

AN ADVANCE REVIEW ON ORAL CONTRACEPTIVES (OC): TYPES, ADVANTAGE, DISADVANTAGE & ITS USAGE**Km. Shiva^{1*}, Suraj Mandal², Deepika Chauhan³, Ankit Sharma⁴, Siddharth Dhaka⁵**¹Assistant Professor, NGI College of Pharmacy, Near SVBP University, Modipuram, Meerut, U.P.²Assistant Professor (Research Scholar), IIMT College of Medical Science, IIMT University, Meerut, India, 250001.³Assistant Professor, Innovative College of Pharmacy, Knowledge Park II, Greater Noida, Uttar Pradesh, 201308⁴Research Scholar, Department of Pharmacology, School of Pharmacy, Bharat Institute of Technology, Meerut.⁵Assistant Professor, Venketeshwara College of Pharmacy, Meerut, 250001 (ORCID I'd- 0000-0003-1361-8857).***Corresponding Author: Km. Shiva**

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ABSTRACT

Oral contraceptive pills have been extensively studied since 1960 and are currently used by more than 70 million women daily. In US-wide research of contraceptive methods, it was found that oral contraceptive use was the most common and that first-graders were more likely to use oral contraceptives (18.9%) than other age groups. Oral contraceptives, also referred to as birth control pills, are used to prevent pregnancy. Any of a group of synthetic steroid hormones that block the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior lobe of the female pituitary gland are referred to as "oral contraceptives." Usually, when FSH and LH are present, the ovaries release oestrogen. Combination Oestrogen Contraceptives are one class of hormonal contraceptives. Progestogen contraceptive preparations come in pill, skin patch, and vaginal ring forms. They are also available in monophasic, biphasic, and triphasic forms. solely progestin-based contraceptives A formulation that is available as pills, injections, implants, hormone spirals that only contain one hormone, synthetic progestogen, and emergency contraceptive pills, sometimes known as "morning after pills," is referred to as a "minipill. " When used correctly, oral contraceptives can prevent unintended pregnancies in between 92 and 99 percent of cases. Readers will learn about several oral contraceptive methods from this review.

KEYWORDS: Oral contraceptive pills, oestrogen, progesterone.**INTRODUCTION**

Wealthy countries have seen a rise in the percentage of women utilising contraception since 1982; as of 2016, 62% of American women of reproductive age were taking contraception. 28% of women most regularly use oral contraceptive pills as a form of birth control. Around the world, 8.8% of women use birth control pills.^[1]

These hormone therapies temporarily but permanently lower fertility. Today's worrying demographic trends need the usage of antifertility drugs. Urbanization has increased birth rates while reduced death rates, particularly in underdeveloped countries. Many people employed contraceptive methods in the early 20th century, including condoms, diaphragms, spermicidal creams, foam tablets, and others. Using spermicidal creams, tablets, or other effective birth control techniques like condoms and diaphragms. These also falter more often.^[2] The Pincus found that an oral history of the usage of progestin for birth control via coitus in addition to contraception. Menstrual cycles can

be thrown off. Progesterone had to be administered parenterally, and it was known that high amounts might stop ovulation. Since powerful oral active progestins have been developed, a variety of oral contraceptives containing oestrogens, progestins, or both are now easily accessible for clinical usage (norethynodrel and norethindrone). The possibility that estrogens may postpone ovulation and eventual pregnancy has long been understood. The use of them for this purpose had two problems, though: first, the dose of oestrogen had to be raised in succeeding cycles to prevent escape ovulation, and second, long-term usage of high doses of oestrogen would result in endometrial hyperplasia. Menstrual cycles can be thrown off.

Progesterone had to be administered parenterally, and high amounts might stop ovulation, it was also known.

A range of oral contraceptives including estrogens, progestins, or both are now widely accessible for clinical usage as a result of the introduction of powerful orally active progestins (norethynodrel and norethindrone).

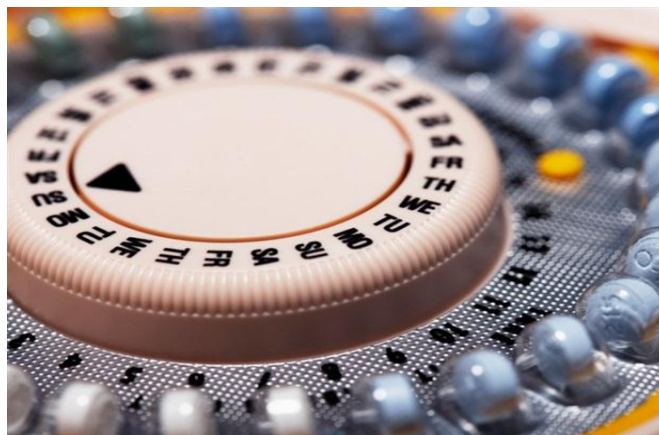


Fig. 1: Epidemiologic status of using an Oral contraceptive around the world.

