WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 2.786
Volume 3, Issue 10, 364-392. Review Article ISSN 2278 – 4357

INCREASING USE OF LONG-ACTING REVERSIBLE CONTRACEPTION: SAFE, RELIABLE, AND COST-EFFECTIVE BIRTH CONTROL

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Article Received on
30 July 2014,
Revised on 30 August 2014,
Accepted on 22 September 2014

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ABSTRACT

Long-acting contraceptions are methods of birth control that provide effective contraception for an extended period without requiring user action. It includes injections, intrauterine devices (IUDs) and sub dermal implants. These are the most effective reversible methods of contraception because these do not depend on patient compliance. So their 'typical use' failure rates, at less than 1% per year, are about the same as 'perfect use' failure rates. In addition to being long-lasting, convenient, and well liked by users, they are very cost effective. Long-acting reversible contraception is recommended for adolescents to help decrease the teen pregnancy rate. LARCs are recommended for women of any age no matter how many times they have given birth. The advent of reversible long-acting contraceptives– IUDs, injectables and implants–has provided women throughout the world with valuable new fertility regulation options. These highly effective methods, together with male and female sterilization, have proven to be enormously popular and are now used by the majority of women and men who are currently contraception worldwide. Despite their safety and effectiveness they are underutilized: only 15.5% of women worldwide use IUDs and only 3.4% use sub dermal implants. Political, ethical, and safety questions have emerged, stemming from the ways in which these contraceptives have been developed and used over the course of this century. At par with the application of long acting contraceptives is concern

one can duly think about the proper implementation and its usage and moreover make the women more understand the poles apart issues of reproductive rights and freedom so far.

Key words: Long-acting reversible contraception, IUDs, Adolescent, Patient compliance.

INTRODUCTION

Following the development and widespread use of oral hormonal contraceptives, it became evident that alternative long-acting delivery systems would be required to improve contraceptive practice in some cultural settings where injectable or subdermal routes of administration are preferred[1]. Long-acting contraceptives constitute an important option in family planning services in many parts of the world. The advent of reversible long-acting contraceptives–IUDs, injectables and implants has provided women throughout the world with valuable new fertility regulation options. These highly effective methods, together with male and female sterilization, have proven to be enormously popular and are now used by the majority of women and men who are currently contraception worldwide[2].

The need for long-acting hormonal methods of contraception became apparent when experience with oral preparations showed the difficulty of maintaining a daily intake of medication. Injectable formulations, taken every two or three months, were the first alternatives to become available. Later, technological advances made it possible to deliver steroidal hormones continuously at a very low dose, thereby avoiding the unnecessary excess exposure which follows each administration. A major breakthrough was achieved in 1983 with the registration of the first implantable device, NorplantR, which offers contraceptive protection for five years. Current research aims at improving injectables and implants and also at developing long-acting hormonal methods which offer more flexibility of use for women, such as the contraceptive vaginal rings[3].

The development of long-acting steroidal contraceptive systems this is believed to be an important solution to the problems of effectiveness, safety, and acceptability of steroidal contraceptives, especially in developing countries. Since side effects from hormones are known to be dose-dependent, the aim is to develop a contraceptive with a great enough amount of hormone to prevent pregnancy but not so great as to cause side effects. There are two different approaches to the delivery of fertility control the pharmacologic and the systems engineering approaches. The pharmacologic approach is typified by an injectable steroid while the systems engineering approach involves inert drug carriers which control the

release of the hormone. Delivery of long-acting substances can either be made locally or systemically. The state of the art regarding long-acting contraception is reviewed with a thorough discussion of the process of development, dosage requirements, and method of delivery of the following types of contraceptives[4]

1) Injectable depot formulations;
2) Subdermal implants;
3) Medical intrauterine systems;
4) Medicated intravaginal systems;
5) Medicated intracervical systems; and
6) Biodegradable systems.

Classification of contraceptives[5]

1.Long Acting Reversible Contraception (LARC) methods

- Injectable contraceptive (Depo-Provera)
- Implants (Implanon)
- IU Devices
- Transdermal systems
- Vaginal rings

2.Non Long Acting Reversible Contraception (LARC) methods

- Oral contraceptives - combined hormonal
- Oral contraceptives - progestogen-only
- Emergency hormonal contraception
- Spermicides

1. Long Acting Reversible Contraception (LARC) methods

The Faculty of Family Planning and Reproductive Health Care has published a comprehensive review of the LNG-IUS states that "the gross rate of expulsion increased from 4.5 per 100 users at 12 months to 5.2 per 100 users at 24 months and up to 5.9 per 100 users at 60 months". It is used up to 60% of women and stop using the LNG-IUS within 5 years. Over a 5-year period, approximately 5.9% of LNG-IUS's are expelled from the body spontaneously.

During the use of the LNG-IUS, the symptoms most strongly associated with its premature removal were excessive bleeding and spotting, infection and pain. The IUD is a safe and reversible method, which requires little effort on the part of the user once inserted and offers 10 years of protection against pregnancy. In spite of these advantages, the use of the IUD in relation to other contraceptive methods is reported to have either stagnated or declined in a number of countries. e.g.

- Progestogen-only implant (Implanon®; lasts three years)
- Copper IUD (TT380 Slimline®; lasts ten years)
- Progestogen-only IUS (Mirena®; lasts five years)
- Progestogen-only depot (Depo-Provera®; given every 12 weeks)

Injectables

Injected contraceptives are given once every 3 months. Most injectables are progestin-only. In the United States, depo-medroxyprogesterone acetate (Depo-Provera) is the only approved injected contraceptive. Depo-Provera (also called Depo, or DMPA) uses a progestin called medroxyprogesterone. Like other progestin contraceptives, Depo-Provera prevents pregnancy by halting ovulation, thickening the cervical mucus, and stopping the implantation of fertilized eggs in the uterine lining.

Depo-Provera is very effective in preventing pregnancies. About 3 in 100 women who use it become pregnant. However, Depo also carries the risk for many mild and serious side effects. The most serious side effect is loss of bone density.Because of this complication Depo-Provera should not be used for more than 2 years.

Once-a-month is

- progestogen-estrogen combinations

Two-to-three monthly:progestogen-only are

- Depot-medroxyprogesterone acetate (DMPA)
- Norethisterone enanthate(NET-EN)

A new low-dose subcutaneous formulation of DMPA, depo-subQprovera104 is now available. Medroxyprogesterone acetate injectable suspension (DMPA-SC) administered once every three months provides a 30% lower total dose than traditional DMPA IM (150-mg injection). In clinical studies, it suppressed ovulation for more than 13 weeks in all subjects

regardless of body mass index, with no pregnancies reported in more than 16,000 woman cycles of use. Although not evaluated in a head-to-head study, the incidence of bleeding and amenorrhea reported with DMPA-SC appeared to be similar to that reported with DMPA.
Prototype long-acting formulations of norethisterone in the form of injectable microspheres made of biodegradable co-polymer of polylactic acid and glycolic acid have been successfully used as injectable contraceptives in women[6].

