Reproduction Biology

Control of Fertility and Sterility in Female

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SUMMARY

Fertility is ability to reproduce or the physiological capacity to produce children. The explosion of information on hormonal regulation of reproductive processes in human have been applied to development of methods for ovulatory induction, avoidance of conception, treatment of infertility, increasing production of farm animals and promoting fertility of rare species. The fertility in female may be controlled artificially by three ways: (a) Sterilization; (b) Medical termination of pregnancy; and (c) Contraception. Female sterilization provides permanent method of birth control. It is a safe and simple surgical procedure. Medical termination of pregnancy is a legitimate choice for couples or women with certain conditions (such as rape, mental or physical stress or disorder) or with abnormal findings (such as a malformed or genetically diseased fetus or a placental tumor). Hormonal methods of contraception inhibit ovulation and bring about other changes in a women's reproductive system. After 30 years of use, the pill is one of the best understood methods of contraception and for nearly all women the benefits of its use outweigh the risks by a wide margin. Continued research is needed for development of newer and safe methods for control of human contraception. Infertility is the state of a diminished capacity to conceive and bear offspring. Infertility is not an irreversible state. In females, the reproductive abnormalities that are commonly found include ovulatory disorders, tubal defects, endometriosis, and unexplained infertility. Assisted reproduction through *in vitro* fertilization offers the highest fecundability across a wide spectrum of reproductive tract disease.

INRODUCTION

Fertility is the physiological capacity to produce children. In other words, fertility is the ability to reproduce or it is a measure of actual outcome of the reproductive process. Both man and woman contribute to bring an offspring to life through a highly specialized physiological event, the reproductive process. Fertility is not always an absolute condition; it may vary between zero and 100% depending upon conditions. Not every mating or insemination results in a pregnancy and offspring.

Fecundability is defined as the probability of conceiving in a menstrual cycle in a woman who has regular periods and engaged in regular unprotected intercourse, whether or not conception goes to term. Fecundity is a measure of the capacity to conceive and produce a live birth under the same circumstances. Both, fecundability and fecundity are therefore measure of reproductive potential of woman. Fecundity is limited by fertility in an absolute sense when only one offspring is produced for each pregnancy as is the usual case for humans, cows, and horse. In this case, fecundity is limited to fertility. When more than one offspring is born in a litter, such as in pigs, rabbit, and mice, fecundity is affected by the number of young in the litter and their survival.

In females, puberty and menopause mark the limits of the period of fertility. However, within this period, most women are continuously reproducing. Traditionally, many factors have limited their fertility; namely social or religious practices, pathology (infertility and subfertility), and the use of contraception and abortion. These factors will be considered in this chapter. The human race has come under scrutiny and criticism for its population growth. We need to be able to understand and deal with both the desirable and undesirable aspects of fertility and fecundity. The advent of assisted reproductive technologies (ART) has changed the ways that fertility can be achieved. Barriers to fertility can now be overcome by a variety of assisted reproductive techniques.

REPRODUCTIVE CAPACITY OR FERTILITY:-

To complete the process of conception, mature oocytes of the female must be released out the ovarian follicle at ovulation, move down the oviduct, unite with the sperm, be fertilized, and then move down to the uterus and implant. Any obstacle to this passage down the oviduct as a result of disease, surgery, or failure to develop embryologically will impede fertility. Any impediment to movement of the sperm through male reproductive system and then to the site of fertilization in the upper oviduct will also prevent fertility. Many of these obstacles can now be overcome by recovering the oocytes directly from the ovarian follicle and fertilizing them *in vitro* and transferring the fertilized embryo back into the uterus, thus bypassing the obstacle. Sperm can be recovered from various segments of the male reproductive tract and used to fertilize oocyte *in vitro*, obviating the need to traverse the males and the females both in whole length of the reproductive tracts. Fertility can be achieved to the extent that an individual sperm can be injected directly into the mature oocyte by a technique known as Intra Cytoplasmic Sperm Injection or ICSI, eliminating the physiological need to pass through the male and female reproductive tract and the zona pellucida.

The fertility of a woman varies with her age. Menstrual cycles begin during puberty, and menarche marks the earliest expression of the potential fertility of the female with its implication that a full ovarian and uterine cycle has been achieved. Failure of menarche indicates a diagnosis of primary amenorrhea. This may result from a failure of normal maturation of the underlying neuro-endocrine mechanisms, such as primary gonadal defects,

or from defects in the genital tract, or, the absence of internal genitalia. However, even in normal females, early menstrual cycles are rarely regular. Some cycles are anovulatory, and may lack, or have short luteal phases. In general, the follicular phase tends to become shorter with age and the luteal phase tends to lengthen, for reasons that are unclear. Hormone production and reproductive tract morphology change with age, as does the fertility level.

Fertility is highest in women in their twenties and declines thereafter. This decline could be due to a reduction in fecundity or changes in sexual behaviour. The abilities to sustain a pregnancy through to successful parturition declines slowly to age 35 years and more rapidly thereafter when an increasing frequency of failed ovulation, perinatal or neonatal mortality, low birth weights, maternal hypertension, and congenital malformations are encountered. Accordingly, it is not surprising that irregular menstrual cycles may begin to reappear in some women in their early forties and mark the onset of the climacteric, a period of reproductive change that may last for up to 10 years before the last menstrual cycle (the menopause). This secondary amenorrhea occurs at a mean age of 52 years in the USA. Symptoms associated with the climacteric onset can include mood changes, irritability, loss of libido and hot flushes. The final cessation of reproductive life is the menopause. However, premature loss of oocytes, and premature menopause, occurs in about 2% of women, in some as early as their late teens and early twenties.

In most cases, natural mating results in optimum fertility. When sperm are collected, cooled, stored, extended in selected media, frozen or in other ways handled, the fertility is usually less than when large numbers of sperm are deposited naturally. Extending the semen almost universally means the concentration of sperm is also reduced. Fertility of semen declines with storage period. The chemical makeup of the extender can influence the effectiveness of the extender; thus, there is an ongoing search for combinations of components that will best preserve the fertilizing ability of stored sperm. Sperm of bulls are now most often stored in a frozen state and there is a continuous attempt to device procedures that will preserve fertilizing ability of sperm of many species both domestic and wild. Removing embryos from the mother and transferring them, freezing and storing them, and otherwise manipulating them reduce their chances of survival. Gamete and embryo manipulation can be a solution to an otherwise infertile condition. Sperm can be recovered from the male, oocytes can be recovered from the female, and fertilization can occur outside the body, and the embryo can be transferred back into uterus of a female and fertility is restored. Assisted reproductive technology (ART) has made it possible for infertile couples to produce young under a wide variety of conditions.

CONTROL OF FERTILITY:-

The socially accepted artificial controls over fertility available to varying extents in different societies are *sterilization*, *medical termination of pregnancy* and *contraception*. Not all of these methods are 100% effective and, thus, they should be seen as interventions for delaying births or increasing the interval between births.

A. STERILIZATION

Female sterilization provides permanent method of birth control for couples who have completed their families or wish to have no children. It is a safe and simple surgical procedure. It can usually be done with just local anesthesia and light sedation. Female sterilization is also known as voluntary surgical contraception, tubal ligation, tying the tubes, minilap, and the operation. In women, sterilization involves ligation, blocking of the fallopian tube (electrocoagulation) or removal of both end of fallopian tubes (salpingectomy) or a section of the oviduct (fimbriectomy). A general anesthesia is usually required, although

regional anesthesia can be used. The two common approaches are non-laparoscopies and laparoscopies.

Non-laparoscopic method:-

The tubes may be approached by conventional laparotomy, minilaparotomy, and colpotomy (an incision made tranvaginally at the top of the vagina between the cervix of the uterus and the rectosigmoid colon). Gynecologists are reluctant to perform a conventional laparotomy solely for tubal ligation except during another gynecologic or surgical procedure. In the immediate post partum period, the uterus is enlarged up to the level of the umbilicus requiring only 1 or 2 cm incision, which heals quickly leaving only a small scar. Several non-laparoscopic methods are used from time to time. Irving in 1924 described a method used exclusively for sterilization. Sterilization failure has not been described but the heavy bleeding may occur during the procedure. It is seldom used now. Pomeroy techniques are the other most widely used method for cesarean section patients or immediate postpartum sterilization. Kroener technique is also called a fimbriectomy, the removal of the end of the fallopian tube. This technique was meant to be used during colpotomy. The serious nature of complications encountered after vaginal tubal sterilization prohibit this procedure as a quick and effective means of performing female sterilization. Though, Uchida technique from Japan claims a zero failure rate.