Development of oral contraceptives^[2]

The hormonal birth control methods used today differ greatly from the original pill. Norelgestrel, various estrogen-progestin administration techniques, a decrease in hormone dosages, and the creation of alternative delivery systems all contributed to this transformation. Aside from pharmaceutical company competition, improvements in our understanding of hormonal systems, and increased monitoring of the effects of OCs on the endocrine and metabolic systems, the desire for oral contraceptives with fewer adverse effects served as the driving force behind development. Creating oral contraceptives^[2] The hormonal birth control methods used today differ greatly from the original pill. During this time, new progestins were released, hormonal dosages were decreased, and numerous original ideas were developed.

Definition

Oral contraceptives are medications intended to prevent conception by oral use. The pills in the packet that contain hormones are referred to as "active pills." The pills that don't contain any hormone and are labelled as inactive or placebos. They are included in the pack to aid a woman in remembering to take her medications on schedule. The colour of a tablet depends on whether it is active or not. There is a good likelihood that a woman will begin her period if she takes the inactive tablets. For a long time, each pill box contained a total of 28 tablets, or 28 pills for a monthly menstrual cycle. There were 28 tablets total, with 21 days of active pills and 7 days of dormant ones.

Combined oral contraceptives pill^[3]

Combined Oral Contraceptive (COC) is composed of estrogen and progestogen. The first COC was introduced in 1957 in the United States for the treatment of menstrual disturbances. The combined oral contraceptive pill is extremely effective, at least in the absence of intercurrent illness and of treatment with potentially interacting drugs. The estrogen in most combined preparations (second-generation pills) is ethinyl estradiol, although a few preparations contain mestranol instead. The progestogen may be, Levonorgestrel,

ethynodiol, or in third generation 'pills – desogestrel or gemstone, which are more potent, have less androgenic action and cause less change in lipoprotein metabolism, but which probably cause a greater risk of thromboembolism than do second-generation preparations. The estrogen content is generally 20-50 μ g of ethinyl estradiol or its equivalent, and a preparation is chosen with the lowest estrogen and progestogen content that is well tolerated and gives good cycle control in the individual woman. This combined pills taken for 21 consecutive days followed by 7 pill free days, which causes a withdrawal bleed. Normal cycles of menstruation usually commence fairly soon after discontinuing treatment, and permanent loss of fertility.

Examples of combination birth control pills include Balcoltra Beyaz, Caziant, Cryselle, Ogestrel, Ortho-Novum.^[4]



Fig 2: Oral contraceptive Pills.

The mode of action is as follows

1. Estrogen inhibits the secretion of FSH by negative feedback on the anterior pituitary, which in turn lowers the size of the ovarian follicle.
2. Progestogen diminishes cervical mucus' appropriateness for sperm passage by reducing LH secretion, which delays ovulation.
3. Oestrogen and progesterone work together to alter the endometrium in a way that hinders implantation.

4. They may also interfere with the synchronised contractions of the uterus, cervix, and fallopian tubes that support fertilisation and implantation.

There are monophasic, biphasic, and tri-phasic preparations for combination tablets.^[5]

Monophasic: In monophasic medications, the amount of progestin and oestrogen in each pill is fixed. On the fifth day of the menstrual cycle, the pill is started, taken every day for 21 days, and then stopped for a 7-day hiatus during which bleeding occurs. The course of treatment is all at once.



Fig. 3: Monophasic pills.

Biphasic: Oral contraceptive preparations are also available in triphasic or biphasic variants. Less hormones are needed, and it more closely follows menstruation cycles. In the case of biphasic tablets, estrogens are given for 10 days, followed by a progestin for the next 11 days. Due to the risk of endometrial cancer after such biphasic hormone therapy, biphasic tablets are not recommended.