The pharmacokinetic and pharmacodynamic effects of a long-acting formulation of levonorgestrel microencapsulated in a biodegradable polymer poly (DL-lactide-co-glycolide) were tested in baboons. The polymer microspheres provided continuous release of levonorgestrel for up to 6 months following a single intramuscular injection. The treatment inhibits ovarian function for 3–6 months, depending on the dose. The duration and pattern of levonorgestrel release varies according to the quality and size of the microspheres. The microsphere delivery system offers a promising new approach to developing a long-acting injectable contraceptive based on levonorgestrel[7].

Dihydroxyprogesterone acetophenide 150 mg + E2 enanthate 10 mg, Spain DMPA 25 mg + E2 cypionate 5 mg Mesigyna norigynon NET-EN 50 mg + E2 valerate 5 mg 17α-hydroxyprogesterone caproate 250 mg + E2 valerate 5 mg Mego-E megestrol acetate 25 mg + 17β E2 3.5 mg

- **Administering Injections**

❖A physical examination is necessary before beginning the injections.
❖Depo is injected into a muscle in the patient's arm or buttock. During months between injections, the hormone slowly diffuses out of the muscle into the bloodstream.
❖Depo requires an injection by the doctor once every 3 months.
❖If more than 2 weeks pass beyond the regular injection schedules, the woman should have a pregnancy test before receiving the next injection.

- **Candidacy**

Because Depo-Provera does not contain estrogen, it is safe for many women who are not candidates for combination oral contraceptives, such as women smokers over age 35.
Depo-Provera should not be given to women who have a history of:
❖Current or past breast cancer
❖Stroke or blood clots

❖Liver disease

❖Epilepsy, migraine, asthma, heart failure, or kidney disease (due to the fact that the drug causes fluid retention)

❖Unexplained vaginal bleeding

❖Risk for osteoporosis

Because of the long lag time between ending treatments and restoration of fertility, Depo-Provera is not recommended for women who are thinking of becoming pregnant within 2 years.

- **Advantages of Depo-Provera**

❖Provides highly effective reversible protection against pregnancy without placing heavy demands on the user's time or memory.

❖Does not increase risk for breast, ovarian, or cervical cancer. May protect against endometrial cancer.

❖May be useful for women with painful periods, heavy bleeding (including heavy bleeding caused by fibroids), premenstrual syndrome, and endometriosis.

- **Disadvantages and Complications of Depo-Provera**

❖Weight gain. Most women gain an average of 5 - 8 pounds.

❖Other common side effects include menstrual irregularities (bleeding or cessation of periods), abdominal pain and discomfort, dizziness, headache, fatigue, nervousness.

❖Most users of Depo-Provera stop menstruating altogether after a year. Depo can cause persistent infertility for up to 22 months after the last injection, although the average is 10 months.

❖Long-term (more than 2 years) use of Depo-Provera can cause loss of bone density. Depo-Provera's label warns that the decline in bone density increases with duration of use and may not be completely reversible even after the drug is discontinued. The FDA recommends that Depo-Provera should not be used for longer than 2 years unless other birth control methods are inadequate. Some studies indicate that this bone loss may be reversible once Depo-Provera use is discontinued.

❖The injections do not provide protection against sexually transmitted diseases.

Fig. 1-The Shot-Depo Provera

Depo-Provera has been produced in the United States since 1969 but was not approved as a method of contraception until 1992. DMPA is a very safe and well-studied method of contraception whose major advantages are that it contains no estrogen and can be administered only 4 times a year eliminating some of the compliance issues associated with pills, patches and rings. Depo-Provera works primarily by inhibiting ovulation. It also causes thinning of the uterine lining (endometrium) and thickening of the cervical mucus causing it to be less penetrable by sperm.

- **Non-contraceptive benefits**

There are several non-contraceptive benefits of DMPA which include a decreased risk of endometrial cancer and pelvic inflammatory disease. Women who receive DMPA generally become amenorrheic (stop having their menstrual periods). Some women, especially those that have had a history of heavy and painful periods, select DMPA for this benefit alone.

Another non-contraceptive benefit of DMPA lay in its ability to reduce pain that may be caused by endometriosis. DMPA, in fact, is one of the oldest effective medical treatments for endometriosis.

- **Side effects**

Return to fertility is delayed after discontinuing Depo-Provera it may take 6-10 months after the last injection to begin ovulation again making it possible to conceive. Irregular bleeding most women taking Depo-Provera will stop having periods entirely (amenorrhea). Some women experience light but continuous spotting or bleeding. This is an uncommon but very annoying side effect. Weight gain—there is considerable debate about whether or not DMPA

causes weight gain. Most controlled studies show its use is not associated with weight gain. However, many women do associate its use with considerable weight gain. Unfortunately, the vast majority of these women continue to gain weight long after discontinuing the use of DMPA suggesting that something else is at play.

Bone loss the prolonged use of DMPA may contribute to bone loss in some women. Depot-medroxyprogesterone acetate (DMPA or Depo-Provera) is injected as an aqueous suspension of microcrystals. Intramuscular injection of 150 mg of DMPA results in more than 3 months of contraception. Irregular bleeding and spotting followed by amenorrhea, constitute the most importance side effects experienced by DMPA users. Because DMPA use can result in prolonged (but not permanent) infertility, DMPA is not an optimum contraceptive choice for women who may want to conceive in the next one or two years[8, 9].

Research for new progestogen-only injectables aims at obtaining an improved pharmacokinetic profile with a decreased peak blood level following injection and a longer duration of action. Approaches under investigation include

1.Biodegradable microspheres consisting of a mixed polymer/drug matrix which releases the drug as the polymer erodes. This system is being tested with a number of progestogens, the most advanced being with norethisterone.
2.Monolithic macrocrystals of pure drug which slowly biodegrade to enter the circulation. This is being tested with the natural hormone progesterone.
3.Controlled particle size distribution of drug microcrystals.
4.Use of a prodrug, such as an ester which needs to be hydrolysed to release the active steroid.

These last two approaches have led to the development of a levonorgestrel ester, levonorgestrel butanoate, as an injectable contraceptive.

- **Combined once-a-month injectable preparations**

As estrogens were known to be an effective treatment for menstrual disturbances induced by progestogens, investigators considered the possibility of developing combined estrogen/progestogen preparations which would induce a more regular bleeding pattern. Short-acting estrogen esters were selected in order to avoid continuous exposure of the subjects to high levels of estrogen. This imposed a more frequent administration of the

injection but offered the possibility of inducing a cyclic monthly pattern. The first injection is given between days 1 and 5 of a menstrual period, to ensure that treatment is not initiated when the woman is pregnant. It is soon followed by a rise in progestogen and estrogen blood levels. When the estrogen level decreases, i.e. approximately two weeks later, depending on the estrogen ester, a bleeding episode occurs which reflects this estrogen withdrawal. With monthly administration of the preparation, this phenomenon recurs on a monthly basis, giving the woman the experience of a first short cycle followed by regular monthly cycles[10].

