1 per hundred women.

**Sources**


Because the LNG IUS failure rate is comparable to that of sterilization, it could be viewed in this context as reversible sterilization, not just reversible contraception.

Even though this schematic depicts a difference, there is no significant statistical difference between the Nova T and LNG IUS.

These data are from the largest study. Other studies have even lower failure rates.

**Sources**


The return to fertility with the LNG IUS is rapid, essentially equal to that of the copper IUD and much more rapid than that of methods such as contraceptive implants.

**Sources**


Vessey MP, Lawless M, McPherson K, Yeates D. Fertility

The graph on the slide is a schematic that contrasts the plasma concentrations of “bolus” administration of oral mini-pills and combined OCs with the sustained release of LNG that occurs in the IUS and the LNG implant. At this level of plasma concentration, ovarian hormonal function is maintained. About 85% of cycles are ovulatory at the end of one year, and estrogen levels are normal. As noted earlier, although plasma concentrations are low, endometrial concentrations are high. The effects of the hormone are thus targeted to where they are needed, not spread systemically.

With the low-dose LNG IUS, LNG is detected in the serum 15 minutes after insertion. After an initial higher concentration, LNG reaches a steady state in several weeks. LNG IUS has a lower plasma concentration than implants. For short periods, combined OCs produce serum concentrations 50 times those of the low-dose products.

Sources
Kuhnz W, al-Yacoub G, Fuhrmeister A. Pharmacokinetics of levonorgestrel and ethynylestradiol in 9 women who received a low-dose oral contraceptive over a treatment period of 3 months and, after a wash-out phase, a single oral administration of the same contraceptive formulation. Contraception 1992 Nov;46(5):455.

Frequency of follicular cysts is no reason for removal of the IUS. Follow-up by ultrasound is recommended until the cysts disappearance. Although persistent follicles are not a cause for practitioner concern, they may be a concern for patients. Some can reach 3 cm in size, and counseling may need to explain that they are not dangerous and ultimately will go away.

Sources

LNG is concentrated locally in the endometrium, targeting the effects where they are desired and minimizing systemic side effects. Suppression is complete in three months. Returns to normal stage one month after removal.

Sources


Source


The effects of LNG IUS on menstrual bleeding are comparable to climbing a mountain. The spotting can be rough going for the first three months, but once the patient gets past that time, the bleeding patterns are very acceptable.

Source


Note the dramatic reduction in bleeding days that occurs with LNG IUS over time vis-à-vis the copper IUD. This is a substantial benefit for many women.

Source


Mechanism on bleeding

Anti-proliferative action decreases menstrual blood loss
Absence of bleeding is due to local effect
Pituitary and ovarian function are normal

Sources


Both the alternative to hysterectomy and treatment of menorrhagia statements are based on data from the cited “before-after” case studies.

**Sources**

Both statements based on the cited randomized controlled clinical trials.

**Source**

The US Preventive Services Task Force analyzed the body of medical research relating to various possible benefits of the LNG IUS to determine the level of scientific support for these assertions. They concluded the research provides fair to good supporting evidence about the benefits listed on this slide and the next slide. Only ratings of B or higher are shown in this table. A = good evidence to support the finding
B = Fair evidence to support the finding

**Source**
US Preventive Services Task Force Ratings (cont)

LNG IUS Finding                      Strength of conclusion
Prevents anemia                        A
Can be used as a vehicle for hormone replacement therapy (HRT) A
Mitigates tamoxifen-induced endometrial effects B

Source

Cumulative Termination Rates Per 100 women

Multinational trial: Egypt, Singapore, United States, Dominican Republic, Brazil, and Chile
1,121 women randomly assigned to CuT380A, 1,124 to LNG IUS
Five-year follow-up
Insertion training may have varied from site to site (expulsion rates varied from site to site)
No predetermined criteria for pelvic inflammatory disease (PID)
The removal rates for PID after five years were low, and there were no differences in rates of discontinuation between the two intrauterine contraceptives

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Source

European study centers: Finland, Sweden, Denmark, Hungary, and Norway
937 women received Nova T (Copper IUD); 1,821 received LNG IUS
Highly trained and supervised study locations
Prospective uniform criteria for diagnosis and treatment of side effects and problems were established.
Definition of PID determined at the outset—in the event of a problem, patients were seen immediately by the investigators for evaluation.
The LNG IUS may lower the risk of pelvic inflammatory disease compared to other IUDs. There is the suggestion that the effect of levonorgestrel on cervical mucus may make the introduction of pathogens into the upper genital tract less likely. The cumulative...
removal rate for PID at 36 months was .5/100 women versus 2/100 women, a significant difference. At 60 months, the cumulative removal rates for PID were .8/100 women for the LNG IUS and 2.2/100 women for the Nova T.