Tri-phasic: Oestrogen levels are slightly greater in the middle of the cycle whereas progesterone doses increase over the course of three successive menstrual phases in tri-phasic formulations. Low oestrogen and progestin dosage triphasic tablets are very effective and rarely cause side effects. If a woman forgets to take one tablet, she should take two the next day to complete the cycle. more than one.

The pregnancy should be terminated if the woman becomes pregnant since these hormones are teratogenic. The hormones are not teratogenic at such low amounts, according to recent research.

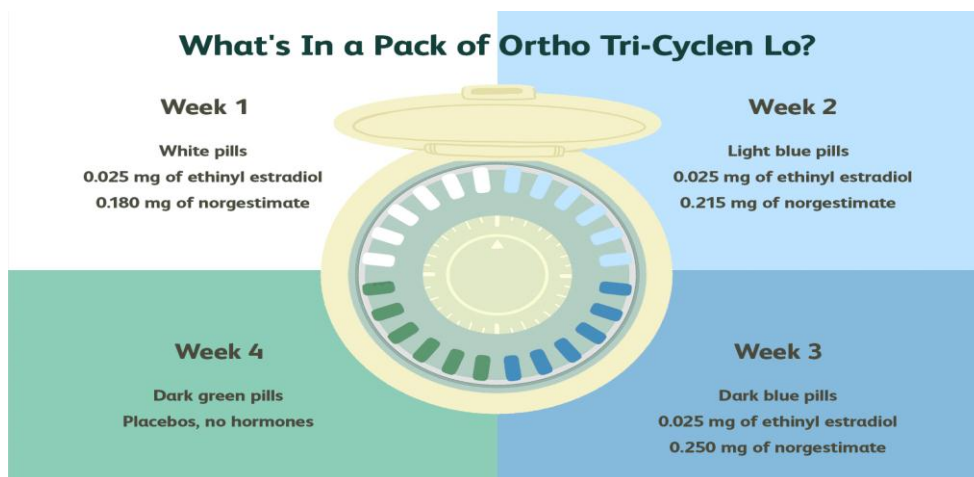


Fig. 4: Triphasic pills.

Sites and feasible action plans^[6]

1. Direct suppression of spermatogenesis has a variety of limitations, including a delayed initiation of action since mature spermatozoa are kept in storage until they are ejaculated or pass away after being kept for a long time.
2. Immunological techniques, such as vaccinations to develop antibodies to sperm, pituitary gonadotrophins, or other reproductive process factors in either sex, are being explored.
3. Suppression of the hypothalamic-pituitary activity, which regulates spermatogenesis.
3. Fertilization prevention: The female genital system may become unfavourable to spermatozoa by

altering cervical mucus or fallopian tube function, for instance.

4. Drugs to treat antizygotic conditions have been produced using substances that are effective in rats.
5. Implantation inhibition: The right endometrial condition, which is dependent on a delicate oestrogen to progesterone ratio, is necessary for implantation to occur. This balance is readily disturbed.
6. The use of spermicides intravaginally (in conjunction with barrier techniques). The gametocidal metal copper is included in both these intrauterine devices and this method of contraception, which is solely chemical rather than hormonal.



How Contraception Works: Mechanisms of Action

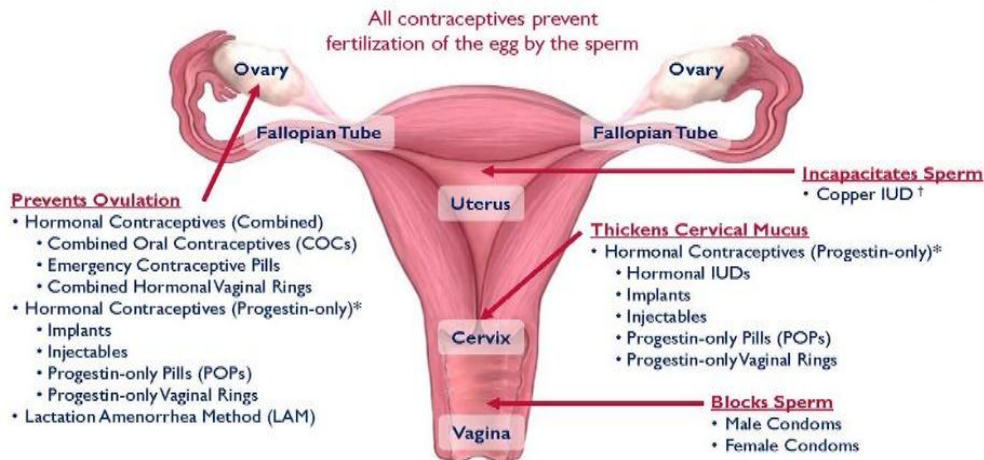


Figure 5: Mechanism of action of contraception.