A large number of contraceptive preparations were developed, however only two are used currently to any large extent, estimated as 1 million women world-wide:

1.Dihydroxyprogesterone acetophenide 150 mg and estradiol enanthate 10 mg: this preparation was withdrawn by the company that originally developed it because of toxicological concerns; however, it is still manufactured by small pharmaceutical companies in Latin America and is marketed under the names of Deladroxate, Perlutal or Topasel. A half-dose preparation is available, known as Yectames.

2.17-hydroxyprogesterone caproate 250 mg and estradiol valerate 5 mg: this is known as Chinese injectable No1 and is used essentially in China and some neighboring countries. It is used according to different schedules of injections such that women receive between 13 and 16 injections per year, thus it is not truly a monthly preparation. In addition, it induces marked irregularities in bleeding pattern in a substantial number of users[11].

Because of the need to develop alternatives which would be safe, effective and acceptable once-a-month preparations, the Special Programme of Research, Development and Research Training in Human Reproduction carried out, in collaboration with industry, the development of two products:

1.Cyclofem, containing 25 mg DMPA and 5 mg estradiol cypionate, previously called Cycloprovera.

2.Mesigyna, containing 50 mg NET-EN and 5 mg estradiol valerate.

In comparison to the two progestogen-only injectables, DMPA and NET-EN, once-a-month preparations are equally effective but are better accepted as shown by lower discontinuation rates at one year for all reasons combined. This is mostly a reflection of lower one-year discontinuation rates for amenorrhea and for bleeding with these preparations.

An estimated 16 million women throughout the world are currently relying on injectable steroids for contraception. The choice of injectable methods includes products effective for 3 months, 2 months, or 1 month. Although little known in Europe, these methods represent the third most prevalent form of reversible contraception worldwide. Trend estimates suggest that this number is rising, due to the reassuring World Health Organization (WHO) data regarding cancer risk, and the recent approval of the 3-monthly injectable depo medroxy-progesterone acetate (DMPA, or Depo-Provera) by the United States Federal Drug Administration (USFDA).

Table 1. Formulation, Injection Schedule, and Availability of Injectable Contraceptives [11]

Formulation	Developer	Brand Name/Manufacturer	Injection Schedule	Availability
Progestin only: 150 mg depot medroxyprogesterone acetate (DMPA)	The Upjohn Company	Depo-Provera/Upjohn Megestron/Organon	Every 3 months, 12 weeks, or 90 days	Registered in over 100 countries; available in both public and private sectors.
Progestin only: 200 mg norethindrone (norethisterone) enanthate (NET EN)	Schering AG	Noristerat[a]/Schering AG Doryxus/ Richter Gedeon Ltd.	Every 2 months[b]	Registered in over 60 countries; available in both public and private sectors.
Progestin + Estrogen: 25 mg DMPA + 5 mg estradiol cypionate	Upjohn, WHO	Cyclofem, Cyclofemina, Novafem/Aplicaciones Farmaceuticas (Mexico), PT Tunggal (Indonesia), Lunelle/Upjohn (US) Cyclogeston/ PT Triyasa Nagamas Farma (Indonesia)	Every month	Registered in 18 countries; available in both public and private sectors.
Progestin + Estrogen: 50 mg NET EN + 5 mg estradiol valerate	WHO	Mesigyna, Norigynon/ Schering AG	Every month	Registered in 35 countries.
Progestin + Estrogen: 150 mg Dihydroxy	Squibb Pharmaceutical Company	Perlutan, Topasel, Agurin Horprotal, Uno-Ciclo/	Every month	Available in pharmacies in many

Progesterone Acetophenide + 10 mg estradiol enanthate		Various manufacturers in Latin Americca		Latin American countries and Spain; generally not available in public family planning programs.
Half-dose: 75 mg Dihydroxy Progesterone Acetophenide + 5 mg estradiol enanthate		Anafertin, Yectames/ Various manufacturers in Latin America	Every month	Latin America
Progestin + Estrogen: 250 mg 17µ -hydroxy-progesterone Caproate + 5 mg estradiol valerate	Chinese researchers; Squibb Pharmaceutical Company	Chinese Injectable No. 1	Every month, 2 injections in first month	China

a.Called Norigest in Pakistan, b. Alternative, less effective schedule: every 2 months for 6 months and then every 3 months

- **Injectable Contraceptives under Development**[12]

1. Steroidal Preparations

A number of approaches are being used in the development of new injectable formulations. These aim at controlling the release of the active compound in order to avoid the peak serum level which follows the injection, and to extend the duration of action. Such improved pharmacokinetic profile would, in principle, allow a lower dose to provide the same efficacy, while minimizing the side effects of the contraceptive preparation.

2. Monolithic microspheres

The method uses a pulsating jet of melted drug to form microspheres, which are then annealed and sieved to obtain the desired range of particle size. These are then formulated to provide stable and long-lasting aqueous suspensions.

This technology is being explored for the development of testosterone microspheres which would have 60-90 days duration of action and could be used as androgen replacement or for male contraception. The technology is also being investigated with progesterone in order to develop a two-monthly injectable contraceptive for lactating women.

The most advanced preparation based on this technology is a combined injectable contraceptive containing 250 mg of progesterone and 5 mg of estradiol. It was tested in 30 women for a single cycle and appeared to block ovulation for a month. Work is continuing on reproducibility of the microspheres, and on the evaluation of the impact of multiple injections on vaginal bleeding patterns. This method is being extended to mixtures of natural steroids and cholesterol, as preliminary data suggest that such microspheres provide an even more favorable pharmacokinetic profile. Finally, the application of this technology to synthetic steroids such as levonorgestrel cholesterol, MPA or nestorone is under investigation.

3. Steroid Esters

In the mid-1970s HRP/WHO, in collaboration with the National Institute of Child Health and Human Development (NICHD, USA), established a program for the synthesis of new long-acting progestogens and androgens. The approach chosen was to develop esters of known steroids, which would act as prodrugs and be converted to an active contraceptive agent by enzymatic hydrolysis in vivo.

4. Microsphere Formulations

The use of biodegradable poly-(lactide-co-glycolide) matrixes has been investigated for the delivery of natural and synthetic steroids as injectables. Investigators at Biotek, Inc. used this approach with progesterone, achieving sufficiently high loading of drug in the polymer to enable delivery of adequate amounts of progesterone for approximately 90 days in vitro and at least 77 days in rabbits. However, this work was stopped when safety issues were raised concerning the solvent used in the process. The same technology was investigated with testosterone and with synthetic steroids (norethisterone, levonorgestrel, norgestimate, nestorone), but these projects were abandoned because of additional concerns over reproducibility and cost.

5. Immunocontraceptives

Immunocontraceptives are based on the principle of using the body's own defense mechanisms to provide protection against pregnancy. Thus, they present a totally new approach to contraception. They have many potential advantages, including:

1) Freedom from menstrual, systemic, metabolic and endocrine side effects
2) Suitability for either men or women, depending on the target antigen
3) No interference with sexual response or activity
4) Sustained, reversible duration of action

5) Use during all stages of a man's or woman's reproductive life

6) Confidentiality of use

7) Low manufacturing and storage costs

8) Ease of distribution and administration within the health-care infrastructure.

