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Intrauterine Contraception

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Abstract

Currently, there are only two basic types of intrauterine devices (IUDs): copper and hormonal. However, other types of IUDs are under development, some of which are in clinical trials around the world. Continued development has focused on increasing efficacy, longer duration of use, and noncontraceptive benefits. This review discusses currently available intrauterine contraceptives, such as the Cu380A IUD and levonorgestrel-releasing intrauterine systems; novel intrauterine contraceptives that are available in select parts of the world including the intrauterine ball, low-dose copper products, frameless devices, and intrauterine delivery systems impregnated with noncontraceptive medication; and novel products currently in development.

Keywords

- intrauterine device
- levonorgestrel
- copper
- frameless
- indomethacin

History of the Intrauterine Device in the United States

Ancient accounts of stones being placed into the uteri of camels to prevent pregnancy during long treks across the sand dunes may represent the first conceptualization of intrauterine contraception. Early intrauterine products started as a metal ring with catgut or silk tied around the ring evolved into variously shaped products that required the uterus to configure around the device.[1,2] Modern-day intrauterine devices (IUDs) evolved in the 1960s with the development of the T-shaped product, a model that configured better to the natural shape of the uterus.[3]

IUDs have been available in the United States since the 1960s and have included nonmedicated, hormonal and copper products.[4] In the 1960s, the IUD appeared to have advantages as an easier to use method with fewer potential cardiovascular risks as compared with the widely used oral contraceptive. By the 1970s, approximately 10% of women using contraception chose an IUD. Introduced in the United States in 1970, the newest IUD, the Dalkon Shield (A. H. Robins Company, Richmond, VA), grew quickly in popularity among physicians. This IUD later became infamous for associated reproductive health problems (septic miscarriages, pelvic inflammatory disease), negative press surrounding the device, and numerous lawsuits. As a result, American women stopped widely considering all IUDs for contraception despite having safer devices.[5] Almost all pharmaceutical companies removed their IUDs from the market by 1986 due to declining utilization and lawsuits. Only a progesterone-releasing IUD (Progestasert), first marketed in 1976, remained available. With the introduction of the ParaGard copper IUD (Teva Pharmaceuticals, North Wales, PA) in 1988, the United States had both a hormonal and nonhormonal option available. Still, utilization remained low until introduction of the Mirena levonorgestrel 52 mg intrauterine system (IUS) in 2001, which had significantly higher efficacy than Progestasert, longer duration of action, and benefits for treating heavy menstrual bleeding and dysmenorrhea. Progestasert was withdrawn from the market in 2001.

While IUD shapes have morphed over many decades, the concept behind them has stayed the same. Worldwide, the IUD is one of the most common forms of contraception used with the highest rates in Asia where IUDs are used by approximately 40% of contracepting women in China, almost 50% in Korea, and 56% in Uzbekistan.[6,7] In the United States, IUD utilization declined from a peak of around 8% of contracepting women in 1973 to less than 2% in 1995; however, the introduction of new options and more focus by medical organizations on the benefits of IUDs have resulted in a rapid increase in IUD utilization beginning in 2007.[8–10] The most recent national data show that IUDs are used by 10.3% of all contracepting women in the United States.[11]

The IUD is one of the most effective contraceptives available, with an overall failure rate of less than 1% in the first year

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of use.[12] Slight differences in efficacy are apparent between the four currently marketed IUDs. First-year failure rates per 100 women are 0.15, 0.20, 0.4, and 0.8 for Liletta, Mirena, Skyla, and ParaGard, respectively.[12–15]

Indication and Contraindications for Intrauterine Device Use

Very few medical contraindications exist for IUD use, particularly for copper-containing IUDs. Contraindications applicable for all IUDs include uterine cavity anomalies, malignancy, and pregnancy. Recommendations for use with medical complications are compiled in the World Health Organization and Centers for Disease Control and Prevention medical eligibility criteria.[16,17]

Most medical conditions create no restriction for copper IUD use. Use of hormonal IUDs has comparatively more restrictions; however, there are still fewer restrictions for the hormonal IUD than for combined hormonal contraceptives. For example, all hormonal contraceptives are not recommended in women with breast cancer, while the copper IUD may be used. However, in women with thrombogenic mutations, hypertension, or deep venous thrombosis, the benefits of hormonal IUD use outweigh the risk of using such a product.[16] In some situations, a hormonal IUD can be used when combined hormonal contraceptives or a copper IUD is contraindicated or relatively contraindicated, such as abnormal uterine bleeding with high risk for unopposed estrogen.[16]