Laparoscopic method:-

Anderson performed the first laparoscopic tubal occlusion in 1947, but this method became most popular in 1969. Laparoscopy offers the following advantages over non-laparoscopic techniques: 1. Small incisions whose scars are barely visible; 2. Same day surgery; 3. No vaginal drainage; 4. No sexual restriction; and Lower cost, etc. The disadvantages of laparoscopic sterilization are few. When compared to non-laparoscopic techniques, laparoscopy requires more training. It is more expensive.

How effective is Sterilization?

It is very effective and permanent. In the first year after the sterilization, failure rate was 0.5 pregnancies per 100 women (fails in 1 in every 200 women undergoing sterilization). Within 10 years after the sterilization, it comes about 1.8 pregnancies per 100 women. Postpartum tubal ligation is one of the most effective female sterilization techniques.

Advantages of Sterilization:

1. A single procedure leads to life-long, safe, and very effective family planning.
2. This procedure requires nothing to remember, no supplies, and no repeated clinic visits.
3. It neither interferes with sex nor affects a woman's ability to have sex. No worry about pregnancy.
4. It has no effect on breast milk.
5. No known long-term side effects or health risk. It helps to protect against ovarian cancer.

Disadvantages of Sterilization:

1. It causes irreversible sterility.
2. Usually painful for several days after the sterilization.

3. Complications of surgery, such as infection or bleeding at incision; infection or bleeding of internal organs, is possible during sterilization.
4. Risk associated with the anesthesia, such as risks of allergic reaction or overdose with local anesthesia and delayed recovery and side effects with general anesthesia, are possible during sterilization.
5. In rare cases when pregnancy occurs, it is more likely to be ectopic.
6. Requires physical examination and minor surgery by a specially trained surgeon.
7. Compared with vasectomy, female sterilization is slightly more risky and often more expensive.
8. It provides no protection against sexually transmitted diseases (STD) including HIV/AIDS.

When can a woman undergo sterilization?

A woman can have a sterilization procedure almost any time when:

1. She decides that she will never want any more children.

2. It is reasonably certain that she is not pregnant.

3. Immediately, after the child birth or abortion, but not between 7th day and 6th week post-partum.

Sterilization Failure:

Unfortunately for patient and physician, sterilization failures occur. Each technique has inherent problems. Of the laparoscopic procedures described, unipolar electrocoagulation without transaction has the lowest failure rate.

Reversal of Sterilization:

The three most common motivating factors for reversal of sterilization are: divorce, death, and disaster. Other factors include changes in life style and economic status that may suddenly permit a couple to have a larger family. The end results of some methods of sterilization are frequently irreversible. For example, a unipolar coagulation may destroy the whole tube, leaving barely a few fimbrias behind. The Kroener technique can remove the fimbria and the entire ampulla. Conversely, if only the fimbria was excised, a complete ampulla may remain, permitting an adequate salpingoneostomy. A bipolar burn or Falope ring ligation can often be reversed by isthmic-ampullary anastomosis. This type of reversal, however, is more difficult than the isthmic-isthmic anastomosis performed in most cases of clip reversal. In short, no method is 100% reversible. The clip method using microsurgical techniques approach nearly 90% success. Other approaches have less success but are sufficient for some patients who request reversal, with a few accepting a success rate of only 10%.

B. MEDICAL TERMINATION OF PREGNANCY

Medical termination of pregnancy or induced abortion is a legitimate choice for couple or women faced with an unwanted pregnancy (such as rape, disorder, malformed, genetically diseased or a placental tumor). It is also one of approach to fertility control. In countries where contraception is prohibited on religious grounds, abortion provides a major artificial control of fertility in South America, Islamic countries, Japan and Spain.

Medical termination of pregnancy is usually performed within first trimester (or 3 months) either by dilating the cervix and scrapping out the conceptus or by uses of vacuum aspiration.

The latter approach is particularly useful in the first month of conception. The failure rate using these approaches is low (1-1.5%) and complications, such as major blood loss, incomplete aspiration or damage to the cervix or uterus, are about 2-3%. The side effects of post operative infection and damage to the uterus or cervix may affect subsequent fertility.

The possibility of conducting totally medical out-patient abortions without the need for surgery under aseptic conditions has been realized with the development of orally active anti-progestins (such as mifepristone or RU 486), which compete for progesterone receptors. They are more than 98% effective if combined with a low dose of orally active prostaglandin (misoprostol) given 36-48 hours later. Treatments are usually given within 7 weeks after the onset of the last menses. However, side effects include nausea, vomiting and abdominal pain.

C. CONTRACEPTION

Contraception is defined as the temporary prevention of fertility. Contraceptives are devices that diminish the likelihood of conception. All contraceptive methods have a failure rate. Each of the various methods of contraception currently available has certain advantages and disadvantages. Therefore, when giving advice about contraception, the clinician should explain to the couple the advantages and disadvantages of each method so that they will be truly informed and can rationally choose the method most suitable to them.

Among all reversible method of contraception, Oral Contraceptives (OC's) or Birth control pills (also known as "the Pill"), are most popular and are used by about 26% of all women in USA. Intra-uterine device (IUD) and progestin implants are two other most effective devices. Other commonly used contraceptive methods are condom, withdrawal, periodic absentinence, diaphragm, and spermicides. IUDs have low failure rates but occasionally cause serious side affects. Vaginal barriers have moderate failure rates and have no systemic effects, although they can be responsible for temporary and local problems. Some vaginal barriers offer protection against sexually transmitted diseases and HIV infection. Details of commonly used contraceptive methods are described under following head:

1. Natural Method
2. Barrier Method
3. Hormonal Contraceptives
4. Intra-Uterine Contraceptive Devices

1. Natural Method:

The Natural method is based on the strategy of avoiding unprotected vaginal intercourse during the unsafe or fertile time of the menstrual cycle. The unsafe or fertile times are the days of the menstrual cycle when woman can become pregnant. Ovulation occurs at approximately mid-cycle. The potential life of spermatozoa in the female genital tract ranges 3 to 4 days and ova or egg survives for about 12 to 24 hours. A woman can use this information together with following ways to determine her unsafe or fertile time: a. Calendar or rhythm method; b. Cervical secretion; c. Basal body temperature.

a. **Calendar or Rhythm Method:** A woman can count calendar days to identify the start and end of the fertile time. Before relying on this method, the woman records the number of days in each menstrual cycle for at least 6 months. The first day of menstrual bleeding is always counted as day 1. The woman subtracts 18 from the length of her shortest recorded cycle. This tells her the estimated first day of her fertile time. Then, subtract 11 days from the length of her longest recorded cycle. This tells her the last day of her fertile time. The couple may avoid conception, using a barrier or withdrawal method during the fertile time.

Example: If her recorded cycles vary from 26 to 32 days: 26-18=8; 32-11=21. So, between day 8th to 21st of the menstrual cycle are unsafe or the fertile period. The woman can have unprotected sex before day 8 and after day 21 of the menstrual cycle.

b. **Cervical secretion:** A woman checks her cervical secretion everyday. She may feel wetness at the opening of her vagina or see secretions on her finger, underpants or tissue paper. The secretions have a peak day, when they are most slippery, stretchy, and wet. When a woman sees or feels cervical secretions, she may be fertile. The couple should avoid sex or use protected sex until the 4th day after the peak day.

c. Basal body temperature: A woman's resting body temperature goes up slightly around the time of ovulation (release of an egg), when she could become pregnant. The woman must take her body's temperature in the same way at the same time each morning before gets out of bed. The woman's temperature rises 0.2^0 to 0.5^0c (0.4^0 to 1.0^0F) around the time of ovulation.

Woman should identify unsafe or fertile and safe or infertile days by combining basal body temperature and cervical secretion observations together with calendar or rhythm method and often, other signs and symptoms of ovulation.

How effective is Natural method?

Natural methods are effective or very effective, when used consistently and correctly. When single – indicator method is used consistently- 3 pregnancies per 100 woman in first year of use occurs in cervical secretion, 1 pregnancies per 100 woman in first year of use in basal body temperature and 9 pregnancies per woman in first year in calendar method. All the three method together showed 2 pregnancies per 100 women per year.