Source

Note that there was no increase in PID seen in relation to the insertion. This may be due to protocol and training criteria. These include the requirement that cervicitis be excluded before insertion and aseptic technique was used at insertion.

Source

It is also important to evaluate the patients for missing strings, which may be a sign of expulsion or dislocation.

Pregnancy is a contraindication whether it is known or suspected.
The uterine abnormality may be a distorted uterine cavity, either congenital or acquired. Infected abortion is a contraindication only if it occurred within the last three months.
Any bleeding of unknown etiology is included.
LNG IUS: Potential Complications

- Expulsions
  - Most occur during the first six months after insertion
  - The five-year cumulative expulsion rate is 4.9 per 100 women
- Perforations
  - Occur at the time of insertion
  - Rare events, fewer than one per thousand

Expulsion rate higher immediate post-abortion than interval insertion
No data on immediate post-partum insertion
Recommend insertion six weeks post-partum

Source

LNG IUS: The Inserter

The principal difference in insertion between the LNG IUS and other is the IUS inserted through the cervix with T arms folded upward, and copper devices are inserted with the T arms folded down. The two types of intrauterine contraception have very different insertion techniques and devices. Well-trained providers will have lower expulsion rates and fewer complications.

LNG IUS: Insertion

- Different insertion technique than other intrauterine contraception
  - New, one-handed insertion
  - Requires hands-on training
- Efficacy and user continuation dependent on skillful insertion

LNG IUS: Counseling

- Efficacy
- Return to fertility
- Side effects
- Changes in bleeding patterns
- Non-contraceptive health benefits
- Safety
- Insertion and follow-up

Counseling for the LNG IUS should include discussion about non-contraceptive health benefits such as reduction in bleeding, prevention of anemia, benefits of hormone therapy, mitigation of tamoxifen-induced endometrial affects. Reduction in bleeding is more than a “side effect” of this product. It may be considered a health benefit to many women and it is useful to present it to the patient in this context.

LNG IUS Counseling: Efficacy

- High efficacy
  - In clinical studies failure rate about that of female and male sterilization
- Continuous contraception for up to five years
LNG IUS Counseling: Side Effects

- Possible hormonal side effects
  - Mood changes
  - Acne
  - Headache
  - Breast tenderness
  - Nausea
- No reported weight gain

Possible side effects are more common in the initial months. They occur less often over time. Breast tenderness and nausea are quite uncommon, and patients should understand this.

Source

Mean Weight Change After Five Years

<table>
<thead>
<tr>
<th>Weight gain in kg</th>
<th>Nova T</th>
<th>LNG IUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
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<td>2</td>
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<tr>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Absence of bleeding may be considered a benefit by many women.

Source

LNG IUS Counseling: Changes in Bleeding

- Bleeding characteristics:
  - 1 – 4 mo frequent spotting
  - 1 – 6 mo reduced duration and amount of bleeding
  - Reduction in menstrual blood loss
  - After 12 mo, about 20 % have no bleeding

Patients should understand that no individual can be guaranteed a 90% reduction in blood loss; that is a group figure. However, marked reduction is likely for all women. Differentiate between bleeding and spotting. Many patients may be confused and perceive spotting as bleeding. Understanding what spotting is and that it is a short-term problem can help motivate continuation of use.

Source

LNG IUS Counseling: Absence of Bleeding

- Local effect
  - No proliferation of endometrium
- This is expected. It is not a sign of:
  - Pregnancy
  - Ovarian or pituitary dysfunction
  - Menopause
- Rapid return to menstruation after removal

Note that a lack of bleeding is an expected effect, neither unusual nor harmful.

Source

LNG IUS Counseling: Health Benefits

- Reduction of
  - Duration and amount of bleeding
  - Ectopic pregnancies
  - Menstrual pain
- Increase of
  - Hemoglobin
  - Iron storage

Note that a lack of bleeding is an expected effect, neither unusual nor harmful.
LNG IUS Counseling: Safety

- > Ten years experience in Europe
- > Two million users worldwide
- Few serious side effects
- Highly effective
- Does not prevent acquisition of STDs
  - Condoms advised for women at risk

LNG IUS Counseling: Insertion

- Steps in the insertion process
  - Pelvic and speculum exam
  - Sensations produced by tenaculum
  - Paracervical anesthesia, if needed
  - Sensations of IUS as it is inserted
  - Measures you will take for her comfort

Briefly describe the steps during the insertion process, including sensations she might experience. The clinician can provide an overview of these before the insertion as well as keep her informed of the process along the way. Letting the patient know she has permission to ask the clinician to slow down or stop may give her a degree of comfort for having some control during the insertion procedure. If there are other comfort measures that the clinician uses—such as offering paracervical anesthesia—describe these to the patient as well.