Ectopic Pregnancy

Ectopic pregnancy occurs rarely, with current estimates ranging from 0.5 to 1.5% of reported pregnancies.[18,19] While pregnancy is very well prevented with IUD use, pregnancies can and do still occur. If a pregnancy does occur with IUD use, it is more likely to be an ectopic pregnancy, as compared with one occurring when no contraception is used. Approximately 6 to 9% of pregnancies occurring with a copper IUD in place are extrauterine and approximately 50% of pregnancies with a levonorgestrel 52 mg IUD are ectopic.[20–22] However, because pregnancy is so well prevented with IUD usage, the overall number of ectopic pregnancies is still very low.

Intrauterine Devices Available in the United States

Copper Intrauterine Device

Currently, the copper TCu380A IUD (marketed as ParaGard) is the only nonhormonal IUD available in the United States. This IUD has copper wire wrapped around the stem of a small plastic "T" frame and has copper collars on the two arms of the frame. These collars prolong the duration of action as compared with IUDs that simply have copper around the stem. The TCu380A is approved around the world for up to 10 years, but studies have shown efficacy of up to 15 years or more.[23,24] The 32-mm-wide and 36-mm-long T-frame is a true "T" and the arms tuck downward into the inserter for IUD placement.

The mechanism of action for the copper IUD is primarily related to copper ions' effect on sperm motility and viability. Cervical mucus changes and polymorphonuclear lymphocyte recruitment to the uterus helps the efficacy of the device.[25] However, a recent study showed no increase in inflammatory cell populations of the cervix with copper IUD use.[26] The results of this study imply that the contraceptive mechanism of action for the copper IUD may be the effects of copper on the sperm or oocyte.

Although copper IUDs typically do not change menstrual frequency, currently available products can increase menstrual flow and cramping-type abdominal pain; approximately 10 to 13% of users will have the IUD removed for bleeding in the first year of use.[27] A multinational study comparing the TCu380A IUD to etonogestrel implant found discontinuation rates due to bleeding of 3.8 and 5.5%, respectively, after 1 year ($p = 0.025$), and 8.5 versus 14.6%, respectively, after 3 years ($p < 0.001$).[28]

The copper IUD has an added benefit of effectiveness as emergency contraception. Copper IUD placement for emergency contraception within 5 days of intercourse or ovulation has a failure rate of less than 1 per 1,000, which is significantly more effective than any hormonal emergency contraceptive.[29,30] Two factors related to higher rates of oral emergency contraception failure are increasing weight and further acts of unprotected intercourse in the same cycle. Both of these risks are not relevant with a copper IUD which has the advantage of providing continued highly effective contraception.

Hormonal Intrauterine Devices

Hormonal IUDs have been available since 1976 but did not have increased acceptability as a contraceptive option until the introduction of Mirena, a levonorgestrel 52 mg IUS in 2001. The levonorgestrel IUS provided a longer duration of use, higher efficacy, and favorable effects on menstrual bleeding and cramping, which made it more attractive than the previously available hormonal IUD, which was only approved for 1 year of use. This first levonorgestrel IUS, Mirena, is approved for 5 years of use, although some clinical studies suggest efficacy may be maintained for at least 7 years.[31,32] Unlike the T-frame of the Copper T380A, the 32-mm-wide and 32-mm-long T-shaped frame is a Nova T in which the arms fold upward for placement. The stem of the polyethylene frame contains a hormone depot surrounded by a rate-releasing membrane, releasing approximately 20 μg of levonorgestrel daily in the first few weeks with a decrease to 18 μg/day by the end of one year and 10 μg/day after 5 years.[14] Studies of plasma levonorgestrel levels suggest release rates that would also support efficacy of this IUS for at least 7 years.[33,34]

A similar levonorgestrel 52 mg IUS, Liletta in the United States and Levosert in Europe, has the same shape, size, and hormone content as Mirena. Interestingly, the package insert lists the levonorgestrel release rate as 19 μg/day initially with a decrease to 16 μg/day by the end of 1 year and 13 μg/day at the end of 3 years. Although these products were introduced in the U.S. and European markets in 2015 with approval for 3 years as a contraceptive, clinical trials are continuing to determine efficacy and safety for up to 7 years.[13]