Advantages:

1. Once learned, can be used to avoid pregnancy or to become pregnant, according to the couple's wishes.
2. No physical side effects.
3. Very little or no cost.
4. Effective if used correctly and consistently.
5. Immediately reversible.
6. No effect on breastfeeding or breast milk. No hormonal side effects.
7. Involves men in family planning.
8. Educates people about woman's fertility cycles.

Disadvantages:

1. Usually somewhat effective.
2. Takes up to 2 or 3 cycles to learn how to identify fertile time accurately using cervical secretions and BBT. Less time to learn the calendar method, although it is best if a woman has records of the last 6 to 12 cycles to identify the fertile time.
3. If using periodic abstinence, requires long periods without vaginal intercourse-8 to 16 days each menstrual cycle. Abstinence may be difficult for some couples.
4. Will not work without continuing cooperation and commitment of both the woman and the man.

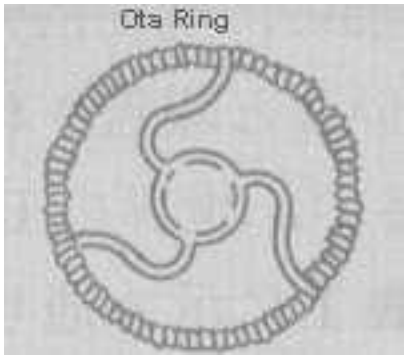
5. Can become unreliable or hard to use if the woman has fever, has a vaginal infection, or breastfeeding, or has any other condition that changes body temperature, cervical mucus, or menstrual cycle length.
6. After childbirth, may be hard to identify the fertile time until menstrual cycle becomes regular again.
7. Calendar method may not be effective for woman with irregular menstrual cycles.
8. Most methods require woman or couples to keep careful daily records and pay close attention to the body changes.
9. Does not protect against sexually transmitted diseases (STDs) including HIV/AIDS.

2. Barrier Method

The Diaphragm, Cervical cap and Female Condom are some of the common barrier techniques. A diaphragm must be carefully fitted by the health care provider. The diaphragm should be used with spermicide. Diaphragm users should also be cautioned not to leave the device for more than 24 hours, because ulceration of the vaginal epithelium may occur with prolonged usage.

The Cervical Cap, a cup-shaped plastic or rubber device that fits around the cervix, has been used as a barrier contraceptive for decades, mainly in Britain and other parts of Europe. There has been recent resurgence of interest in the use of this. The cervical cap can be left in place longer than the diaphragm. Failure rate with the cap is similar to that of the diaphragm.

Female Condom consists of a soft, loose-fitting sheath and two flexible polyurethane rings. One ring lies inside the vagina at the closed end of the sheath and serves as an insertion mechanism and internal anchor. The outer ring forms the external edge of the device and remains outside the vagina. It is intended for one-time use only. No data exist in which the effectiveness of the female condom for reducing sexually transmitted disease is analyzed. Female condoms work in a similar way as the male condom in preventing the passage of sperm. The failure rate is a little higher than 21%. Because female condom covers the external genitalia, it offers greater protection against STDs, but not as effectively as the male condom.



Spermicides: Foams, and Creams –

All spermicidal agents, including foaming tablets or suppositories, melting suppositories, foam, melting film, jelly and cream, contain a surfactant, usually nonoxynol 9 that immobilizes or kills sperm or make sperm unable to move towards egg on contact. They also provide a mechanical barrier and need to be placed into the vagina before each coital act. The effectiveness of these agents increases with increasing age of the woman.

Advantages: It is safe method that almost every woman can use. It has following advantages: Help to prevent some STDs and conditions caused by STDs; May offer some protection against HIV/AIDS; No daily action needed; It offers contraception just when needed; No hormonal side effects; Can be stopped at any time; Easy to use with little practice; May increase vaginal lubrication; and Can be used immediately after childbirth.

Disadvantages: Spermicides may cause irritation to woman or her partner, especially if used several times a day. It may cause local allergic reaction and can make urinary tract infections more common. Interrupt sex if not inserted beforehand.

3. Hormonal Contraception:

Hormonal method of contraception inhibits ovulation and brings about other changes in a woman's reproductive system that prevents pregnancy. The introduction of the pill revolutionized family planning because use of the pill does not interfere with sexual intercourse. Some of the effects of pills are unrelated to contraception; some are harmful, such as changes in the cardiovascular system, whereas others are beneficial, such as marked reduction in the incidence of some important female concerns. After 30 years of use, the pill is one of the best studied drugs and for nearly most women the benefits of use outweigh the risks by a wide margin.

Hormonal contraceptives can be divided into: i. Oral Contraceptives; ii Implants, iii. Injectable Contraceptives; and iv. Emergency Contraceptives.

i. Oral Contraceptives:

Oral contraceptives (OCs) are commonly of two types: (a). Combined OCs; and (b). Progesterone only pills (Mini pill)

a. Combined Oral Contraceptives (COCs):

The combination formulations are the most widely used and most effective. They consist of tablets containing both an Estrogen (E_2) and progesterone (P_4) given continuously for 3 weeks (20 days). The treatment is stopped for 1 week (5-7 days). The OC's promotes breakthrough bleeding. Withdrawal bleeding usually occurs in the week when no steroid is ingested. It lasts 3 to 4 days and uterine blood loss is relatively less than during menses in normal ovulatory cycle. COC's with more than 50 µg of E_2 were associated with greater incidence of adverse effects without greater efficacy; they are no longer marketed for contraceptive use in the USA, Canada, and UK. The present day COCs contain very low doses (about 20-30 ug of Estradiol) of hormone. They are called low dose COCs (second generation pill).

All currently marketed formulations are made from synthetic steroids and contain no natural estrogens or progestins (**Table 1**). There are two major types of synthetic progestins: 19-nortestosterone derivatives and 17 α-acetoxyprogesterone derivatives. Medroxyprogesterone acetate and megestrol acetate are C_{21} progestins. The 19-nortestosterone progestins used in OC's are of two major types, called estranes and gonanes. The various estranqes used in OCs are norethynodrel, norethindrone acetate and ethynodiol diacetate. The parent compound of the gonanes is dl-norgestrel, which consists of two isomers, dextro and levo. The levo form is biologically active. The progestins are combined with varying dosages of two estrogens, ethinyl estradiol and ethinyl estradiol 3-methyl ether, also known as mestranol **(Fig. 1).**

Fig- 1: Chemical formula of estrogen and progestin used in cotraceptive pills.