LNG IUS Counseling: Post-Insertion

- Schedule a follow-up visit at 1 – 3 months post-insertion
  - Check for partial or complete expulsion
  - Address any questions or concerns

A follow-up visit can be scheduled from one to three months to check the placement of the device. Most importantly to determine if she has questions or concerns about her method. If she is unhappy with the system or experiencing side effects, provide appropriate counseling. Reassure her when side effects will diminish and let her know she can discontinue the method if she continues to be unhappy with it.

LNG IUS: Therapeutic Possibilities

- Range of non-contraceptive benefits, including:
  - Treatment of heavy menstrual bleeding
  - Endometrial protection for women receiving estrogen replacement therapy

We are now transitioning to a discussion of potential non-contraceptive benefits of LNG IUS.

Source

LNG IUS: Treatment of Heavy Bleeding

Overall reduction in menstrual blood loss is 90–97%
Before-after study of 25 women
Decrease menorrhagia in women with adenomyosis
Significant increase in hemoglobin and decrease in uterine volume at 12 months

Sources
This slide represents the reduction over a 12-month period for all methods, although the patterns/timeframes of reduction differ among the methods.

As this slide shows, the LNG IUS reduces menstrual bleeding substantially more than other contraceptive methods.

Source

IUS provides contraception
Reversible
Preserves fertility

Source

56 women ages 33-49, scheduled to have hysterectomy for heavy uterine bleeding, three hospitals in Finland
Randomly assigned to LNG IUS or current medical treatment
At an average follow-up of three years (range 23-49 months), 13 of 27 women (48%) were still using the LNG IUS
The system may provide a long-term alternative to hysterectomy
A case-series report of 50 women in Britain shows similar results. Of 50 women scheduled for hysterectomy due to heavy bleeding, 41 who received LNG IUS were taken off the list after nine months, with four developing complete amenorrhea.

Source
LNG IUS: Hormone Replacement

- Prevention of endometrial hyperplasia from estrogen therapy
- "Local is logical"
- Oral progestins can cause depression
- LNG IUS avoids systemic side effects of oral progestins

Source:

LNG IUS: Hormone Replacement

- Bleeding is the most common reason why women discontinue HRT
- LNG IUS suppresses endometrium
  - 83% – 88% have no bleeding/spotting at 12 months
  - 82% continuation rate at three years

Source:

General Discussion

- New methods are coming to U.S. market
- This should translate into more contraceptive choices, fewer unintended pregnancies
- These new methods share the common advantage of not requiring daily attention

Sources:

Intrauterine Contraception in the U.S.

<table>
<thead>
<tr>
<th>LNG IUS</th>
<th>Copper IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mcg levonorgestrel/day</td>
<td>copper ions</td>
</tr>
<tr>
<td>Approved for 5 years</td>
<td>Approved for 10 years</td>
</tr>
<tr>
<td>Approved 2000</td>
<td>Approved 1988</td>
</tr>
</tbody>
</table>

22,908 IUD insertions, 51,399 woman-years of use
Overall rate of PID was 1.6 cases per 1000 woman years of use
This graph shows an exponential decrease in risk after the first month. Even during the first month, the PID rate is only about one in 1,000
This is no different from the baseline of all women using no method of contraception
An increased risk of PID with IUDs associated with insertion
was not seen in the European LNG IUS/Nova T comparative trial.

Source

Asymptomatic IUS users with documented GC or chlamydia infections need treatment not IUD removal.

**Sources**

Studies found an absence of any detectable hCG in the sera of 30 users of non-medicated IUDs over a thirty-month period, which suggests that disruption of implantation is not a major mechanism.

Other mechanisms of action that prevent fertilization include thickening the cervical mucus and creating a barrier to sperm penetration.

**Sources**
Recent survey shows that physicians are more likely to use IUD themselves. IUD is a very popular method of contraception in Europe. 

**Source**

**Sources**

**Summary**
1. Several new contraceptive methods are available in the U.S.
2. LNG IUS was approved by the FDA in 2000.
3. Fewer than one in 100 women will get pregnant in five years with LNG IUS.

**Summary**
- LNG IUS bleeding patterns:
  - 1–4 mo frequent spotting
  - 1–6 mo reduced duration and amount of bleeding
  - > 12 mo, about 20% have no bleeding
- Treatment of heavy menstrual bleeding and endometrial protection with HRT.