A levonorgestrel IUS is also available which contains levonorgestrel 13.5 mg on a smaller Nova T frame than the levonorgestrel 52 mg products, measuring 28 mm wide and 30 mm long. This IUS, known as Skyla in the United States and Jaydess in the rest of the world, is approved for 3 years. This levonorgestrel 13.5 mg IUS releases approximately 14 µg of levonorgestrel daily after the first few weeks with a rapid decrease to 10 µg/day by 2 months, and 5 µg/day by the end of three years.[15]

The levonorgestrel IUS products primarily work locally by thickening the cervical mucus which prevents sperm from traveling up into the uterus.[35] Additional effects within the uterine cavity, causing decidualization and atrophy of the endometrium, provide a decrease in menstrual flow.[33]

All levonorgestrel-releasing IUS products initially cause irregular light bleeding. Over time, the levonorgestrel 52 mg IUS products result in a continued decrease in bleeding with 19 to 20% achieving amenorrhea within 1 year.[13,15] With the levonorgestrel 13.5 mg, bleeding becomes lighter with longer use with the number of days of bleeding or spotting decreases dramatically during the second month. In general, there are more spotting-only days than bleeding-only days during levonorgestrel 13.5 mg IUS use.[36] However, the bleeding patterns are more irregular than with the 52 mg products with lower rates of amenorrhea (6% at 1 year and 12% at 3 years).[15]

Noncontraceptive Benefits of Hormonal Intrauterine Device

The levonorgestrel 52 mg IUS confers multiple noncontraceptive benefits, most notably as a treatment for heavy menstrual bleeding.[37–39] Lethaby et al showed that menstrual bleeding decreased by 86% in 3 months, and by 97% by 12 months with Mirena use.[40] Hormonal IUDs are a cost-effective alternative to hysterectomy/surgery for patients with anemia from abnormal uterine bleeding who are not ideal surgical candidates.[41,42] This IUS has also been shown to significantly reduce the number of bleeding days and amount of dysmenorrhea and increase hemoglobin levels in women with adenomyosis.[43] The IUS can also provide endometrial protection against the proliferative effects of Tamoxifen which can lead to polyps or endometrial carcinoma.[42,44] Finally, the IUS has also been used as the progestin component for combined hormone therapy in menopausal women with an improved bleeding profile compared with oral preparations.[42]

Innovative Intrauterine Devices (Not Widely Available)

There are multiple variations of the IUDs commonly available (►**Table 1**). Numerous products have been available in Europe for many years but are not marketed or approved in the United States. Examples of such IUDs include the following:

- Femilis (levonorgestrel 60 mg—effective for 5 years, or Femilis slim with 40 mg levonorgestrel—effective for 3 years)
- NovaT (Nova-T 380 effective for 5 years and Nova-T 200 effective for 30 months)
- Multiload (MLCu-375 effective for 5 years, and MLCu-250 effective for 3 years)
- Cu Safe300, Cu7, Cu-Fix/Flexiguard (prototypes of Gynefix) and multiple other T framed IUDs, some with less copper/shorter duration (Flexi-T 300/380 in Canada)

Additionally, there are a myriad of IUDs produced in other countries such as India, which often copy products available elsewhere in the world. It is unclear whether these products undergo the same rigorous testing as the approved IUDs in the United States and Europe. Some products, however, are unique and may serve as early models for further development.

Copper Indomethacin Intrauterine Device (Available in China)

The Chinese have produced five different copper IUDs containing indomethacin with the goal of reducing menstrual-related complaints that occur with currently available copper IUDs.[45–47] The indomethacin does not interfere with copper ion release and the copper does not interfere with indomethacin action.[47]

One such device, the Medicated Gamma IUD, is a gamma-shaped stainless steel wire frame, with 250 mm^2 of spiraled copper wire on a 26 mm × 26 mm frame. Silicone elastomer beads containing a total of 25 mg of indomethacin are located in the center of the gamma and at the distal end of each horizontal arm (►**Fig. 1**).[48] Another gamma-shaped IUD, the Medicated Gamma Cu380, contains 380 mm^2 of copper and 25 mg of indomethacin. A study of 600 women using the Medicated Gamma Cu380 IUD found no pregnancies over 2 years of use.[49]