Potential unwanted and beneficial effects of the combined pill: Potential negative and positive effects of the combo therapy. More than 200 million women have used this method since the 1960s, and the combination pill is generally regarded as a trustworthy and secure method of birth control. The medication has definite health benefits, and serious adverse effects are rare. However, there are a few minor drawbacks to using it, as well as a number of important factors to consider.

Common negative impact

- Mild nausea
- flushing
- dizziness
- sadness, or irritability
- Weight gain due to fluid retention, anabolic action, or both
- Acne and/or a rise in pigmentation are examples of skin alterations
- Variable-duration amenorrhea after stopping the pill

Positive results (Benefits)

Premenstrual tension, iron deficiency anaemia, irregular periods, intermenstrual bleeding, benign breast disease, uterine fibroids, and functional ovarian cysts are all significantly reduced by the combination pill. It is best to avoid unintended pregnancies, which have a maternal mortality rate of 1 in 10,000 in wealthy nations and 1 in 150 in Africa.

Further usage for blended preparations^[7]

The use of hormone replacement therapy

1. The endometriosis tissues may atrophy if combination tablets are taken regularly. Amenorrhea is a thing.
2. **Menstruation postponement:** Combined pills are taken until desired results are achieved, starting 2

tablets per day, 3-6 days before the anticipated menstruation day. Menstruation begins two to three days after stopping the medication. This could cause nausea and vomiting if used more often. One low-dose combination tablet should be taken daily from days 7 to 10, for the remainder of the cycle, and only when menstruation is desired.

3. **Premenstrual syndrome:** Oral contraceptives are taken for 3-6 cycles to stop ovulation.
4. **Dysmenorrhea:** If analgesics are not an option, oral contraceptive pills may be used for 3-4 cycles.
5. **Idiopathic hirsutism:** Combination drugs are beneficial in treating hirsutism when taken on a regular basis.

Species-specific birth control methods

Norethisterone, Levonorgestrel, and ethynodiol are the only medications in this progestogen pill. Compared to combination oral contraceptives, which are 96-97% effective, they are much less effective. The medication is taken without fail each day. The primary focus of the method of action is the cervical mucus, which is made hostile to sperms. Undoubtedly, the progestogen makes implantation more challenging. The injection of 150 mg of depot medroxyprogesterone acetate three times annually is another technique of effective contraception. This preparation should not be used if you plan to become pregnant soon after discontinuing your prescription. This is because ovulation suppression may persist for up to 18 months after the last dose. Heavy, irregular menstrual bleeding, breast discomfort, headaches, and migraines are some of the side effects. Progestogen-only contraceptives provide a suitable alternative to the combo pill for those women in whom oestrogen is contraindicated (e.g., venous thrombosis, smoking, old age, and undesirable rise in blood pressure).

Examples of progestin-only pills include^[4]

- Camila
- Errin
- Heather
- Jolivette
- Nora-BE

Additional benefits of progestogen-only tablets^[8]

Lactation: Lactating women can use progestogen-only contraception since there is no reduction in milk supply or risk to the unborn child. Menstrual symptoms: Contraceptive progestogens may reduce the frequency and severity of uterine bleeding because of their antimitotic and transformational effects on endometrial cells. Ovulation-inhibiting contraceptive progestogens can reduce dysmenorrhea. Progestogens also stop or reduce prostaglandin production in the endometrium, which increases endometrial breadth.

Menstrual migraine: The severity of menstrual migraine is lessened by prolonged usage of a progestogen.

Progestogens: can reduce the endometrium's proliferative activity in endometriosis.

Prolonged-cycle contraception

Extended-cycle contraceptives (such as vaginal rings, implants, transdermal patches, and COCPs) can stop both monthly bleeding and pregnancy by continually releasing hormones. Seasonique and Seasonable COCPs have been given approval for the 91-day extended cycle. Use extended-cycle contraception if you want to prevent monthly bleeding in women for activities like travel, sports, vacations, parties, the honeymoon, a hectic schedule, and other reasons. The hormone-free time, the frequency of scheduled bleeding episodes, and withdrawal symptoms like hypermenorrhoea, bloating, cramps, and unpleasant periods are all reduced with extended-cycle contraception methods.