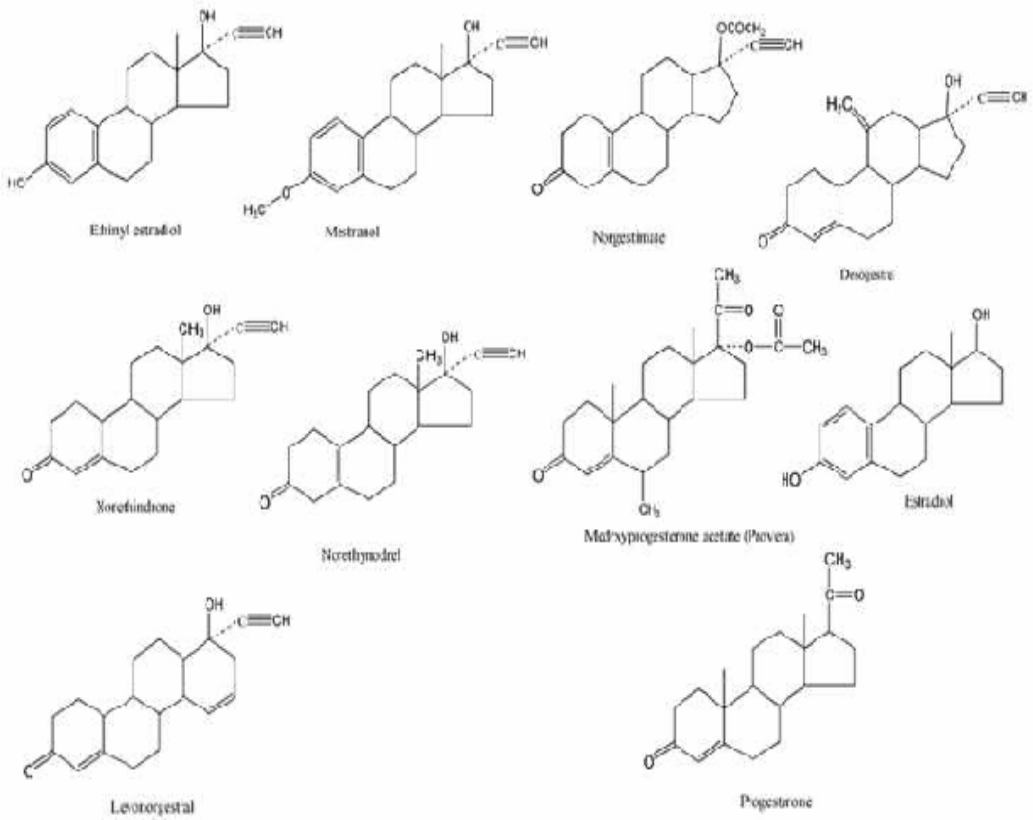


Table 1: Composition of several commercially available oral contraceptives

Trade name	Progestogen	Estrogen
Enovid	Norethynodrel	Mestranol
Norinyl, orthonovum	Norethindrone	Mestranol
Metrulin,ovulen	Ethynodiol diacetate	Mestranol
Lormin	Chlormadinone	Mestranol
Delpregnin	Megestrol acetate	Mestranol
Provest, farlutal	Medroxyprogesterone acetate	Ethinyl estradiol
Norlestrin	Norethindrone acetate	Ethinyl estradiol

Mode of action of COCs: It prevents conception by several mechanisms.

The primary effect: The COCs prevent ovulation by inhibiting gonadotrophin surge (negative feedback) via an effect on both pituitary and hypothalamic centers.

Secondary effects: The secondary mechanism prevents pregnancy in case ovulation occurs. This occurs by several mechanisms e.g. by preventing sperm transport by altering cervical mucus, preventing fertilization by altering of ova transport through oviduct, affecting endometrial implantation and preventing sperm capacitation.

Advantages and Disadvantages of COCs:

Advantages:

1. It is very cheaper method and easy to use.
2. There are 65 million users of the pill. It is very effective (99.9%) when used correctly.
3. No need to do any thing at time of sexual intercourse. Does not affect sexual activity. No interference.
4. Monthly periods are regular. Lighter monthly bleeding at fewer. Combined oral contraceptive users have fewer menstrual disorders than the control subjects.
5. Can be used as long as a woman wants to prevent pregnancy. No rest period needed.
6. Can be used at any age from adolescent to menopause.
7. User can stop taking pills at any time. Fertility returns soon after stopping.
8. Help to prevent: (a). ectopic pregnancy; (b). ovarian cysts; (c). endometrial cancer; (d). pelvic inflammatory disease; (e). ovarian cancer; and (f). benign breast disease- estrogen exerts a proliferative effect on breast tissue through its receptor. Progesterone may inhibit the synthesis of estrogen- receptors in this organ. COCs reduce the incidence of benign breast disease.
9. COC users have not been shown to inhibit the action of other drugs.
10. Benefits of COCs result from their main action- inhibition of ovulation. Some disorders, such as dysmenorrhea (painful menstruation) and premenstrual tension, occur more frequently in ovulatory than in anovulatory cycles.
11. Use of COC resulted in about a 50% reduction in functional ovarian cysts.
12. The risk of development of rheumatoid arthritis in COC users was only about half that in control subject.
13. Limited epidemiologic data indicate that COCs may reduce bone loss in premenstrual women.
14. COCs also offers significant improvement in endometriosis.

Disadvantages:

1. Symptoms of pseudopregnancy: It causes many side effects: such as vomiting, dizziness, nausea, headache especially if a woman forgets to take her pills. Mild headaches, breast tenderness; these symptoms found in early users and disappear later, except in few it may persists which may need discontinuous with COCs.
2. Symptoms related to the menstrual cycle: In some, spotting or breakthrough bleeding occurs in the middle of the cycle. In other it may cause amenorrhea.

3. Not highly effective unless taken every day. Difficult for some women to remember everyday.
4. New packets of pills must be at hand every 28 days.
5. Not recommended for breast feeding women because they affect quality and quantity of milk.
6. Blood clots in deep veins of the legs or heart attack. Those at higher risk are women with high BP and women who are age 35 or older and at the same time smoke more than 20 cigarettes per day.
7. Do not protect against sexually transmitted diseases (STDs) including AIDS.
8. Body weight: Some women gain weight, but the majority show no change. The increase has a variety of different causes. In some cases it is a simple result of increased appetite and food intake. Other women may show mild fluid retention, due to the estrogenic component. Finally, there is evidence that some COCs have an anabolic effect, so that muscle mass increases.

Effectiveness of COCs:

1. Commonly or typical uses is associated with 3-6% failure rate during the first year of use.
2. Very effective when used correctly and consistently- 0.1 pregnancies per 10 women in the first year of use (1 in every 1000).
3. Efficacy decreases significantly when estrogen component is removed.
4. Many women may not take pills correctly.
5. The most common mistake is to forget to take the pill, starting new packets late, and running out of pills.

b. The Progestin Only Pill or Mini Pill:

Administration of small dose (500 ug) of progesterone to women results in pregnancy failure. Thus, the mini pill was designed containing a small dose of a progestational agent and must be taken daily in a continuous fashion (day 5-25). Mini pill contained one half to one third as much progestin as combined OCs. They do not contain estrogen. The mini-pills are also called as progestin-only pills. The dose level of progesterone appears to be fairly critical. It must be sufficiently high to have an adequate antifertility effect but low enough to avoid a high incidence of irregular bleeding (**Table 2**).

Table 2: Composition of commercially available mini pills (Progesterone only pills)

S.No.	Trade Name	Name and dose of hormone
1.	Micronor, NOR-QD, Norod	0.350mg Norethindrone
2.	Microval, Noregeston, Microlut	0.030mg Levonorgestrel
3.	Ovrette, Neogest	0.075mg Norgestrel
4.	Exluton	0.500mg Lynestrenol
5.	Femulen	0.500mg Ethynodiol diacetate

Mechanism of action:

Progesterone only pills have complex effect that relates to the dosage of progesterone. Its major actions are:

1. Suppresses gonadotrophin secretion and inhibit follicular development.
2. Thicken cervical mucus, making it difficult for sperm to pass through and enter into the uterine cavity. May also affect the transport of ova, this may affect the fertilization process. Progesterone inhibits the intensity and frequency of peristaltic movement of fallopian tube.
3. In addition, endometrial histology may be altered and thus interfere with implantation of the ovum should fertilization occur. Low progesterone may not induce typical development of endometrium suitable for implantation. So, high incidence of irregular menstruation occurs.
4. Prevent ovulation (release of eggs from ovaries in about half of menstrual cycle).

Besides this, the increased progesterone level prevents ovulation due to failure of gonadotrophin-surge. The contraceptive effect is more dependent upon endometrial and cervical mucus effects because gonadotrophins are not consistently suppressed. Progestin-only OCs does not work by disrupting existing pregnancy.

Effectiveness:

1. For breast feeding women: It is very effective. About 1 pregnancy per 100 women was reported in the first year of use. It is more effective than COCs- because breast feeding itself provides much protection against pregnancy.
2. Failure rates have been documented to range from 1.1 to 0.96 per 100 women in the first year of use.
3. The failure rate is higher in younger women (3.1 per 100 women) as compared with women older than 40 years (0.3 per 100 women- years).
4. Mistakes in the pill-taking lead to pregnancy more often than with COCs.
5. It is very effective when used correctly and consistently- 0.5 pregnancies per 100 women in the first year of use (1 in every 200).
6. It is most effective when taken at about the same time every day.

Advantages and Disadvantages of Mini Pill or Progestin Only:

Advantages:

1. It can be used by nursing mothers starting 6 weeks after child birth. Quality and quantity of breast do not seem to be affected. As well as there is no adverse effect on infant growth.
2. No estrogenic side effects. Do not increase risk of estrogenic related complications such as heart attack or stroke.
3. Women take one pill every day with no break. Easier to understand than taking 21 day combined pills.