An example of a differently shaped indomethacin-containing copper IUD is the Medicated Cu200 IUD (►**Fig. 1**), which contains 200 mm^2 of copper on a stainless steel frame with a broad, open stem (the IUD resembles an outline of the uterus). Silicon rubber containing indomethacin 18 mg lines the inside of the stainless steel wire tube that makes up the IUD frame.[46]

Unfortunately limited data are available in the English literature to understand all of the various frames, efficacy, and side effects of these medicated IUDs; however, one review article includes a nonreferenced table of a few Chinese copper IUDs, with pregnancy rates ranging from 0.46 to 2.73%, and effective duration between 5 and 10 years.[46]

Copper Intrauterine Ball (Available in Austria and Israel)

The SCu300A/SCu380A is a copper-containing intrauterine ball (IUB). Once inserted into the uterine cavity, it takes the shape of a sphere. The IUB is made from a shape-memory alloy wire (nitinol), which allows it to flex while returning to original shape. This wire is coated with a thin white polymer to improve visibility. The wire is then strung with 17 pure copper spheres, with the distal sphere attached to the wire end to reduce sharpness. The proximal sphere attaches to a 20-cm-long double-tailed uncolored nylon monofilament thread which allows for removal of the device (►**Fig. 2**). The ball comes in three sizes ranging from 12 to 18 mm in

Table 1 Various IUDs available or in development

IUD name	Frame type	Frame size	Active component	Availability	Duration of action (y)	Other benefits and uses
Copper IUDs						
T380A	Plastic T-frame with copper collars at arms and wire on stem	32 mm × 36 mm	380 mm^2 copper	Worldwide	Approved 10 (likely 15 +)	Effective as EC
Multiload 250 Multiload 375	U frame with copper wire wound around stem	19.5 mm × 29.4 mm 19.5 mm × 32.5 mm	250 mm^2 copper 375 mm^2 copper	Europe, Oceana, India, Asia, S. America, Canada	3 5	
Nova-T 380	Polyethylene T-frame with copper wire around silver core	32 mm × 32 mm	380 mm^2 copper	Europe, Asia, Canada, Oceana, India	5	
VeraCept	Copper beads on Nitinol frame	30 mm × 32 mm	175 mm^2 copper	Under investigation	3	Fewer changes in bleeding pattern and cramping
GyneFix 200 GyneFix 300	Frameless (on polypropylene suture)	[5 mm × 2.2 mm] x 4 [5 mm × 2.2 mm] x 6	200 mm^2 copper 300 mm^2 copper	Europe, Canada, Israel, Turkey, China	3–5 5	Effective as EC
IUB	Nitinol spherical frame	12–18 mm	300 mm^2 or 380 mm^2 copper	Under investigation	5	
Medicated Gamma Gamma Cu380	Stainless steel wire frame with embedded copper	26 mm × 26 mm	250 mm^2 copper 380 mm^2 copper 25 mg indomethacin	China	8	
Medicated Cu200	Stainless steel wire frame with embedded copper	Unavailable	200 mm^2 copper 18 mg indomethacin	China	Unavailable	
Levonorgestrel IUDs						
Mirena IUS	Polyethylene Nova-T	32 mm × 32 mm	52 mg LNG	Worldwide	Approved 5 (likely 7)	Treatment of heavy menstrual bleeding, hyperplasia, hormone replacement therapy
Liletta IUS Levosert IUS	Polyethylene Nova-T	32 mm × 32 mm	52 mg LNG	Europe, United States, Africa	Approved 3 (likely 7)	Treatment of heavy menstrual bleeding, hyperplasia, hormone replacement therapy
Skyla IUS Jaydess IUS	Polyethylene Nova-T	28 mm × 30 mm	13.5 mg LNG	Europe, North America	3	
19.5 mg LNG IUS	Polyethylene Nova-T	28 mm × 30 mm	19.5 mg LNG	Under investigation	3–5	
Fibroplant	Frameless (on nonresorbable thread)	1.6 mm × 3 cm 1.6 mm × 4.6 cm	14 μg LNG daily 20 μg LNG daily	Under investigation	5 5	
Femilis slim Femilis	T-shaped EVA device	24 mm × 30 mm 28 mm × 30 mm	40 mg LNG 60 mg LNG	Europe	3 5	

Abbreviations: Cu, copper; EC, emergency contraception; EVA, ethylene vinyl acetate; IU, intrauterine; IUD, intrauterine device; IUS, intrauterine system; LNG, levonorgestrel.