Contraceptives for use right away^[9,10]

Pre- or post-sexual activity is when most contraceptives are used (e.g., vaginal rings, implants, COCPs). Emergency contraceptives (EMCs) are used after unprotected sex or after a contraceptive technique has failed. Morning after pills and "postcoital contraceptives" are other names for emergency contraceptives. Instances of failed coitus interruptus, ineffective contraceptive methods (such as a diaphragm that slips out of place, a condom that is broken or misused during sexual activity), sexual assault, consecutive missed contraceptive pills, and when no other method of contraception has been tried call for the use of emergency contraceptives.

Table 1: Emergency contraceptives.

Si. No.	Method	Use within time of unprotected intercourse	Dose and duration	Failure	Comments
1	Levonorgestrel (lmg)	72 hours	1.5 mg (oral) single dose	2%	Can be used up to 12 hours however less efficacy
2	Oc pills	72 hours	2 tablets followed by another 2 Within	3%	-
3	Mifepristone	72 hours	600 mg oral single dose	1%	-

Emergency contraceptives must halt or postpone ovulation in order to function. The implantation of the fertilised egg in the uterine wall may occasionally be hampered by EMCs. Sexual assault victims may find emergency contraception useful since they can avoid unintended pregnancies by taking the EMC pills within the recommended time limit. Emergency contraceptive regimens advise taking the pills 3 to 5 days after unprotected intercourse to prevent pregnancy.

Additional birth control methods

Topically placed patches and implants as long-acting substitutes for other contraceptive medications.

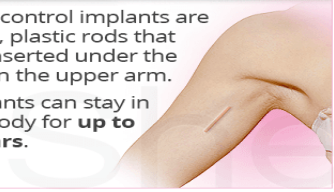
Levonorgestrel, a synthetic progesterone, is delivered through an implant using the Norplant, a subcutaneous device. as a reliable, long-term birth control strategy. Both of the six extremely tiny capsules that were surgically placed into the upper arm contained synthetic progesterone. greatest birth control technique. Levonorgestrel is used to provide birth control for up to five years by slowly and consistently diffusing at a rate of about 80 mcg every day. The An implant must be surgically removed if it is no longer required. useful or desired.

Birth Control Implants

Although less common than other methods, contraceptive implants are a valid option for women searching for reliable and safe birth control.

INSERTION

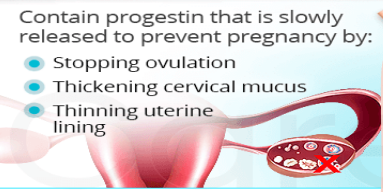
Birth control implants are small, plastic rods that are inserted under the skin in the upper arm. Implants can stay in the body for **up to 3 years**.



HOW THEY WORK

Contain progestin that is slowly released to prevent pregnancy by:

- Stopping ovulation
- Thickening cervical mucus
- Thinning uterine lining

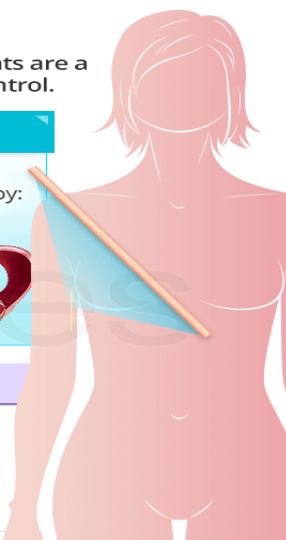


PROS

- 99% effective
- Work for up to 3 years
- Do not reduce fertility
- Does not contain estrogen

CONS

- Don't protect against STDs
- Can deregulate periods
- May cause skin irritation
- High up-front cost



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Fig 6: Implant.

A transdermal patch for contraception is a monophasic patch that comprises a combination of ethinyl estradiol and norelgestromin to offer contraception comparable to

oral preparations with the same indications and contraindications.



Fig 7: Birth control patch.

Injection-based birth control

With just one injection, Depo-Provera (medroxyprogesterone) can prevent pregnancy for three months or more. The injections stop ovulation, thicken cervical mucus, and change the endometrium to prevent the fertilised ovum from implanting. These three methods all work together to prevent pregnancy.

Copper Intrauterine devices: The success rate of copper intrauterine devices is high (>99% at 1 year), they last for 5 years, and occasionally for 10 years. They are particularly useful for older women, for whom one IUD will last beyond menopause and in whom oral contraceptives may gradually cease to be effective. The damaging effects of copper ions on the gametes augment

the anti-fertilization actions of the IUD, which also prevent the fertilised ovum from implanting.