6. hCG Immunocontraceptives

The most advanced immunocontraceptives are those based on hCG. Three main types have been developed to the stage of clinical testing:

✓ hCG beta subunit conjugated to tetanus toxoid (hCG-TT)

✓ hCG beta subunit - ovine LH alpha subunit heterodimer conjugated to tetanus toxoid and diphtheria toxoid (HSD-TT-DT)

✓ hCG beta subunit C-terminal 37 residue synthetic peptide conjugated to diphtheria toxoid (CTP-DT).

All three preparations have been tested in phase-I (safety) clinical trials; they generated antibody levels estimated to provide protection against pregnancy in fertile women and no health hazards were noted. The HSD-TT-DT preparation was tested in a phaseII (efficacy) clinical trial and this study demonstrated that an hCG immunocontraceptive can be effective in preventing pregnancy.

7. Sperm and Ovum Immunocontraceptives

Both sperm and ovum immunocontraceptives are currently being developed as methods to be used by women to prevent fertilization. Sperm antigens suitable for immunocontraception include sperm enzymes and sperm membrane glycoproteins.

The most promising enzyme is the sperm-specific isoenzyme of lactic dehydrogenase (LDH-C4) and preliminary studies in female baboons using recombinant and chemically-synthesized LDH-C4 peptide antigens have shown varying degrees of antifertility efficacy. A number of glycoproteins have also shown anti-fertility effects when used in *in vitro* systems or to immunize experimental animals. However, none of these antigens has reached the stage of clinical testing in humans.

Future Prospects

As a totally new approach to fertility regulation, immunocontraceptives will present new clinical challenges in order to ensure their safe delivery in family planning services, including

monitoring the time to effect, maintenance of effect, and reversibility in individual users. Researchers are addressing these points by improving the formulations in order to reduce inter-individual variability, and by developing a means of inducing reversibility at will. The practicality of these methods remains to be confirmed.

IUDs [13, 14]

The modern IUD has been around since the early 1960s when the first plastic devices became available for the sterile insertion of a plastic or combination plastic and metal device into the uterus. These IUDs were in widespread use for about 15 years.

The intrauterine device (IUD) is a small plastic T-shaped device that is inserted into the uterus. An IUD's contraceptive action begins as soon as the device is placed in the uterus and stops as soon as it is removed. IUDs have an effectiveness rate of close to 100%. They are also a reversible form of contraception. Once the device is removed, a woman regains her fertility.

The intrauterine device (IUD) is one of the safest, least expensive, and most effective contraceptive devices available. In spite of its clear advantages and current safety record, only 2% of American women who practice contraception currently use the IUD. (Over 10% of European women have chosen the IUD.) This low use in America is mainly due to persisting and now unwarranted fears of serious infection and other complications.

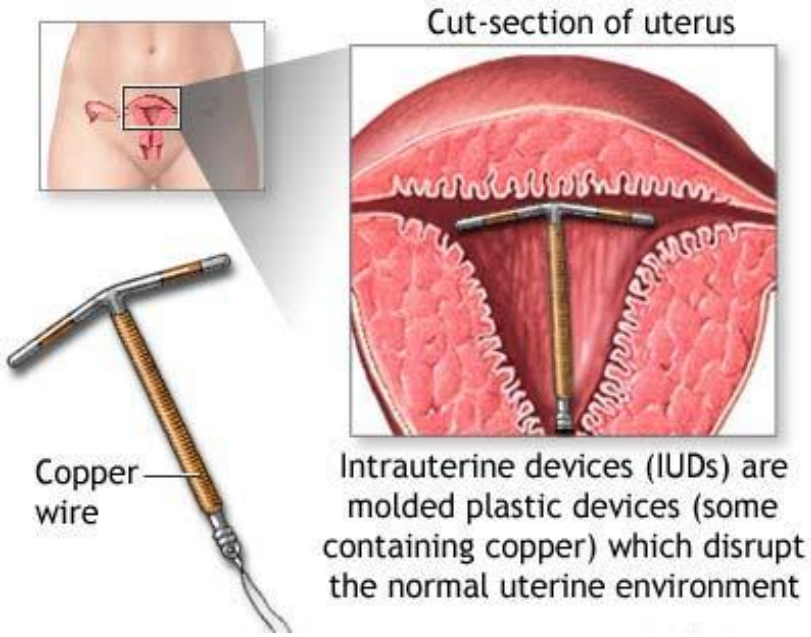


Fig. 2 Intrauterine Devices

The intrauterine device (IUD) shown uses copper as the active contraceptive. Others use progesterone in a plastic device. IUDs are very effective at preventing pregnancy (less than 1% chance per year). IUDs come with increased risk of ectopic pregnancy and perforation of the uterus and do not protect against sexually transmitted disease. IUDs are prescribed and placed by health care providers.

- **Intrauterine Device Forms**[15]

Two types of intrauterine devices (IUDs) are available in the United States:

➢ **Copper-Releasing (ParaGard)**. This type of IUD can remain in the uterus for up to 10 years. Copper ions released by the IUD are toxic to sperm, thus preventing fertilization.

➢ **Progestin-Releasing (Mirena).** This type of IUD can remain in the uterus for up to 5 years. Mirena is also known as a levonorgestrel-releasing intrauterine system, or LNG-IUS. Levonorgestrel impairs sperm motility and viability, thus preventing fertilization. LNG-IUS is long-acting, safe, very effective in preventing heavy bleeding, and helps reduce cramps. In fact, some doctors describe it as a nearly ideal contraceptive. It is also helpful for women with menstrual disorders, particularly heavy bleeding.

- **Inserting an Intrauterine Device**

With some exceptions, an intrauterine device (IUD) can be inserted at any time, except during pregnancy or when an infection is present. It may be inserted immediately postpartum or after elective or spontaneous miscarriage. It is typically inserted in the following manner by a trained health professional:

- A plastic tube containing the IUD (the inserter) is slid through the cervical canal into the uterus.
- A plunger in the tube pushes the IUD into the uterus.
- Attached to the base of the IUD are two thin but strong plastic strings. After the instruments are removed, the health care provider cuts the strings so that about an inch of each dangles outside the cervix within the vagina.

The strings have two purposes

➢ They enable the user or health care provider to check that the IUD is properly positioned. (Because the IUD has a higher rate of expulsion during menstruation, the woman should also check for the strings after each period, especially if she has heavy cramps.)

➢ They are used for pulling the IUD out of the uterus when removal is warranted. The insertion procedure can be painful and sometimes causes cramps, but for many women it is painless or only slightly uncomfortable. Patients are often advised to take an over-the-counter painkiller ahead of time. They can also ask for a local anesthetic to be applied to the cervix if they are sensitive to pain in that area. Occasionally a woman will feel dizzy or light-headed during insertion. Some women may have cramps and backaches for 1 - 2 days after insertion, and others may suffer cramps and backaches for weeks or months. Over-the-counter painkillers can usually moderate this discomfort.

- **Candidates for the Intrauterine Device**

Intrauterine devices are an excellent choice of contraception for women who are seeking a long-term and effective birth control method, particularly those wishing to avoid risks and side effects of contraceptive hormones. The LNG-IUS may be better suited for women with heavy or regular menstrual flow.

