**CONTRACEPTION**

 The term “contraception” is defined as the intentional prevention of pregnancy. Contraceptives are therefore; *pharmaceuticals or devices used to prevent unintended pregnancy without causing adverse effects and at the same time to preserve fertility when desired.*

**Menstrual Cycle Physiology:**

Biological feedback mechanisms involve the hypothalamus, anterior pituitary gland, ovaries, and endometrial lining of the uterus. These structures control the menstrual cycle.

* Hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulse like manner with varying frequencies throughout the menstrual cycle.
* GnRH stimulates the anterior pituitary to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
* FSH and LH act on the ovaries to produce estrogen and progesterone.
* Estrogen in turn acts on the hypothalamus and anterior pituitary, in a negative feedback manner, to stop FSH and LH secretion.

The menstrual cycle is divided into three phases:

1- Follicular phase

2- Ovulation phase

3- Luteal phase.

The average length of the menstrual cycle is 28 days (range 21-40 days). The day bleeding begins is referred to as the first day (or day 1) of the menstrual cycle. Menstrual bleeding usually occurs between days 1 to 5 of the cycle.

Follicular phase:

* Lasts about 10-14 days and it begins at the onset of menstruation. Also at the beginning of the follicular phase, several follicles begin to develop within the ovary.
* In the second half of the follicular phase, most of the developing follicles atrophy except one “dominant” follicle that will develop further and produce increasing amounts of estrogen.
* Elevated estradiol levels stop menstrual blood flow from the previous cycle & cause a surge of LH. This LH surge is responsible for final-stage growth and maturation of the follicle, ovulation, and the formation of the corpus luteum.
* Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.
* Ovulation usually occurs 14 days before the last day of the cycle. After ovulation, the remaining follicle becomes the corpus luteum which produces estrogen, androgen and progesterone in increasing amounts.
* In 90% of women, the luteal phase lasts 13 to 15 days and is the least variable part of the human reproductive cycle.
* During this progesterone-dominant phase, progesterone prepares the endometrium for implantation of a fertilized ovum.
* ***If pregnancy occurs***, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone.
* ***If pregnancy does not occur***, the corpus luteum degenerates, progesterone declines, endometrium cannot be maintained and is sloughed off and menstruation occurs. Using the average 28-day cycle as an example, day 28 is the last day of the cycle and is the day before bleeding begins again for the next menstrual cycle.



**Non hormonal contraception:**

Includes:

1- **Diaphragms**: are effective because they are barriers and because of the spermicideplaced in the diaphragm before insertion. It should be inserted up to 6 hours before intercourse and must be left in place for at least 6 hours after. It should not be left in place for more than 24 hours because of the risk of toxic shock syndrome (TSS).

2- **Spermicidal agents** are composed of an active spermicidal chemical, which immobilizes or kills sperm, and an inert base (e.g., cream, jelly, tablet, or suppository), which localizes the spermicidal chemical in proximity to the cervical os.

The FDA-approved spermicidal agent is nonoxynol-9 (surfactant destroys sperm cell wall & block entry into the cervical os).

3- **Male condoms**: are used to prevent the transmission of sperms into the vagina. Male condoms are intended to prevent HIV and other sexually transmitted infections, but caution that they do not completely eliminate the risk, particularly human papillomavirus (HPV) and herpes simplex virus (HSV).

4- **Female condom**: is a disposable nitrile sheath that fits into the vagina, and provides protection from pregnancy and some sexually transmitted infections. It may be inserted up to 8 hrs before intercourse, and can be removed at any time after coitus. Female condoms should not be used concurrently with a male condom. Female condoms have higher failure rates than the male condoms.

**Hormonal Contraception:**

Contain either a combination of synthetic estrogen & synthetic progestin or a progestin alone.

1- ***Estrogens***: prevent the development of the dominant follicle by suppressing FSH secretion. Estrogens also stabilize the endometrial lining to minimize the breakthrough bleeding.

2- ***Progestins***: have multiple mechanisms of action providing contraception:

 a- Progestins may prevent ovulation by suppressing LH secretion.

 b- Progestins may impede the transport of sperm through the cervical canal by thickening cervical mucus.

 c- Progestins also may inhibit implantation by causing alterations of the endometrial lining or alter the transport of sperm or ovum within the fallopian tubes.