Fig 8: Intrauterine devices.

The abdominal gadgets: The implantation of intrauterine devices is another reasonably long-term effective reversible birth control option that needs just minor surgical procedures. The two IUDs that are readily available are the intrauterine progesterone contraceptive device and the copper T 380A (Paragard) IUD (progestasert).

Intrauterine Levonorgestrel system: Mirena is a progestogen used in hormone replacement therapy, as a contraceptive, and as a treatment for idiopathic menorrhagia. Because of less dysmenorrhea and lighter menses, it is well-liked. A silastic capsule enclosing 52 mg of Levonorgestrel makes up the Mirena, which releases 20 micrograms every day for the course of five years before needing to be replaced.

Vaginal preparations that immobilise or kill (spermicide) spermatozoa are added for safety when using various mechanical contraceptives. They are so unreliable that they should only be utilised independently in dire circumstances.

Non-oxinolins are used as pessaries, gels, and foams. These surfactants alter the sperm lipoprotein membrane's permeability.

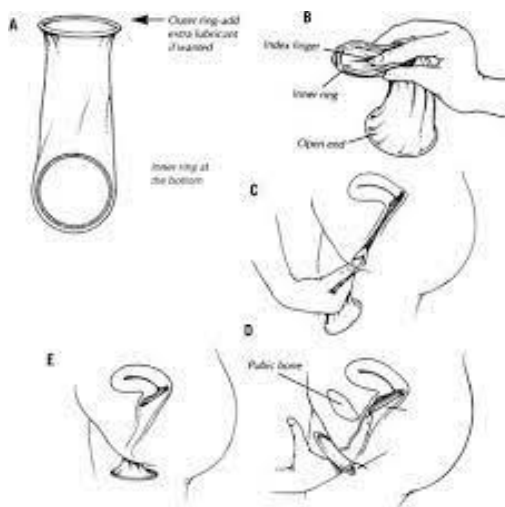


Fig 10: Spermicides.

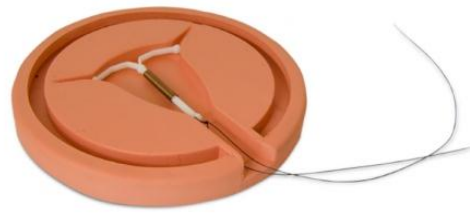


Fig. 9: Copper IUD.

Benefits of oral contraceptives without contraception^[11]

Oral contraceptives are used to treat the symptoms of...

1. Hyperandrogenism in women Comedonal acne and acne vulgaris are two related skin conditions.
2. Heroticism
3. Seborrhoea
4. Female hair loss
5. A reduction of 50% in endometrial cancer (when administered for more than three years, with the greatest benefit).
6. After three years of use, but already present in the first three to six months, there is a 40% reduction in the risk of developing ovarian cancer.
7. reduction in the prevalence of benign breast illness.
8. improvement in haemoglobin levels, blood loss, and dysmenorrhea protection against pelvic inflammatory illness
9. Possible advantages include decreased risk of uterine leiomyoma, colon cancer, and ectopic pregnancy.

Drug interaction

Drugs may reduce the effectiveness of OCPs or OCPs may interfere with the metabolism of other chemicals in pharmacological interactions between OCPs and other medications. Interactions of the first sort are related to interference with the absorption, metabolism, or excretion of oestrogen, and interactions with the second kind are due to competition for metabolic pathway.

A. Anticonvulsants like phenobarbital, phenytoin, and carbamazepine, as well as the antibiotic rifampicin, stimulate a cytochrome P450 enzyme, which increases the clearance of OCPs. These medications may make OCPs less effective. Other antibiotics including tetracycline, quinolones, ampicillin, and metronidazole reduce enterohepatic recirculation and the bacterial flora of the gastrointestinal tract since EE has a low bioavailability. Due to competition for sulfation, paracetamol with ascorbic acid causes raised blood levels of EE, which could increase the likelihood that it will have unfavourable consequences.

B. OCPs may influence the metabolism of other medications. They reduce the clearance of benzodiazepines such diazepam, chlorthalidoxepoxide,

alprazolam, and diazepam. Theophylline, prednisolone, caffeine, and cyclosporine are also less prevalent in the systems of OCP users. As a result, taking these drugs in smaller doses may be advantageous for OCP users. Temazepam appears to be eliminated more quickly, as are salicylic acid, paracetamol, morphine, and clofibric acid. Users of OCPs may require larger doses of these drugs.