Around the time of insertion and shortly afterwards, women should be considered at low risk for sexually transmitted disease (mutually monogamous relationship, using condoms, or not sexually active). Women with risk factors that preclude hormonal contraceptives should probably avoid progestin-releasing IUDs, although the progestin doses are much lower with LNG-IUS and probably do not pose the same risks.

Women with the following history or conditions may be poor candidates for IUDs:

a. Current or recent history of pelvic infection
b. History of menstrual disorders -- mostly for the copper-releasing IUDs, however
c. Current pregnancy
d. Abnormal Pap tests
e. Cervical or uterine cancer
f. A very large or very small uterus

- **IUDs have the following advantages:**

1) The IUD is more effective than oral contraceptives at preventing pregnancy, and it is reversible. Once it is removed, fertility returns. (In spite of outdated concerns, studies have found no adverse effects on fertility with the current IUDs.)

2) Unlike the pill, there is no daily routine to follow.

3) Unlike the barrier methods (spermicides, diaphragm, cervical cap, and the male or female condom), there is no insertion procedure to cope with before or during sex.

4) Intercourse can resume at any time, and, as long as the IUD is properly positioned, neither the user nor her partner typically feels the IUD or its strings during sexual activity.

5) It is the least expensive form of contraception over the long term.

a. Additional advantages, depending on the specific IUD, include:

6) The progestin-releasing LNG-IUS (Mirena) is now considered to be one of the best options for treating menorrhagia (heavy menstrual bleeding). (However, irregular breakthrough bleeding can occur during the first 6 months.) It may even be appropriate and protective for women with uterine fibroids.

7) The copper-releasing IUDs do not have hormonal side effects and may help protect against endometrial (uterine) cancer.

- **Complications of Specific Intrauterine Devices**

Menstrual Bleeding Both intrauterine device (IUD) forms have effects on menstruation, although they differ significantly by type:

❖ Copper releasing IUDs can cause cramps, longer and heavier menstrual periods, and spotting between periods. Prescription medications are available to control the bleeding and pain, which, in any event, usually subside after a few months.

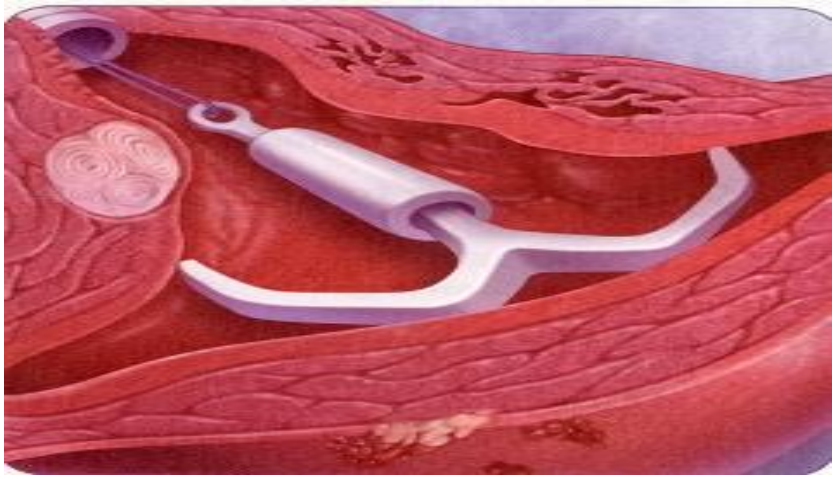
❖ Progestin-releasing IUDs produce irregular bleeding and spotting during the first few months. Bleeding may disappear altogether. (This characteristic is a major *advantage* for women who suffer from heavy menstrual bleeding but may be perceived as a problem for others.)

Ovarian Cysts The LNG-IUS may increase the risk for benign ovarian cysts, but such cysts usually do not cause symptoms and resolve on their own.

Expulsion An estimated 2 - 8% of IUDs are expelled from the uterus within the first year. Expulsion is most likely to occur during the first 3 months after insertion. Expulsion rates may be higher than average if the IUD is inserted immediately after delivery of a child. In 1 in 5 cases, the woman fails to notice that the device is gone, and thus faces the risk of unintended pregnancy. The risk for expulsion is highest during menstruation, so women should be sure to check the strings to make sure the IUD is in place.

Effects on Pregnancy None of the current IUDs increase the risk for infertility. In the very unlikely event that a woman conceives with an IUD in place, however, there is a higher risk of an ectopic pregnancy or miscarriage. If the IUD is removed right after conception, the risk for miscarriage is close to average (about 20%). There is no evidence that the IUD in a pregnant woman increases the risk for birth defects in the infant[16].

There are two choices available today.



Fig, 3 IUD

The first, the Mirena IUD (Berlex Pharmaceuticals, Inc), is a plastic device embedded with the hormone, levonorgestrel. This particular IUD is designed to last 5 years (although it contains 7 years of hormone) but can be easily removed any time prior to that should a woman wish to conceive. The advantage of the Mirena IUD is that after 2 or 3 cycles women experience lighter and lighter periods—many women stop having periods altogether. The Mirena IUD is ideal for a woman who would like a spontaneous and safe method of contraception that is also seeking relief from otherwise heavy or painful menses and who wishes to avoid the inconvenience of a daily pill, a weekly patch or a monthly ring. Importantly, the Mirena contains no estrogen whatsoever What little progesterone is in the IUD (about 20 micrograms per day) is largely confined to the uterus and causes only minimal levels of the progestin, levonorgestrel, in the blood stream.

The second IUD available today ParaGard (Duramed Pharmaceuticals, Inc)—which is a device made of plastic and copper. This is a non-hormone containing IUD that can be left in place for 10 years. Intrauterine devices are among the safest methods of spontaneous contraception available to a woman who is in a mutually monogamous sexual relationship. The Mirena IUD has an added advantage inasmuch as it can be used to assist women who

suffer heavy and painful periods. Both IUDs are very cost-effective. Presently the most expensive IUD averages out to 5 – 7 dollars a month--compare that to birth control pills that can cost between 20 and 45 dollars a month[17, 18].

- **Formulation**

A contraceptive device containing a contraceptive gel for insertion into the vagina. The gel is made of natural ingredients and has a pH of approximately 2. The gel includes citric acid for providing the low pH; glycerine which acts as an emollient lubricant, and an emulsifier; aromatic malic acid, which acts as a stabilizer and an aromatic deodorant; kelco and/or wood celulose, which keeps the gel from liquifying at high temperatures; and distilled water.

The contraceptive device includes a delicate elongated inside sausage casing containing the gel, and having a closed insertion end that will open to release the gel when the inside casing is squeezed a lubricant covering the outside of the inside casing at the insertion end; a semi-sausage casing covering the lubricated insertion end of the inside casing for maintaining the lubricant in a lubricant state and at the insertion end, the semi-sausage casing having a closed end fitted over the lubricated insertion end of the inside casing and an open end fitted over the inside casing near the longitudinal mid-portion of the inside casing; and a tear strip having a first length removably attached to the open end of the semi-sausage casing and to the inside casing for hygienically sealing the lubricated insertion end of the inside casing and a second length attached to the semi-sausage casing to enable removal of the semi-sausage casing for exposing the lubricated insertion end of the inside sausage casing.