4. Can be very effective during breast feeding. There are two situations where excellent efficacy probably nearly total effectiveness is achieved: lactating women and women older than 40 years. In lactating women the contribution of mini pill is combined with prolactin induced suppression of ovulation, adding up to effective protection. In women older than 40 years, reduced fecundity adds to the mini pills effects.
5. There are no significant metabolic effects, and there is an immediate return to fertility upon discontinuation (unlike the delay seen with the COC).
6. The incidence of minor side effects is low. Less risk of progesterone related side effects such as acne and weight gain.
7. The mini pill is a good choice in situation where estrogen is contradictated, such as for patients with serious medical condition (diabetes with vascular disease, severe systemic lupus erythematosus or cardiovascular disease).
8. May help to prevent: (a). Benign breast disease; (b). Endometrium and ovarian cancer; and (c). Pelvic inflammatory disease.

Disadvantages of the Mini pill:

1. Less effective than COCs. Failure rate is 2 ^{per} 100 women/year.
2. The major disadvantage observed is the incidence of irregular and frequent bleeding and breakthrough bleeding. Variation in menstrual cycle length and heavy menstrual bleeding.
3. Less effective in preventing ectopic pregnancy than COCs.
4. Forget to take just one / or two pills or failure to absorb a pill because of vomiting or diarrhea enough to cause loss of contraceptive protection. Pill should be taken at about same time each day.

ii. Long Acting Implant Contraceptives:

Implants: This system employs silastic tubing permeable to steroid molecules to provide stable circulating levels of synthetic P_4 over months, and years. In this, progesterone is available at levels 25% to 10% of those obtained with OCs. Norplant system is commonly used as implants.

What is Norplant: Norplant is the registered trademark of the Population Council for levonorgestrel subdermal implants. The Norplant system consists of six capsules, each measuring 34 mm in length with a 2.4 mm outer diameter and containing levonorgestrol. The capsule is made of flexible, medical-grade Silastic (poly-dimethyl-siloxane) tubing capsule of releasing lipophilic drug (steroids), which is sealed with Silastic medical adhesive (silicone type A).The cavity of the capsule has an inner diameter of 1.57 mm and inner length of 30 mm. Each capsule contains 36mg of dry crystalline levonorgestrel for a total of 216 mg in the six capsules. The levonorgestrel is stable and has remained unchanged when examined after more than 7 years of use. The relative rate of release from the capsule is determined by its total surface area and the thickness of the capsule wall. The levonorgestrel diffuses through the wall of the tubing into the surrounding tissues, where it is absorbed by the circulating system and distributed systemically. Within 24 hrs after insertion, plasma core levonorgestrel range from 0.4 to 0.5 ng/ml, high enough to prevent conception. The capsule release approx. 80 µg of levonorgestrel per 24 hrs during the first 6 to 12 months of use. This rate declines to 30 to 35 µg/day for the remaining duration of use. After 5 years, implants release

levonorgestrel 25µg/day. Norplants are placed subcutaneously in a fan like manner in the upper arm.

Effectiveness:

Norplants is highly effective, with low pregnancy rates 0.7 per 100 women at 4 years of use. Pregnanacy rate 0.01/100 in the first year of use.

Mode of action: The various mechanisms by which Norplant affect fertility are described below:

1. Effects on ovarian activity: The long term inhibition of the reproductive functions and is not always associated with a suppression of estrogen. Many studies have confirmed irregular estrogen peaks, indicating un-suppressed follicular activity. Enlarged follicles and transient ovarian cysts found in these women may be the source of the high estrogen levels found in the study. It causes functional cyst formation.
2. In half of the cycles it suppresses ovulation: During the first year, 80% of Norplant users are anovulatory. The findings of follicle rupture and corpus luteum formation with a low gonadotrophin peak show that ovulation may occur in some cases.

3. Luteal function- Insufficient luteal phase could be at least partially responsible for the contraceptive effects. This effect can be either the result of defective gonadotrophin stimulation of the ovary, leading to failure of granulose cells luteinization or due to a direct effect of levonorgestrel on progesterone synthesis in corpus luteum.

4. Effect on cervical mucus and sperm transport: Thicken cervical mucus, making it difficult for sperm to pass through.

5. Endometrial environment altered - prevent implantation.

Advantages:

1. Norplant is a safe, effective, continuous method of contraception. It does not require user compliance or motivation. Since, there is no requirement for daily pill taking therefore, nothing to remember.

2. Rapidly reversible.

3. No estrogen- related side effects.

4. Independent of coitus related contraceptive method. Not affect breast milk, so can be used by nursing mothers.

5. May be useful for following women: a. Heavy smoker; older than 35 years; b. History of ectopic pregnancy; c. Suitable for diabetic women; d. Hypercholesterolemia; severe acne; hypertension; e. History of cardiovascular diseases, Gall bladder disease; and f. Severe depression, migraine.

Disadvantages:

1. Abnormal menstrual bleeding. 60% users show irregular cycle. Light spotting or bleeding between monthly periods (common). Prolonged bleeding (decrease after a few months). Amenorrhea.
2. Pregnancy related effects: Headaches, enlargement of ovaries or cysts, Dizziness, Breast tenderness and/or discharge, Nervousness, Nausea, Acne or Skin rash, change in Appetite, weight gain (in a few weight loss), hirsutism. Many women do not have

any of these side effects and most side effects go away without treatment within the first year.

3. One can not start or stop use on her own. Capsule insertion or removal requires assistance of clinicians.
4. As many as 1 in every 6 pregnancies is ectopic.
5. In a few endogenous estrogen suppressed. So, no estrogen to provide stable maintenance of endometrium- unstable endometrium.
6. Provide no protection to STDs, HIV.
7. Norplant use is not recommended to women have: a. Acute thrombophlebites or thromboembolic disease; b. Undiagnosed genital bleeding; c. Acute liver disease; d. Benign or malignant liver tumors; and e. Known or suspected breast cancer.

iii. Injectable Contraceptives:

The most common type of injectable contraceptives are: 1. **DMPA:** Depot-medroxyprogesterone acetate or Depot-provera. Use dose of 150 mg given every 3 months and 2. **NETEN:** Also called Noristerat (Norethisterone enanthate). It is in the dose of 200 mg given every 8 to 10 weeks. Monthly injectable contraceptives are also available. These includes: 1. **Cyclofem**: Oestradiol valerate 5 mg plus medroxyprogegterone acetate 25 mg; and 2. **Merigyna:** Oestardiol cypionate 5mg plus norethisterone enanthate 25 mg.

How effective:

Very effective- 0.3 pregnancies per 100 women in the first year of use (1 in every 333).

Mode of action: The various mechanisms by which injectable contraceptives affect fertility are described below:

1. Inhibition of ovulation by blocking gonadotrophin surge.
2. By thickening cervical mucus, making it difficult for sperm to pass through.
3. Transport of fertilizable egg through the fallopian tube.
4. Affecting the endometrium- atypical development.

Advantages:

1. Almost as effective as OCs.
2. Long term pregnancy prevention but reversible. One injection prevents pregnancy for at least 3 months. No daily pill taking.
3. Does not interfere with sex.
4. Quality and quantity of breast milk do not seem harmed. Suitable for lactating mother.
5. No E_2 related effect.
6. Helps to prevent, (a). Ectopic pregnancy (b). Endometrial cancer (c). Uterine fibroids (d). Ovarian cancer (e). Iron deficiency anemia (f). Make seizures less frequent in women with epilepsy (g). Make sickle cell crises less frequent and less painful.

Disadvantages:

1. Changes in menstrual bleeding: either light spotting or bleeding; Rare heavy bleeding can occur at first or amenorrhea.
2. May cause weight gain.
3. Delayed return of fertility.
4. May cause headaches, breast tenderness, mood changes, nausea, hair loss, less sex drive and/or acne.

iv. Emergency Contraceptions:

Emergency pill is usually given a day after coitus during the pre-implantation period to women faced with an undesirable pregnancy. Various estrogenic compounds have been used for emergency contraception. The estrogen compounds that have been used for this purpose include diethylstilbestrol (20-25 mg/day), ethinyl estradiol (5 mg/day) and conjugated estrogen (30 mg/day). Treatment is given for 5 days starting within 72 hours after the mid cycle coitus. The estrogenic compounds promote vigorous contractions of musculature of female reproductive tract with the result tubal transport of fertilized egg is accelerated and reached uterus in premature condition. This leads to failure of implantation.