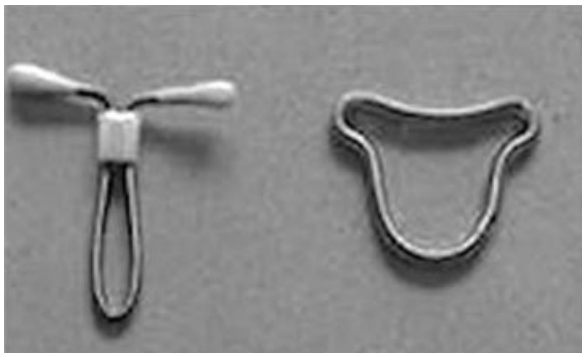

Fig. 1 Copper indomethacin intrauterine device (IUD). Gamma IUD (left) and medicated 200 IUD (right).

Fig. 2 Intrauterine ball.

diameter with copper ranging from 300 to 380 mm^2. The IUB is being evaluated for a lifetime of 5 years.[50,51]

The concept behind this IUD is that the spherical shape will be less irritating than T-shaped IUDs and have a lower risk of perforation because, once inserted, the tip of the ball curves away from the fundus. Additionally, a spherical IUD may have little to no concern for malpositioning.

A small trial conducted with 15 participants suggested insertion was easy with no perforations, expulsions, pregnancies, or complications noted. Some women reported abdominal discomfort, and 43% reported changes in bleeding pattern at 1 year. Most women in the trial reported being very satisfied.[50] However, a recent Canadian study evaluated 51 women for up to 1 year using a 10-mm IUB with 380 mm^2 of copper.[52] Ultrasonography after the procedure demonstrated correct placement. Fourteen (27%) women experienced expulsion during the first year while 8 (16%) had the IUB removed for pelvic symptoms. Importantly, 9 (18%) experienced expulsion within 8 weeks of placement. One pregnancy occurred between 6 and 9 months of use. Of the 21 (41%) women who completed 1 full year of use, 6 (29%) were dissatisfied and complained of bleeding or pain. As this IUB is smaller than the other products currently under development, the larger IUBs may have lower expulsion rates. However, the relative intolerance of the tested IUB creates concern that larger devices may not be better tolerated.

Frameless Intrauterine Devices

Frameless IUDs have been under development since the 1980s. Several iterations of the same concept have come to the market. Just like traditional IUDs, the frameless IUDs have hormonal and nonhormonal varieties. The frameless IUD follows the idea that not all uterine cavities are the same size and shape, and that the size of the cavity can change during menses. Without a frame, this IUD is truly flexible.

Copper

The GyneFix 200 contains four copper beads each measuring 2.2 mm long and 5 mm wide in diameter. The GyneFix 330 is similar but contains six beads. The beads are threaded over a polypropylene thread and crimped at the ends over the thread to prevent the beads from slipping off. The proximal end of the thread is then anchored into the myometrium using the inserter. The Gynefix 200 contains 200 mm^2 of copper, while GyneFix 330 contains 330 mm^2 of copper. This device has been approved for 5 years of use and is available in Europe, Turkey, and Israel.

Failure rates in clinical trials range from 0 to 2.5/100 users over 1 to 9 years of use. A randomized trial enrolling 4,063 women compared the copper frameless IUD (Gynefix) with the Copper TCu380A over 8 years.[53] Failed insertion occurred in 43 (2.1%) women randomized to GyneFix but none of the copper-T users. Women using both IUDs experienced no perforations. However, expulsion occurred more commonly in GyneFix than in Copper T users with first-year expulsion rates of 5.3% (95% confidence interval [CI]: 4.4, 6.4%) per 100 and 2.5% (95% CI: 1.9, 3.3%), respectively. Expulsion rates in years 2 to 8 were similar. Over 8 years, pregnancy rates did not differ significantly. However, women using the GyneFix experienced fewer ectopic pregnancies (0.1/100 vs. 0.8/100) and fewer removals for pain.[53]