Implantable contraceptives

The only implant currently available is the non-biodegradable NorplantR implant. It consists of six Silastic capsules, each containing 36 mg of levonorgestrel and having a diameter of 2.4 mm and a length of 3.4 cm. These capsules are inserted subcutaneously in a fan-like manner in the upper arm. They release levonorgestrel at a rate of 80µg per 24h during the first 6-10 months of use. This rate declines to 30µg/24h over the next few months and is maintained at that level until the end of the five year life of the implant. This system is highly effective with a 5-year cumulative pregnancy rate of 3.9% during the first year of use, ovulations are suppressed in the majority of women; in subsequent years, about half of the women have ovulatory like cycles but contraceptive efficacy is maintained through cervical mucus thickening. Like other progestogen-only methods, it induces menstrual irregularities,

particularly during the first year. With prolonged use, the bleeding pattern improves, reflecting the return of ovulation. Other side-effects with this method include headaches, dizziness, nervousness or breast tenderness however, these occur mostly during the first year of use and are infrequent. Return to the previous level of fertility is prompt after removal of the implants. NorplantR is manufactured and distributed by the Leiras company and is currently registered in 26 countries world-wide[19].

A second-generation system, NorplantRII, is being developed. It consists of only two rods in which levonorgestrel is homogeneously dispersed within a Silastic matrix and covered by a layer of Silastic. It will also probably offer five-year contraceptive protection. Single implant systems are being developed, releasing a progestogen: 3-keto-desogestrel, over three year's nomegestrol acetate for one year over two years. These will have the advantage of being more easily inserted and removed than the current NorplantR system. Biodegradable systems are also being developed, which dissolve in the body and do not require removal. Capronor II consists of 2 rods of poly (e-caprolactone) each containing 18 mg of levonorgestrel. Capronor III is a single capsule of copolymer (caprolactone and trimethylenecarbonate) filled with 32 mg of levonorgestrel. It releases the drug and biodegrades more rapidly than Capronor II. With both systems, the implant remains intact during the first year of use, thus could be removed if needed. Over the second year, it biodegrades to carbon dioxide and water, which are absorbed by the body. Norethisterone pellets, made of 90% drug and 10% pure cholesterol, are also being developed as biodegradable systems.

Table 2 Implantable Devices

Progestin	Tradename	Units	Duration of action
Levonorgestrel	Norplant*	Six capsules	7 y
Levonorgestrel	Jadelle*	Two rods	5 y
Etonogestrel	Implanon	Single rod	3 y
levonorgestrel.	Capronor	Two rod	5 y

The Norplant implant method is an effective, long lasting, reversible contraceptive developed by the Population Council.

- **Norplant and Jadelle**

This system consists of One-rod system-*Implanon*®, The two rod system *Jadelle*®,,*Sino-Implant (II)*®, The six-capsule system implant *Norplant*®, Mechanism of action of implant is

thickening cervical mucus. This blocks sperm from meeting an egg. Disrupt the menstrual cycle, including preventing the release of eggs from the ovaries (Ovulation). Do not interrupt an existing pregnancy or interfere with implantation mostly ovulation inhibition, lutealphase abnormalities.

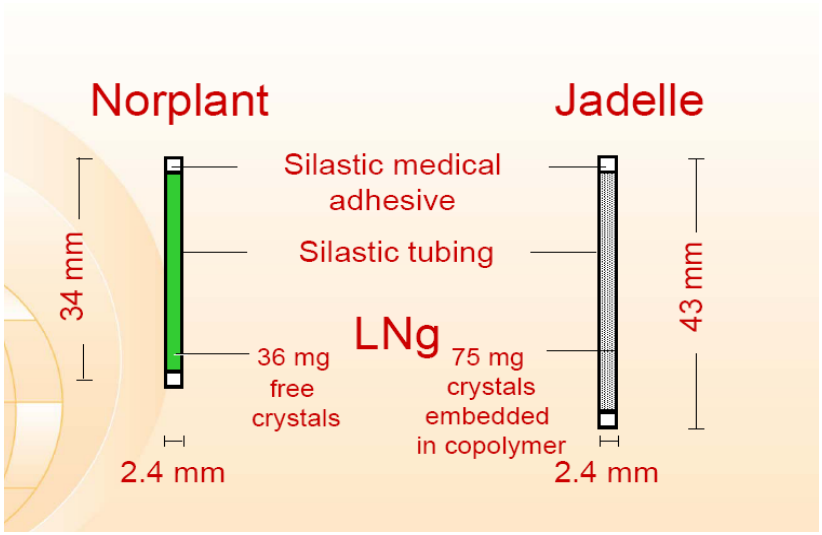


Fig. 4 Marketed products of Implants

The most frequently reported side effect with Norplant is change in the menstrual bleeding pattern. Irregularities may include prolonged bleeding during the first month of use, untimely bleeding or spotting between periods, no bleeding at all for several months or, for a few women, for a year or longer, or a combination of all these changes. Bleeding irregularities frequently diminish after several months, and menstruation often becomes regular. Irregular bleeding associated with Norplant could mask symptoms of cervical or uterine cancer. An annual Pap smear with a check up is recommended. Other side effects women have noted have been headache, nervousness, nausea, dizziness, acne, changes of appetite, weight gain, breast tenderness, skin rash, moodiness, excess hair growth, or hair loss. Occasionally an infection this document was prepared by the staff of the UWSP University Health Service. This information should not be used in lieu of medical care. The implants are comfortable

and barely visible under the skin. If seen at all, they look similar to veins but without colour. There may be a small scar at the insertion site. Many physicians and health plans advise a 2-3 month trial of an oral contraceptive containing levonorgestrel (e.g. Nordette, Ovrette) to help determine if Norplant will be tolerated.

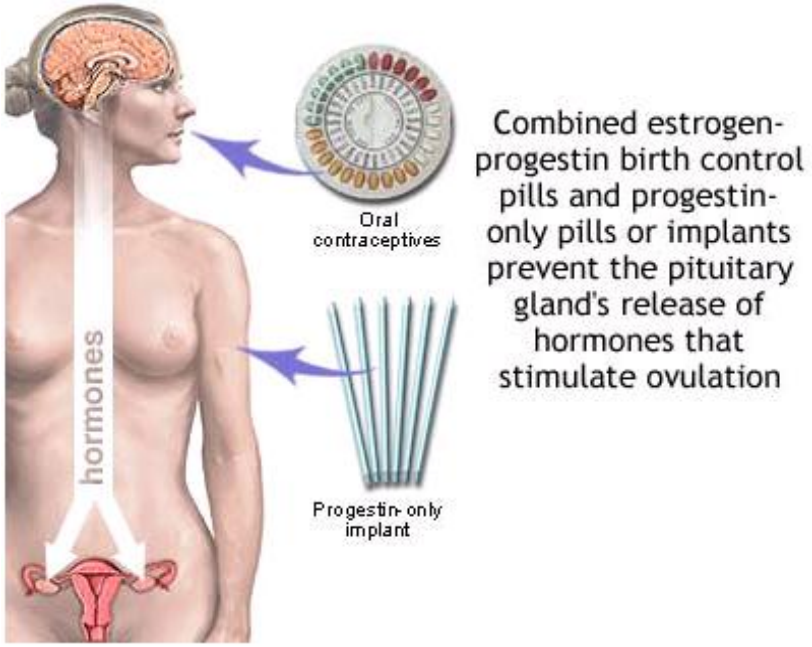


Fig. 5 Progestin implants

Implant contraception involves inserting a rod under the skin. The rod releases into the bloodstream tiny amounts of the hormone progestin.