A variety of other agents for post coital use are under investigation including progestagens, anti estrogens and non-steroidal agents. The fully effective non-toxic preparation has yet to be developed. Some studies have shown that insertion of intra-uterine devices (IUD) within 5-10 days of mid-cycle coitus is an effective method to prevent pregnancy. A woman can take four low dose combined oral contraceptive pills as soon as she realizes that she is exposed to the risk of pregnancy and four more pills 12 hour later.

Some recent advances include use of antibodies to hCG which do not affect LH function, specific antibodies to sperm antigens and prostaglandins, PGE_2 and PGF2α, the powerful stimulants of uterine muscle. They are effective at all stages of pregnancy, and have been used to impede implantation, induce abortion and hasten labor.

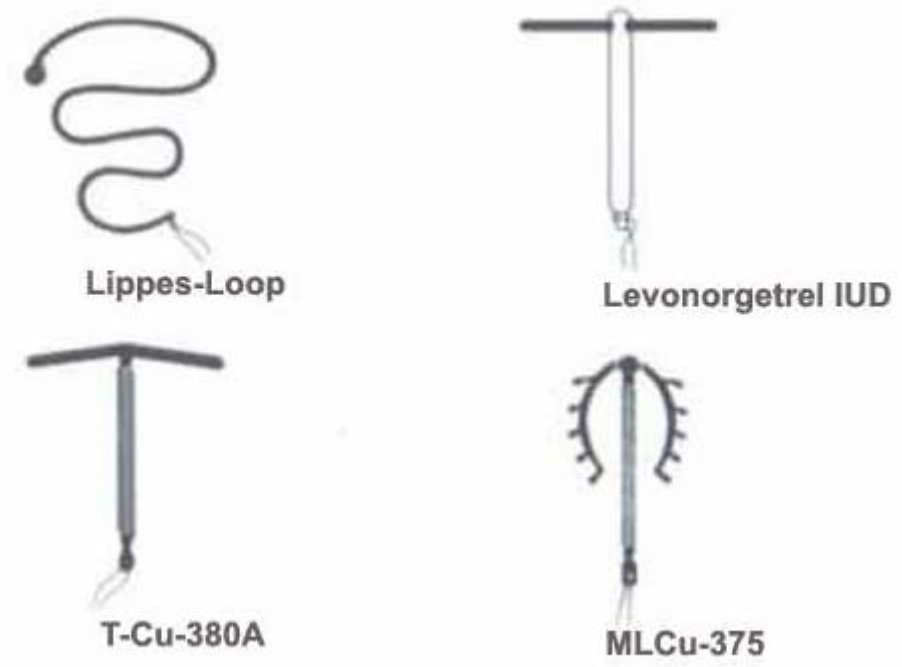
Progesterone antagonist is recently developed emergency contraceptive. This compound, called RU 486 or mifepristone, because of its high receptor affinity prevents progesterone from binding to its receptors and thus inhibits the action of circulating progesterone on target tissue, including uterus. A single 600 mg dose of RU 486 orally in early pregnancy before 7^{th} weeks after the onset of the last menses, spontaneously terminates the 85% of pregnancies. When RU 486 combined with prostaglandin analogues the efficacy increased to 98%.

4. Intrauterine contraceptive devices (IUD):

An intrauterine device (IUD) usually is a small, flexible plastic frame. It often has copper wire or copper sleeves on it. It is inserted into woman's uterus through her vagina. Almost all brands of IUDs have one or two strings, or threads, tied to them. The strings hang through the opening of the cervix into the vagina. The user can check that the IUD is still in place by touching the strings. A provider can remove the IUD by pulling gently on the strings with forceps. IUDs are also called IUCDs (intrauterine contraceptive devices). Specific IUDs are called "the loop,'' *Lippes Loop* (no longer available), copper-T, TCu-380A, MLCu-375 (*Multiload*), *Nova T, Progestasert*, and LNG-20 (**Fig. 2**). The type now most widely used is:

Copper-bearing IUDs (made of plastic with copper sleeves and/or copper wire on the plastic). TCu-380 and MLCu-375 are this type.

Figure-2- Different types of IUDs.



Less widely available are: (a). Hormone-releasing IUDs (made of plastic; steadily release small amounts of the hormone progesterone or another progestin such as levonorgestrel). LNG-20 and progestasert are this type. (b). Inert, or unmedicated IUDs (made of plastic or stainless steel only). Lippes Loop was this type- all plastic.

How does it Work?

The biological action of IUDs, like that of pill, probably depends on interrupting a number of processes essential for conception. IUDs work chiefly by preventing sperm and egg from meeting. The device greatly reduces the number of sperm reaching the fallopian tubes, where the egg is fertilized. If fertilization takes place, an IUD may also act by preventing implantation.

How Effective?

TCu-380A IUD (widely available and lasts at least 10 years): Very effective as commonly used- 0.8 pregnancies per 100 women in first year of use (1 in every 125). Slightly more effective when used correctly-0.6 pregnancies per 100 women in the first year of use (1 in every170). Rates for the MLCu-375 (which lasts 5 years) are nearly as low. Various other copper-bearing and inert IUDs: Effective as commonly used- 3 pregnancies per 100 women in first year of use (about 1 in every 30).

Advantages:

1. A single decision leads to effective long term prevention of pregnancy.
2. Long lasting. The most widely used IUDs (outside China), are the TCu-380A, lasts at least 10 years does not need any replacement.
3. Very effective. Little to remember.
4. No interference with sex.
5. Increased sexual enjoyment because no need worry about pregnancy.
6. No hormonal side effects with copper-bearing or inert IUDs.
7. Immediately reversible. When women have their IUDs removed, they can become pregnant as quickly as women who have not used IUDs.
8. Copper-bearing and inert IUDs have no effect on amount or quality of breast milk.
9. Can be inserted immediately after childbirth (except hormone releasing IUDs) or after induced abortion (if no evidence of infection).
10. Can be used through menopause (one year or so after last menstrual period).
11. No interactions with any medicines.
12. Helps to prevent ectopic pregnancies. (Less risk of ectopic pregnancy than women not using any family planning method).

Disadvantages:

1. Common side effects: Menstrual changes (common in the first 3 months but likely to lessen after 3 months): Longer and heavier menstrual periods; bleeding or spotting between periods; and more cramps or pain during periods.
2. Other, uncommon side effects and complications: Severe cramps and pain beyond the first 3 to 5 days after insertion. Heavy menstrual bleeding or bleeding between periods, possibly contributing to anemia. More likely with inert IUDs than with copper or hormone-releasing IUDs. Perforation (piercing) of wall of the uterus (very rare if IUD properly inserted).
3. Does not protect against sexually transmitted diseases (STDs) including HIV/AIDS. Not a good method for women with recent STDs or with multiple sex partners (or partners with multiple sex partners).
4. Pelvic inflammatory disease (PID) is more likely to follow STD infection if a woman uses an IUD. PID can lead to infertility.
5. Medical procedure, including pelvic exam. Needed to insert IUD. Occasionally, a woman faints during the insertion procedure.
6. Some pain and bleeding or spotting may occur immediately after IUD insertion. Usually goes away in a day or two.
7. Clients cannot stop IUD use on her own. A trained health care provider must remove the IUD for her.
8. May come out of uterus, possibly without the woman's knowledge (more common when IUD is inserted soon after childbirth).

9. Does not protect against ectopic pregnancy as well as it does against normal pregnancy.
10. The woman should check the position of the IUD strings from time to time. To do this, she must put her fingers into her vagina. Some women may not want to this.

INFERTILITY OR STERILITY

Failure to conceive within 1 year of unprotected intercourse is defined clinically as subfertility. Subfertility may be contributed to by both partners such that a relatively minor problem for each may become a more serious problem for both. The World Health Organization (WHO) task force on diagnosis and treatment of infertility conducted a study of 8500 infertile couples using a standardized diagnostic protocol. In developed countries, diseases that were identified as contributing to the infertile state were attributed to the female partner in 37 % of couples, to the male partners in 40 % of couples, and to the both partners in 20% of couples. Ten to fifteen percent of the couples had no identifiable cause of infertility. In a review of 21 published reports containing 14,141 infertile couples, it was reported that the primary diagnoses in the couples were ovulatory disorders (27%), abnormal semen parameter (25%), tubal defect (22%), endometriosis (5%), others (4%), and unexplained (17%).