**Combined Oral Contraceptive Pills (COC)**

COC containing an estrogen and a progestin and are the most commonly used reversible method of contraception.

The side effects caused by the early high dose COC prompted a search for lower dose & better tolerated products.

* Virtually all of the combined hormonal contraceptives (CHCs) available contain the synthetic estrogen *ethinyl estradiol (EE).* *Mestranol* is another estrogen that has been used. Mestranol is inactive (prodrug) and is converted in the body to EE. Mestranol 50 mcg has approximately same activity as EE 35 mcg.
* COCs contain one of the following synthetic progestins: desogestrel, norgestril, levonorgestrel, norethindrone acetate, ethynodiol diacetate, or norgestimate.
* These progestins differ significantly in their progestational potency and also in the extent of their metabolism to estrogenic substances.
* Progestins have both estrogenic and antiestrogenic effects because they are metabolized to estrogenic substances.
* Because the progestins have a chemical structure similar to that of 19-nortestosterone, they have varying degrees of androgenic activity. Their androgenic effects depend on the presence of sex hormone (testosterone) binding globulin; this globulin level is related inversely to the androgenic effects.

**21-Day versus 28-Day Cycle:**

Most 28-day COC pill packs contain 21 days of active pills (pills that contain estrogen and progestin) followed by 7 days of placebo or iron tablets.

The 21-day pill packs contain only the active pills. Many clinicians prefer the use of 28-day cycle COC to minimize confusion and to promote adherence. With a 28-day pack, users take one tablet daily. After taking the last tablet of a 28-day pack, a new pack should start the next day.

When continuous ovarian suppression is used for extended cycles or to treat estrogen-dependent disorders, such as endometriosis, the 21-day cycle packs may preferred (no placebo week).

**Proper Pill Taking**

* The woman should take the COC tablets at exactly the same time each day. If she experiences nausea, she may take her pill at bedtime or with food. The best time for pills to be taken depends on her schedule.
* If woman forgets to take one pill, she should take the missed pill as soon as she remembers. Most manufacturers recommend that if one pill is missed, the woman should take two pills when she remembers.
* If she misses two tablets in a row in weeks 1 or 2 of her pack, she should take two pills on the day she remembers and two the following day, then she should take the remaining pills in the pack as usual. Here, alternative method of contraception may required.
* If a woman misses three or more pills in a row anytime during the period, she wills likely experience bleeding or spotting. At the time she remembers, she can discard the rest of her pack and start a new pack that same day.

**Drug Interactions:**

1-Antibacterials

Ethinyl estradiol is conjugated in the liver, excreted in the bile, hydrolyzed by intestinal bacteria, and reabsorbed as active drug. Certain broad-spectrum antibiotics, by reducing the population of intestinal bacteria, may *interrupt the enterohepatic circulation* of the estrogen, resulting in a decreased concentration of circulating estrogen.

The antibiotics rifampin and griseofulvin are known to cause contraceptive failure, but not by this mechanism. These agents reduce contraceptive efficacy by increasing the metabolism of estrogen.

A practical approach to managing co-administration of COC and antibiotics is to educate women about the potential for increased risk of pregnancy and to recommend a back-up method of contraception until menses occurs.

2- Liver Enzyme Induction

Ethinyl estradiol is a substrate of cytochrome P450 therefore, medications that are enzyme inducer may decrease COCs efficacy. Conversely, enzyme inhibitors increase COC levels & the potential side effects.

* With the older high-dose COCs, efficacy was not decreased significantly by many enzyme inducers because of their high hormone content.
* The estrogen and progestin doses in newer COC are much lower, therefore menstrual irregularities (e.g., spotting, breakthrough bleeding [BTB] and unintended pregnancies attributable to drug interactions have been increasing with lower dose formulation).
* Carbamazepine, phenytoin & phenobarbital, are enzyme inducers known to cause increased metabolism of COCs.

**Oral Contraceptive Risks and Adverse Effects**

Some women may not be candidates for a COC because of the risks and adverse effects associated with use. Other women may experience minor side effects with COC that may be managed by changing to a formulation with a different type or dose of estrogen or progestin.