The first implant was the Norplant system, which used six rods that contained levonorgestrel. Due in part to serious complications, Norplant was withdrawn from the U.S. market in 2002. The main complication was difficulty inserting and, in particular, removing the rods. (Many women experienced scarring.) In addition, some women who used Norplant experienced heavy irregular bleeding. A two-rod implant called Jadelle is sold in other countries, but not the United States[20].

In 2006, the Food and Drug Administration approved Implanon, a new implant contraceptive.

In contrast to Norplant:

❖Implanon uses one rod, not six.

❖It is not inserted as deeply into the skin.

❖It uses etonogestrel, a different type of progestin than the levonorgestrel used in Norplant.

❖Only specially trained health care providers are allowed to insert and remove Implanon.

Implanon insertion takes about a minute and is performed with a local anesthetic in a doctor's office. The rod remains in place for 3 years, although it can be removed at any time. (The removal procedure takes a few minutes longer than insertion.) After the rod is removed, a new one can be inserted. Studies indicate that Implanon is safe. Irregular bleeding and headaches are the main side effects. However, some doctors are concerned that Implanon may have some of the same risks as Norplant.

As currently formulated, levonorgestrel implants (Norplant) consist of six 34 x 2.4 mm soft plastic implants, each filled with 36 mg of crystalline levonorgestrel. Irregular and often persistent menstrual bleeding and spotting constitute the most important side effects experienced by and leading to method discontinuation in implant users. Implant removal is technically more difficult and time-consuming than insertion. Implant removal is technically more difficult and time-consuming than insertion[[16], 24]

- **Implanon**

It is EVA rod releasing etonogestrel more consistent ovulation inhibition.No pregnancies observed in years of exposure (women > 70kg were excluded)Vaginal bleeding patterns: 30-40% amenorrhea throughout 3 years, 30% infrequent bleeding 10-20% prolonged bleeding Its metabolic effect are Lipid effects: small or non

Transdermal systems

- **Patches**

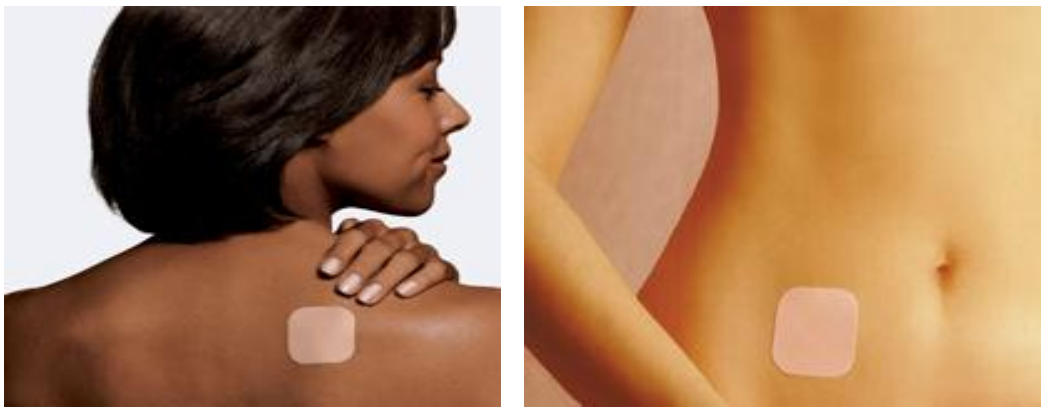


Fig. 5 Contraceptive Patch

The contraceptive transdermal patch was approved by the FDA in 2001 (Ortho Evra). The patch offers a different means of obtaining the hormones that are contained in birth control

pills. Its main advantage lies in the fact that it can be placed on the skin and requires only a weekly patch change. Each patch is equivalent to a week of oral contraceptives typically 3 patches are required per cycle. The patch allows for the release of approximately 20 microgram per day of ethinyl estradiol and 150 micrograms/day of norelgestromin or about the same as a low dose birth control pill. The side effects of the patch are similar to that of oral contraceptives. Any weight gain associated with the patch is minimal. Most women experience a decrease in menstrual flow and associated cramps while using the contraceptive patch. The contraceptive patch has been shown to be less effective in women who weigh more than 200 pounds. If you are approaching or have exceeded this weight you should consult your health care provider before relying on it.

Intradermal patch consist of 20 cm^2 (4.5 cm side), three-layered patch:

1) outer polyethelene+polyesterprotective layer
2) middle layer that contains an adhesive and the two contraceptive steroids
3) inner, clear polyester liner, peeled off before use

releasing 150 µg/day norelgestromin(active metabolite of norgestimate)+ 20 µg/day EE blood levels reach steady state in < 48 hours and are maintained over 7 days (+2 days as safety window). The transdermal patch (Ortho Evra) is another effective contraceptive option that is especially appealing to women who don't want to remember to take a pill every day, Dr. Cwiak said. Ortho-Evra (transdermal norelgestromin/ethinyl estradiol patch), is applied once weekly for three weeks; subsequently, withdrawal bleeding is anticipated during a patch-free week. In a randomized clinical trial, the contraceptive efficacy of the patch was comparable to that of oral contraception. Application site reactions, breast discomfort, and dysmenorrhea were each significantly more common in women treated with the patch. This may, in part, be explained by a significantly higher overall estrogen exposure[25] In a randomized, open-label pharmacokinetic study, mean area under the time versus concentration curve 0–24 hours for the patch was 1.6 times higher than reported for combination OC therapy containing 30 mcg ethinyl estradiol ($p < 0.05$). Although this observation led to the FDA adding a warning to the prescribing information for the contraceptive patch, available published epidemiologic data indicates that the risk of venous thromboembolism in users of the patch is similar to that in women using combination OCs.

5. Vaginal rings[25]

It had been recognized since 1918 that the vagina is a suitable site for the administration of drugs that will reach the systemic circulation but it was not until 1968 that a patent was issued to Dr Gordon Duncan of Upjohn Ltd., which describes a vaginal ring composed of a silicone polymer which could release a number of progestational steroids for contraceptive purposes.