The infertility in females can be grouped into four major conditions:

1. Abnormalities in the production of a fertilizable oocyte or ovulatory factors;

2. Abnormality in transport of oocyte and embryo or Disorders of female reproductive tract;

3. Abnormalities in the implantation process including early defects in embryo development and embryo-endometrium interaction;

4. Other conditions.

(1). Ovulatory factors or disorder of ovulation:-

Disorders of oocyte production are the most common cause of female infertility. Anovulation is typically associated with amenorrhea or severe oligomenorrhea. Ovulation is monitored directly by sonographic examination and indirect by measurement of gonadotropins. During menses, the follicles in the ovary are approximately 4 mm in diameter. Before ovulation, the dominant follicle reaches a diameter in the range of 20 to 25 mm. Demonstration of follicle growth and rupture of dominant follicle are presumptive evidences that ovulation has occurred. Demonstration of gonadotrophin surge also evidence for ovulatory cycle. Ovulation typically occurs 34 – 36 hours after the onset of gonadotrophin surge and approximately 10 to 12 hours after the peak gonadotrophin.

There are a number of disorders that can cause anovulation and infertility. Some of the common causes of anovulation are described below:

(a). **Hypothalamic-Pituitary-insuffiency**:- Deficiency of GnRH reaching the pituitary results in deprived gonadotrophin and estrogen levels and this may lead to ovarian failure or failure of ovulation. It is also known as functional hypothalamic amenorrhea and accounts for 15-35% of anovulatory patients. Functional hypothalamic amenorrhea is reversible. There are a few genetic mutations affecting the pituitary that causes amenorrhea. Patients can be treated therapeutically with exogenous gonadotrophins or pulsatile infusion of GnRH.

(b). **Hyperprolactinaemia:-** It is a relatively common cause of menstrual irregularity and ovulation failure. Hyperprolactinaemia is treated by bromocryptine therapy.

(c). **Idiopathic ovulation failure**: - In other cases, gonadotrophin secretion seems to be occurring within the normal range of levels, but is insufficient to support a normal cycle due to end organ insensitivity. In this, estrogen level do not rise and antral follicles fail to mature. The endogenous LH-surge is usually attenuated and, hence is supplemented or replaced by hCG or LH. Clomiphene therapy may be used for therapy.

(d). **Anovulatory cycle**:- Chronic anovulation may be defined as repetitive ovulation failure, which differs from ovarian failure in that viable oocytes remain in the ovary. There are several causes; those associated with hypothalamic and pituitary disorders have previously been mentioned. Other conditions that cause anovulation include the peripheral endocrinopathies. These disorders result in a hormonal imbalance-mainly elevated androgens or estrogens – and lead to inappropriate feedback mechanisms and ovulatory failure. Luteinization can occur with the oocyte remaining *in situ*, the so called luteinized follicle syndrome, and in circumstances such as this, the cycle may appear normal but infertile. There is some evidence that oocytes recovered from follicles laparoscopically in women classified in this way are deficient when *in vitro* fertilization is completed. Thyroid disease can occasionally be associated with anovulation.

(e). **Hyperandrogenism or Polycystic ovary syndrome (PCOS):** - The clinical manifestations of PCOS are oligomenorrhea or amenorrhea with symptoms suggestive of hyperandrogenism such as acne or hirsutism (**Table 3**). Approximately 50% of women diagnosed with PCOS are obese and insulin resistance, and most have polycystic ovaries as confirmed by sonography. Underlying these features are numerous biochemical abnormalities that have been associated with this syndrome, including elevated circulating total and free testosterone, DHEAS, and insulin as well as decreased sex hormone binding globulin (SHBG) and an elevated LH/FSH ratio. Androgens are mildly elevated in the follicular phase and many small follicles are present ultrasonographically. The primary cause of ovarian failure of this kind is not known.

Table 3: Characteristic Features of PCOS.

Reproductive feature	Polycystic ovaries (a number of antral follicles located on periphery) Hyperthecosis Hyperandrogenism Increased frequency and multiple of LH secretion Normal to low FSH Increased GnRH pulse frequency
Metabolic features	Hyperinsulinemia Insulin resistance Obesity (abdominal adiposity) Hyperlipidemia (Elevated level of cholesterol, triglycerides and LDL and low level of HDL and apolipoprotein A) Impaired pancreatic β-cell function.
Clinical features	Menstrual disturbances (amenorrhea, oligomenorrhea)

	Hirsutism, Acne Alopecia Anovulatory infertility Recurrent miscarriage Obstructive sleep apnea Acanthosis nigricans
Long term risk consequences	Endometrial cancer Endometrial hyperplasia Impaired glucose tolerance and diabetes Increased risk factors for cardiovascular Diseases (Hypertension, Myocardial infarction) Impaired fibrinolysis (risk for vascular lesions) Gestational diabetes

(f). **Luteal Phase Deficiency**:- Some women with evidence of ovulation, none the less show slow or reduced rises in progesterone and this is associated with infertilirty. Such a pattern is also observed more frequently in women who have undergone gonadotrophin therapy. Whether it follows follicle formation, a deficiency in the maturation of granulosa cells leading to poor luteinization, or whether it is a primary defect of development of LH or prolactin receptor is unclear. Treatment with progesterone during luteal phase is helpful sometimes.

(g) **Ovarian amenorrhea or Ovarian Agenesis or The Aging Follicle:-** Many factors may account for the relationship between the age of the female partner and fecundability. Premature menopause is defined as ovarian failure prior to the age 40, which is reported to occur in 1% population. A major cause of the relationship appears to be the relatively poor quality of the oocytes due to an elevation in the FSH concentration (> 40 IU/L) during menses. FSH receptor mutations have also been identified in human with premature ovarian failure. Once a diminished ovarian follicular pool has been identified, it is "often too late''. Fertility treatments at this point have lower success than with the same treatments in women having a normal follicular pool. Consequently, many authorities are recommending that infertility evaluation and treatment be initiated in women not older than 35 years and after only 6 months of failure to conceive following cohabitation. Evaluation of day 3 FSH concentration is probably warranted in infertile women older than 30 years. Measurement of day 3 and day 10 FSH concentrations after a clomiphene challenge is probably warranted in infertile women older than 37 years. The aging oocyte that is fertilized and implants in the endometrium appears to be associated with a markedly increased rate of spontaneous abortion. The rate of clinically detected spontaneous abortion increases 100% between 20 and 40 years of age. In IVF programs, the rate of pregnancy loss is approximately 19 % in women younger than 40 years and greater than 35 % in women older than 40 years. The increase in spontaneous abortion associated with the aging oocyte also contributes to the decreased fecundity apparent in aging women. When the gonad fails to develop, this is known as gonadal agenesis.

(2). Disorders of female tract:

Tubal obstruction is major disorder of female tract. Oviduct is provided with numerous cilia on the intraluminal side. The ciliary movement helps in transportation of ova and sperm. Due to tubal infection cilia get damaged and causes impaired transportation of ova and sperm. Pelvic Inflammatory Disease (PID), appendicitis, septic abortion, previous tubal surgery, and use of intra-uterine device resulting in a pelvic infection are major contributors to tubal disease and subsequent infertility. The diagnosis of tubal obstruction is made with laparoscope. The tubal damage is usually a secondary consequence of pelvic infection. Its incidence is being elevated after STDs. Surgical treatment has a low chance of success. More effective therapy is provided by aspiration of oocyte from the ovary and followed by *in vitro* fertilization and embryo transfer into the uterus. Subclinical pelvic infections with *Chlamydia trachomatis* may be another major cause of tubal disease associated with infertility.

Cervical Factor Infertility:- The cervix is an active participant in transporting sperm from the vagina to the upper reproductive tract. In the normal cervix, the secreted mucus has physicochemical properties that facilitate the transport of sperm. Congenital malformation and trauma to the cervix may impair the ability of the cervix to produce normal mucus.

(3). Defects in embryo development and embryo-endometrium interaction:

(a). Endometriosis:- In endometriosis, endometrial tissue grows inappropriately in ectopic sites, such as oviduct, ovary or in peritoneal cavity. Women with endometriosis usually present for treatment of pelvic pain, infertility, or an adnexal mass (an ovarian endometrioma). The treatment of women with endometriosis and infertility is complex. The fecundability of women with endometriosis is probably related to the stage of disease.