Breakthrough Bleeding, Spotting, and Amenorrhea

* Bleeding during active pills days of the cycle (intermenstrual bleeding) is designated breakthrough bleeding (BTB), whereas a lesser amount of inter-menstrual bleeding that does not require protection is called ***spotting***. Spotting and BTB are the most frequent reasons cited by women for the discontinuation of COCs.
* If irregular bleeding is the only complaint, most clinicians will continue with the same formulation for at least 3 months because BTB or spotting usually resolves without intervention.
* If inter-menstrual bleeding continues more than 3 months; a formulation with the same estrogen dose and more progestin should be prescribed.
* If amenorrhea present; COC formula with the more estrogen and less progestin can be tried.

Women over 35 years of age:

* Use of COCs containing less than 50 mcg estrogen may be considered in healthy non-smoking women older than 35 years.
* COCs are not recommended for women older than 35 years with migraine, uncontrolled hypertension, smoking or diabetes with vascular disease.
* Studies have not demonstrated an increased risk of cardiovascular disease with low dose COCs in healthy non-obese women.

Cardiovascular Diseases

* High serum concentrations of triglycerides, total cholesterol, LDL, and VLDL cholesterols are associated with the risk of developing atherosclerotic circulatory diseases, whereas HDL cholesterol has an inverse relationship.
* Estrogen tends to increase serum concentrations of HDL. Progestins, depending on the dose and potency, may decrease HDL concentrations.
* Women with uncontrolled dyslipidemia (LDL >160 mg/dL, HDL <35 mg/dL, triglycerides >250 mg/dL) and additional risk factors (eg, coronary artery disease, diabetes, hypertension, or smoking) should use an alternative method of contraception.

Headache

* Headaches can occur while taking the active pills (estrogen related) or during the placebo week, owing to the withdrawal of estrogen.
* Women with migraines may find that their headaches worsen when COCs are initiated.
* Women who develop migraines (with or without aura) while receiving COCs should immediately discontinue their use and consider a progestin-only option.
* Ischemic stroke is more likely to occur in COC users with a history of classic migraines (migraines with aura), especially if they are smokers. Women with classic migraines should use COCs with caution or not at all, particularly if they smoke, are >35 years of age, or have other significant medical problems.
* Mild headaches may abate over time or if the woman is changed to a pill with less estrogen.

Hypertension

* The underlying mechanisms for COC-induced hypertension may be sodium and water retention and increased renin activity.
* COCs can cause small increases in blood pressure (6–8 mm Hg). In women with hypertension, oral contraceptives have been associated with an increased risk of myocardial infarction (MI) and stroke.
* Use of low-dose CHCs is acceptable in women younger than 35 years with well-controlled hypertension.
* Hypertensive women with end-organ disease or who smoke should not use COCs. Systolic blood pressure ≥160 mm HG or diastolic blood pressure ≥100 mm Hg is a contraindication to use of CHCs.

Diabetes

* The new progestins are believed to have little effect on carbohydrate metabolism.
* Women younger than 35 years with diabetes but no vascular disease who do not smoke can safely use COCs.
* Diabetic women with vascular disease or diabetics of more than 20 years’ duration should not use COCs.

VTE Events

OCs contributes to thromboembolic events (DVT & PE) especially those women with risk factors by several mechanisms.

* Estrogens increase coagulability and thereby increase the possibility of clot formation (increase factor VII, X, & XII and reduce antithrombin III).
* Long-term OC use is associated with an increased platelet count and increased platelet aggregation similar to that seen late in pregnancy.
* The risk of VTE in women using low-dose OCs (<50 mcg EE) was four times the risk in nonusers.
* For women at increased risk of thromboembolism (older than 35 years, obesity, smoking, personal or family history of venous thrombosis, prolonged immobilization), consider low-dose oral estrogen contraceptives or progestin-only methods.

Non-contraceptive benefits of Oral Contraceptives

Acne

Depending on the woman, COC use may cause acne to appear, disappear, or significantly improve.

* Most women will have improvement in acne with any COC used.
* Progestins with higher androgenic activity may be more likely to increase acne because they stimulate sebaceous glands to produce more sebum.
* Higher doses of estrogen may decrease acne by suppressing the activity of sebaceous glands, decreasing the production of androgens, and increasing the synthesis of SHBG.
* Both desogestrel and norgestimate-containing COCs are less androgenic, thereby increasing SHBG levels and decreasing acne.