- C. Some antiepileptic medications (AEDs), such as lamotrigine, may experience cycle-related changes in serum levels when OCPs are being used. Lamotrigine levels decrease by about 50% when using the medicine, making it challenging to manage seizures. The dose should be decreased because the level could increase during the "pill-free" period, leading to lamotrigine toxicities include sleepiness, double vision, and unsteadiness.

Adverse effects of oral contraception^[12]

The current low-dose preparations were created as a consequence of the widespread agreement that low-dose medications only slightly increase the health risks for women who don't already have predisposing factors. The prior oral contraceptives resulted in a variety of metabolic and endocrine problems, as well as negative cardiovascular effects such hypertension, myocardial infarction, stroke, venous thrombosis, and embolism. Low-dose oral contraceptives do not frequently cause such adverse effects.

- 1. Thromboembolism:** There is an increased risk of deep vein thrombosis, cerebral thrombosis, and pulmonary embolism. The risk is affected by the amount of the oestrogen component. The little dose of the Pills reduces this risk. The drug should not be taken by anyone who has cerebral apoplexy, thromboembolic conditions, thrombophlebitis, or a history of any of these issues. Any of the aforementioned symptoms, such as vascular headaches, leg cramps, altered vision, or hypertension, should prompt a permanent discontinuation of the medicine.
- 2. Hypertension:** It occurs in about 5% of users after five years and is connected with usage frequency. It most likely stems from the oestrogen-induced increase in angiotensinogen.
- 3. The liver and the gall bladder:** Alkaline phosphatase and plasma conjugated bilirubin may rise in as many as 2% of individuals. Both estrogens and progestogens may be involved in the

development of acute hepatitis in women; as a result, the medicine needs to be stopped and shouldn't be started again until the liver function tests have been normal for at least six months. Women on the pill experience gallstones twice as often as non-users.

The harmful effects

The first dose of the pill may cause nausea and vomiting, but these side effects may pass with prolonged use. The oestrogen component is what causes the consequences. To reduce them, the medication should be taken right before bedtime on an empty stomach.

Breast engorgement, weight gain, mastalgia, and leucorrhoea may be caused by the oestrogen concentration (increased vaginal secretion). A migraine attack can be triggered or intensified. Depression may be more prevalent in pill users, and it is more likely to occur in women who have had premenstrual tension syndrome or past episodes of depression.

The following are centchroman's advantages

1. A success percentage of 97-99% is mentioned.
2. Teratogenicity, carcinogenicity, or mutagenicity were not reported.
3. It is well tolerated.

Disadvantages

1. Polycystic ovaries ought to stay away from it because it might cause ovarian hypertrophy.
2. It should also be avoided by those with tuberculosis, liver disease, renal failure, and nursing mothers.

Packaging and Use

LevlenED blister pack with partial use Oral combined contraceptives should be taken every day at the same time. There will be a reduction in contraceptive protection if one or more tablets are left unattended for longer than 12 hours. The majority of brands of combined tablets come in one of two different packet sizes, each having the days divided into a 28-day cycle. The 21-pill packet of a pill should be taken every day for three weeks before taking no pills for a week. For the 28-pill package, 21 pills are taken first, then a week's worth of sugar or placebo tablets. Yaz 28 and Loestrin 24 Fe, two more recent combination birth control pills, contain 24 days of active hormone pills followed by 4 days of placebo.



Fig 11: Use and Packaging of oral contraceptive pills.

Packaging and Use

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Trends in oral contraceptive use today^[13]

A once-per-month contraceptive tablet has been developed by scientists. A six-armed star-shaped polymer structure that stays in the stomach for at least three weeks and releases artificial hormones to prevent pregnancy is released when the gelatine capsule dissolves in the stomach. So far, pigs have been the only animals used to test this gelatin capsule. The use of common medications incorrectly could prevent unwanted pregnancies, say scientists.

CONCLUSIONS

Because they are easy to use, don't interfere with sexual pleasure, don't require surgery, don't cause any device-related discomfort, can be stopped easily if a couple wants to start a family, and are highly effective when used as instructed, oral contraceptive pills are among the most widely used birth control methods. When administered consistently in line with suggested regimens, OCPs have a success rate of above 99%.

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