(b). Uterine Leiomyomas:- Uterine leiomyomas, also known as fibroids or uterine myomas, are benign smooth muscle tumors of the uterus. This study suggests that uterine leiomymas that distort the uterine cavity may be associated with a decrease in fecundability.

©. Disorders of Implantation:-Implantation is one of the least understood processes in human reproduction. Findings in laboratory models offer the best hope of furthering our understanding of the process of implantation.

(d). Luteal-phase deficiency:-Luteal-phase deficiency is the delayed maturation of the endometrium as determined by histologic dating of the tissue obtained by endometrial biopsy that lags appropriate development by at least 2 days. Most commonly, luteal-phase deficiency is caused by abnormal follicular development and ovulation, which results in abnormal estradiol and progesterone production, leading to delayed endometrial maturation. Many authorities believe that crucial feature of luteal-phase deficiency is a relative deficiency of progesterone production. The effect of progesterone on the endometrium is probably both dose and time dependent. If length of time of progesterone secretion is subnormal, then luteal-phase deficiency could ocuur. Two commonly recommended treatments of luteal-phase deficiency are induction of ovulation with clomiphene or gonadotropin injections and supplementation of luteal progesterone production with vaginal progesterone suppositories. Both clomiphene and exogenous gonadotropin stimulation can overcome the abnormal follicular development that is most likely cause of lutael-phase deficiency. Alternatively, progesterone vaginal suppositories

at dose of 25 to 50 mg twice daily starting 3 days after ovulation can be used to treat the delayed endometrial maturation.

(e). Recurrent Abortion:-Recurrent abortion is defined as the occurrence of two consecutive spontaneous abortions. The most common causes of recurrent abortion include genetic factors (major chromosome abnormalities), 5 %; anatomic factors, including uterine anomalies, 10%; endocrine factors, including luteal-phase deficiency, 10%; infectious factors, less than 5%; immunologic factors, 5%; and unidentified factors, 65%. It is now believed that functional defects in sperm may also lead to recurrent abortion.

Management of the Infertility

It is important to remember that in most couples there is a chance for spontaneous conception. Treatment should be diagnosis-specific. The cause of the defect should be determined and specific treatment then instituted. The treatment might include the use of dopamine agonists (hyperprolactinemia), thyroid replacement (hypothyroidism), pulsatile GnRH (hypogonadotropic), or clomiphene citrate (for anovulation). Patients with anovulation have the greatest success with infertility therapy. Treatment of anovulatory disorders can result in fecundability similar to that observed with the normal couple. Common treatment choices include: i. Clomiphene citrate; ii. Modulation of body weight; iii. Clomiphene citrate plus hormone adjuvants; iv. Gonadotrophin treatment; v. pulsatile GnRH treatment; vi. Bromocriptine; and vii. Glucocorticoid. PCOS has recently been associated with insulin resistance, insulin sensitizers such as metformin have been used to enhance ovulatory response in women with PCOS. Patients with tubal occlusion- unless it is mild- are most often better served by Assisted Reproductive Technology (ART). The treatment of unexplained infertility can be frustrating for the physician. The main treatments are superovulation plus intrauterine insemination (IUI) and *in vitro* fertilization (IVF), or gamete intrafollicular transfer (GIFT). ART is the major treatment option for infertile patients with endometriosis.

Indications for IVF include tubal factor infertility, endometriosis, male factor infertility, immunologic infertility, and unexplained infertility. Treatment most commonly starts with the down regulation of endogenous gonadotropin release by a GnRH agonist to prevent interference with the ovulation induction process. Then the ovaries are stimulated to produce maximal numbers of oocyte-containing follicles using hMG and/or a pure FSH compound. All these medications must be given by injection (either subcutaneous or intramuscular). Patients are monitored by ultrasound and through the evaluation of serum estradiol levels. When the follicles are found mature an injection of hCG is given as in superovulation cycles. The distinct difference is that during IVF, 34-36 hr after this injection the eggs are retrieved, usually by a transvaginal ultrasound guided approach. The oocytes are then fertilized with sperm *in vitro*. Depending on the degree of male factor, this may involve simply coincubation of sperm and egg or the use of micromanipulation techniques. One technique that has recently revolutionalized the treatment of male factor infertility is ICSI. This procedure introduces a single sperm directly into the cytoplasm of the egg and can produce fertilization even in cases with very few poor quality sperm. Fertilized eggs are then allowed to grow and divide in culture. Currently, most IVF centers will transfer embryos into the uterus on the third day after the egg retrieval, when they are often at the eight cell stage. This is accomplished by simply placing a catheter through the cervix and into the uterus and expelling the embryos into the uterine cavity. The number of embryos transferred to the uterus is determined by many factors, including the embryo quality, age of the patients and concern for multiple

pregnancies. In general, pregnancy rates rise as the number of transferred embryos is increased; however, most center limit the number of embryos transferred to two or three. Excess embryos may be cryopreserved for the future attempts at conception, though conception rates in these cycles are low. After transfer, the patient is given lutea phase support with progesterone. A serum pregnancy test is obtained 2 weeks after the date of oocyte retrieval. The society for Assisted Reproductive Technologies registry in 1905 showed 281 programs performing 41,087 treatment cycles of IVF with an average delivery rate per oocyte retrieval of 22.5%. Success rates vary significantly by diagnosis and age. For example, some centers report delivery rates of 50% or more in couples under the age of 40 with tubal factor infertility, whereas patients over the age of 40 may experience success rates of <15%.

Zygote intrafallopian transfer (ZIFT) is the same procedure as IVF except that embryos are transferred into the Fallopian tubes rather than the uterus. The main advantage of this technique is the exposure of the embryos to the possible beneficial effects of the tubal environment which *in vivo* is thought to be an important component of the conception process. Disadvantages include the need for normal tubes and the need for laparoscopy to perform the transfer. ZIFT is a much less commonly employed procedure compared to other IVF. Gamete intrafallopian transfer (GIFT) utilizes the same oocyte stimulation protocol as IVF; however, once the eggs are retrieved, they are mixed with sperm and immediately transferred in to the tubes. This does not allow for documentation of fertilization and also requires laparoscopy.

In couples with inadequate gametogenesis, the use of donor sperm or donor eggs is possible. Donor sperm is easily obtained through commercial sperm banks. An insemination of the sperm sample via a catheter introduced in to the uterus is performed on the day of ovulation as predicted by LH surge detection or other means. Donor egg therapy requires IVF. In this case, a donor undergoes oocyte stimulation and egg retrieval with the resultant embryos being placed in the recipient's uterus. Since the donors are usually fertile and young, this form of therapy is often more successful than standard IVF.

CONCLUSIONS

Continued research is needed for development of newer and safer methods for control of human conception, since all existing procedures have limitations and drawbacks. There is growing awareness that methods introduced on the basis of what appeared at one time to be sound theoretical principles are actually effective for very different reason. After 30 years of use, the pill is one of the best understood drugs in medicine and for nearly all women the benefits of use outweigh the risks by a wide margin. There are fewer side effects now as there used to be because oral contraceptives today contain a much lower level of estrogen. The hormone levels in pills of yesteryear were "five to twenty times greater than what they are today. Lower hormone levels usually mean fewer side effects, but side effects do still occur. All contraceptive pills are known to carry some risk of blood clots that are a side effect of the hormones - oestrogen and progestin - contained in the pill.

Several significant developments are already there and more likely to occur in the near future to improve the success rates of infertility treatment as well as to broaden the choices of therapy. These advances include the availability of recombinant DNA-produced gonadotropins and the GnRH antagonist, both of which are likely to improve ovulation induction and superovulation treatments. With respect to IVF, preliminary data suggest that the ability to mature embryos to the blastocyst stage prior to uterine transfer will significantly improve pregnancy rates. Since the implantation rate per embryo may

also be higher, fewer embryos can be transferred to uterus, which it is hoped will reduce the multiple pregnancy rate associated with IVF. In addition, the ability to select embryos for transfer based on genetic information obtained through preimplantation genetic diagnostic technology may decrease the spontaneous pregnancy loss rates seen with IVF. For patients who need to delay child bearing or who are going to undergo gonadotoxic therapy (eg, radiation or chemotherapy), oocyte cryopreservation is likely solution. The procedure may also simplify and expand the availability of donor egg therapy.