Dysmenorrhea and Premenstrual Syndrome

* Dysmenorrhea (painful menstruation) may be of unknown etiology; it may be caused by endometriosis or uterine fibroids.
* Complaints of menstrual pain may be decreased by >60% after starting COCs.
* A formulation with decreased estrogenic and increased progestational activity may be the best at relieving dysmenorrhea.
* Premenstrual tension has been reported to be reduced in COC users, and other premenstrual symptoms seem to be relieved as well.

Menorrhagia (Heavy Menstrual Bleeding)

* The total amount of menstrual flow in COC users is decreased by the progressive thinning of the endometrium due to COC use or a lack of irregular bleeding.
* Bleeding may be decreased by COCs that have a high ratio of progestin to estrogen, because endometrial thinning is maximized.

Benign Breast Disease

* 50% - 75% reductions in the risk of fibroadenomas (chronic cystic breast disease) occur in COC users. Protection seems directly related to length of use.
* Because the progestin component may be primarily responsible for this protection, progestin-dominant COCs that contain a less estrogenic progestin, such as levonorgestrel, are preferred.

Endometrial Cancer

A cyclic COCs contain sufficient progestin help to prevent endometrial hyperplasia and reduce the risk of endometrial cancer.

Ovarian Cancer and Functional Ovarian Cysts

* The risk of developing functional ovarian cysts is decreased, pre-existing cysts are more rapidly resolved, and surgery rates for ovarian masses are reduced in women taking COCs.
* This is likely owing to reducing ovulation, suppressing androgen production, or increasing progesterone levels.

**Progesterone-Only Pill (Minipill)**

The advantages of minipill are devoid of:

* Some of the side effects caused by estrogen (e.g., headaches).
* More importantly, estrogen-mediated hypertension and clotting factor changes will be avoided in woman who has a strong family history of cardiovascular disease.
* Confusion with pill taking is minimized because there is no placebo week and all 28 tablets in each pack are the same.
* The missed-dose directions are the same whenever any pill is missed; take two pills as soon as possible and use back-up contraception for 48 hours.
* The minipill is less effective for preventing pregnancy than a COC.
* Minipills have non contraceptive benefits, including decreased dysmenorrhea and bleeding.

Disadvantages of the minipills, is;

* failure rate of 0.5% to 5%, & they should be taken nearly at the same time each day.
* Minipills are not often used except in women who are breastfeeding or have CI to estrogen.

Most women using progestin-only pills have fewer bleeding days because there is no withdrawal bleeding induced by pill-free days. Some women on minipills will continue to ovulate and experience regular cyclic bleeding.

The contraceptive actions of progestins include alteration of cervical mucus, endometrial changes, and tubal transport changes and, therefore, most users do not experience contraceptive failure despite continuing to ovulate.

Minipills should be avoided when there is a personal history of breast cancer or undiagnosed vaginal bleeding. Caution should be exercised when using minipills in women with hepatic disease, certain cardiovascular conditions, a current DVT or PE.

Long-Acting Injections: Depo-Provera ®

* Depot medroxyprogestron acetate (DMPA) most often given as a 150-mg deep intramuscular injection.
* It inhibits ovulation, thickens the cervical mucus, and suppresses endometrial growth, making it a very effective contraceptive.
* DMPA is administered by deep intramuscular injection within 5 days of onset of menstrual bleeding, and the dose should be repeated every 12 weeks. A newer lower-dose 104-mg formulation for subcutaneous injection also is available.
* Depo-Provera is a good contraceptive choice for woman with a risk for estrogenic side effects or had a history of thromboembolism. Among its benefits are a low failure rate, ease of use, decreased dysmenorrhea, reduced monthly blood loss, and a reduced risk of endometrial cancer.
* Other non-contraceptive benefits may include decreasing pain and frequency of sickle cell crises, & reduction in seizure frequency in epileptic patients.
* Furthermore, contraceptive efficacy is not reduced by the concurrent use of anticonvulsants as is seen with COC.
* DMPA should not be continued beyond 2 years unless other contraceptive methods are inadequate.

Disadvantages

Should be used with caution in women with breast cancer, with undiagnosed vaginal bleeding, or a current DVT or PE. Some experts disagree with the Depo-Provera package insert, which lists a history of prior thromboembolism as a contraindication, because clotting factors have not been shown to be clinically affected by it.