A number of rings are being developed; the most advanced being the levonorgestrel-releasing vaginal ring. It consists of a core containing 5 mg of levonorgestrel which is molded and then enclosed by two half rings. The thickness of the outer layer of the Silastic determines the release rate, which has been set at 20µg/day. The ring has an outside diameter of 55.6 mm and a cross-section of 9.5 mm. This device is placed in the vagina and worn continuously for 90 days, at which time it is replaced with a new one. Its effectiveness is due to a combination of effects on the cervical mucus, the endometrium and the ovarian function. Clinical trials (13-16) have shown that it is not quite as effective as the combined oral contraceptives, but is more effective than the progestogen-only pills. Approximately half of the users experience an irregular bleeding pattern, but the total menstrual blood loss is reduced compared to pre-treatment values.

This form of contraception offers a number of specific advantages:

1.The ring can be inserted, removed and replaced by the woman herself without the need for medical or paramedical personnel.

2.The fact that it is in situ can be easily checked by the user herself—this is not always the case with an IUD.

3.The ring provides a constant release rate of drug which results in steady plasma levels.

4.Important in the case of accidental pregnancy, plasma levels fall rapidly to zero following removal of the ring.

5.The use of the ring is not coitally-related.

A number of other progestogen-only rings are being developed, which release: levonorgestrel, megestrol acetate, progesterone.

Other rings have been designed to deliver two hormones, a progestogen and an estrogen. They are inserted for three weeks, then removed for one week and can be used for a total of six months. A withdrawal bleeding episode occurs during the week when the ring is not used,

thereby giving a regular bleeding pattern. The devices currently being tested release: norethisterone acetate/ethinyl estradiol ethinyl estradiol; or 3-keto-desogestrel/ethinyl estradiol.

Fig. 6 Contraceptive Ring

The NuvaRing is the only contraceptive ring approved by the FDA (2001). It is a two inch diameter ring that is worn in the vagina for 3 weeks. The ring contains a combination of hormones similar to what is found in oral contraceptives or patches. The ring releases ethinyl estradiol 0.015 mg/day and etonogestrel 0.12 mg/day. Its advantage is that one ring lasts 3 weeks and is then removed for one week before inserting another one. The menstrual period will usually occur during the week when the ring isn't being worn.

- **Nuvaring**

It consist of releasing estrogen + progestogen (3 weeks in/1 week out)

- **Progering**

Relesing progesterone (continuous over 3 months)

Carbohydrate metabolism: mild insulin resistance in some users Clotting and fibrinolyticsystems: minor changes. Liver function: elevated bilirubin in some women, within normal range.

CONCLUSION

Long-acting hormonal methods of contraception offer new perspectives to women for the control of their fertility. They facilitate compliance and ensure prolonged contraceptive protection. New systems allow the delivery of the minimum dose required for effectiveness and thereby reduce the level of unwanted side-effects. Injectable contraceptives are a significant and growing share of worldwide contraceptive use. They offer many positive

attributes, including a high measure of safety, high method effectiveness, the chance to avoid a daily pill, no interruption of coitus, different options for the length of effectiveness, and the chance for a woman to contracept without knowledge of her partner or family. An injectable mode of delivery for contraception has proven appeal for many women. Continuing research efforts to ensure the safety of available methods is very much warranted, particularly regarding the impact of progestogen-only methods on the risk of vaginal HIV transmission, and the long-term integrity of bone. Continuing research efforts to develop new, long-acting injectable contraceptives is to be encouraged if new products will offer measurable reductions in unwanted side-effects associated with current methods, particularly the disturbances to menstrual bleeding, and the delayed return of fertility.

REFERENCES

1. Josue GF, Peter E. Hall and Gregorio Perez-Palacios J. of Steroid Biochemistry and Molecular Biology, 1991; 40(4-6): 697-704.
2. Moskowitz EH. Moral and policy issues in long-acting contraception, Annual Review of Public Health, 1997; 18: 379-400
3. Arcangues C. d Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland.
4. Beck LR, Cowsar DR, Pope VZ. Long acting steroidal contraeptive system, 1980; 1(1):1-16.
5. Jacobstein R, MPH, MD. Long-Acting and Permanent Contraception:An International Development, Service Delivery Perspective, J Midwifery Womens Health. 2007; 52(4): 361-367.
6. Cong H. and L. R. Beck. Preparation and pharmacokinetic evaluation of modified long acting injectable norethisterone microspheres, Adv. in Contracep. Publisher Springer Netherlands, 1991; 7: 251-256.
7. Beck LR, Pope VZ, Tice TR, Gilley RM. Long-acting injectable microsphere formulation for the parenteral administration of levonorgestrel. Adv Contracept, 1985;1(2):119-29
8. Kaunitz AM. Long-acting contraceptive options, Int J Fertil Menopausal Studies,1996; 41(2): 69-76.
9. WHO Special Programme of Research, Development and Research Training in Human Reproduction. Task Force on Long-acting Systemic Agents for Fertility Regulation: Contraception. Geneva Foundation for Medical Education and Research, 1986; 34: 2[16]-[16]5.

10. WHO Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation, 1987; 35:591-610.
11. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives 1991: Lancet, 338:833-838.
12. d'Arcangues C, Snow R. Injectable contraceptives. In: Rabe T, Runnebaum B, eds. Fertility Control - Update and Trends. Berlin: Springer-Verlag, 1999; 121-149.
13. World Health Organization, Family and Reproductive Health (2000) Improving access to quality care in family planning. Medical eligibility criteria for contraceptive use. Second edition [Doc. WHO/RHR/00.02].
14. World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation (1996) Human Reproduction 11 [suppl 2]:1-13
15. Zhou XF, Shao QX, Han XJ, Weng LJ, Sang GW. Pharmacokinetics of medroxyprogesterone acetate after single and multiple injection of Cyclofem in Chinese women. Contraception, 1998; 57(6): 405-11
16. Blythe MJ and Diaz A. Contraception and adolescents, American Academy of Pediatrics Committee on Adolescence, 2007; 120(5): 1135-48.
17. Cheng L, Gulmezoglu AM, Piaggio G, Ezcurra E and Van Look PF. Interventions for emergency contraception. Cochrane Database Syst Rev: 2008, 16(2): CD001324.
18. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstet Gynecol, 2007; 109(2 Pt 1): 339-46.
19. Cauley M, Gellar JS, Long acting hormonal contraceptive methods for women (1992): Popul.Rep, 4:1-31.
20. Bruce, J. Fundamental elements of the quality of a simple framework. Studies in Family Planning, 1990; 21(2): 61-91.
21. Blythe MJ and Diaz A. Contraception and adolescents, American Academy of Pediatrics Committee on Adolescence, 2007; 104 (5): 1161
22. Cheng L, Gulmezoglu AM, Piaggio G, Ezcurra E and Van Look PF. Interventions for emergency contraception. Cochrane Database System Rev, 2008; (2): 1-148.
23. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstet Gynecol, 2007; 109(2): 339-46.

24. Tolaymat LL, Kaunitz AM. Long-acting contraceptives in adolescents. Curr Opin Obstet Gynecol. 2007; 19(5): 453-60.
25. Zheng SR, ZhengHM, Qian SZ, Sang GW, and Kaper RF. Contraceptive failure in the United States. European Journal of Contraception and Reproductive Health Care, 1999; 4(2): 85-93.