The bleeding pattern and amount for the GyneFix is reported to be generally less than that of the TCu380A. Perforations appear to be uncommon with none reported during this 8-year trial period.[53] However, numerous case reports of perforations with this device are published.[54–62]

Hormonal

The Fibroplant is a frameless levonorgestrel-releasing IUD which is basically a contraceptive implant with a nonresorbable thread through the center. The thread has a knot on the proximal end which is implanted into the myometrium of the uterine fundus. The thread holds a 3-cm-long (Fibroplant 14) or 4.5-cm-long (Fibroplant 20) delivery system that is 1.6 mm wide and releases 14 or 20 µg of levonorgestrel, respectively, each day. Both versions of Fibroplant are approved for 5 years.

Fibroplant is highly effective with one pregnancy in a 5-year trial of 304 women, with a resultant pregnancy rate of 0.4/100. Two (0.7%) women experienced expulsion and another two (0.7%) experienced uterine perforation.[63] A study of 154 adolescent and young women using the Fibroplant (50 users) and Gynefix (104 users) found no pregnancies with the Fibroplant.[64]

The Fibroplant has similar effects on uterine bleeding patterns as seen with levonorgestrel T-shaped IUS products. Women using Fibroplant experience a significant reduction

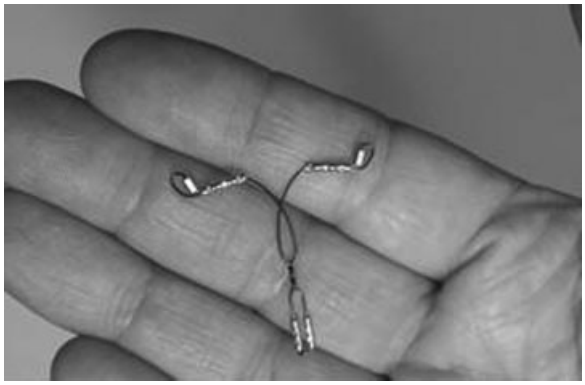

Fig. 3 VeraCept.

in menstrual bleeding with 80% experiencing amenorrhea in a 2-year study of 40 Brazilian women.[65]

VeraCept

VeraCept, which is still in development, is a low-dose copper contraceptive and is constructed of a flexible 30 mm × 32 mm nitinol frame with copper beads. Unlike IUDs with plastic frames, nitinol has flexibility and memory that allows the arms to compress inward with pressure from the uterine walls (►**Fig. 3**). The 175-mm^2 copper surface area is lower than other available T-shaped IUDs and may decrease the potential for worsening menstrual flow and cramping. To account for the lower total amount of copper, the beads are concentrated where they are theorized to be most needed: at the ends of the arms (at the tubal ostia) and at the base of the stem (at the internal os). With a lower amount of copper, the duration of efficacy is expected to be shorter than currently available copper-containing IUDs.

In an early trial comparing VeraCept and the copper T380S, VeraCept users had less pain with insertion, higher continuation rate at 9 months, fewer expulsions, and fewer removals for pain or bleeding symptoms.[66] Additional human clinical trials are ongoing to determine efficacy, tolerability (bleeding pattern), ease of insertion, and pain with insertion.

LNG 19.5 mg Intrauterine System

Another IUS currently under development is a levonorgestrel 19.5 mg product manufactured by the same company as Mirena and Skyla. The device is intended for up to 5 years of use. In pharmacologic and randomized control trials, the 19.5 mg IUS had similar outcomes over 3 years as compared with the levonorgestrel 13.5 mg IUS.[36] A Phase III clinical trial comparing the levonorgestrel 13.5 and 19.5 mg systems showed similar pregnancy rates for 18- to 25-year olds in the first year (0.18 vs. 0.18%, $p = 1.0$) and third year (0.71 vs. 0.35%, $p = 0.69$). The pregnancy rates for 26- to 35-year-old groups also showed similar pregnancy rates for year 1 (0.46 vs. 0.11%, $p = 0.21$) and year 3 (0.69 vs. 0.9%, $p = 0.80$).[67]

Conclusion

Many varieties of IUDs are available today which allows the clinician and patient to choose a product which best fits the patient's medical and reproductive needs. Although the idea that placing something inside the uterus for contraception is not new, technologic advances have resulted in novel highly effective long-acting contraceptives that may provide more options and benefits.

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