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A Review of Recent Findings for Obstetricians about Combined Oral Contraceptive Pills

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Abstract

Combined oral contraceptive pills (OCPs) contain estrogen (ethinylestradiol) and progesterone (first-generation levonorgestrel and fourth-generation drospirenone). Progesterone has peripheral effects on the endometrium, fallopian tubes, and cervix and can promote contraception. These pills are used to prevent pain caused by Mittelschmerz syndrome and endometriosis and to treat hyperandrogenism. To prescribe contraceptives, it is adequate to take the patient's medical history and blood pressure. In the absence of risk factors, patients should be followed-up by history-taking, blood pressure measurement, urinalysis, Pap smear test, and examination of breasts, pelvis, and liver. The risk of venous thrombosis in new OCPs is twice higher than that of older generations and usually occurs in the first year of consumption. The only absolute contraindications for the use of new OCPs include chronic and acute cholestatic liver diseases. In fact, use of new OCPs increases the risk of liver adenoma, but not hepatocellular carcinoma. On the other hand, in female patients with genital tract cancers, risk of endometrial and ovarian epithelial cancers decreases following the use of OCPs. However, the risk of cervical adenocarcinoma increases after 5 years of consumption due to cervical eversion and impaired vitamin metabolism. These pills are contraindicated in women above 35 years who smoke more than 15 cigarettes daily or have uncontrolled hypertension, venous thromboembolism, migraine aura, severe hyperglycemia, breast cancer (diagnosed or suspected), or diabetes mellitus associated with cardiovascular diseases.

Keywords: Oral Contraceptive Pills, Contraception, Pregnancy, Thrombosis

1. Context

The main mechanism of oral contraceptive pills (OCPs) involves the inhibition of luteinizing hormone surge and ovulation, mainly caused by estrogen. In addition to the contraceptive properties of OCPs, they are used to treat other gynecological problems.

2. Evidence Acquisition

Although birth control seems to be a recent phenomenon, it has been used since ancient times, based on the manuscripts from old civilizations (1). The estrogen component of OCPs suppresses follicle-stimulating hormones (FSH) and prevents the emergence of dominant follicles. Besides, the progesteron component prevents implantation through affecting the endometrium and makes the cervical mucus thick and impermeable against sperms (2, 3); therefore, it has both central and peripheral effects.

In addition to the contraceptive properties of OCPs, they are also used to treat dysmenorrhea, menorrhagia, pelvic pain (Mittelschmerz syndrome), menstrual cycle disorders (eg, hypothalamic amenorrhea), and hypogonadism (4). Continuous use of OCPs has been also suggested for premenstrual dysphoric disorder. Hyperandrogenism or acne, endometriosis, and polycystic ovarian syndrome are among other diseases treated by OCPs (5). Low-dose OCPs contain less than 50 μg of ethinylestradiol (6), while the high-dose pills contain 50 μg or more of ethinylestradiol.

In multiphasic products, both estrogen and progesteron components change periodically during consumption. There is no major difference between multiphasic and low-dose monophasic products in terms of metabolic effects. All OCPs can be administrated for long periods alternatively or continuously (7). Since 1989, the age limit for OCP consumption (ie, 35 years for smokers and 40 years for nonsmokers) has been removed. The common practice in the United States seems logical, as OCPs are only administrated for female nonsmokers above 35 years without cardiovascular diseases (8).

Regarding OCP consumption, 0.1% theoretical failure and 8% experimental failure have been reported in the literature, mostly resulting from improper use of pills. In the following section, the necessity of OCP use will be discussed (9). Overall, use of OCPs can be initiated through proper history-taking and blood pressure measurements. Although breast examination, Pap smear test, and screening for sexually transmitted diseases are important measures, most medical associations, such as the American College of Obstetricians and Gynecologists (ACOG), World Health Organization (WHO), and Royal College of Obstetricians and Gynecologists (RCOG), have not acknowledged

the necessity to perform such tests before starting OCPs (10).

History-taking and blood pressure measurements are adequate in the first visit, and in the absence of risk factors, women should be followed-up every 12 months via history-taking, blood pressure measurements, urinalysis, Pap smear test, and breast, liver, and pelvic examinations. On the other hand, cases with risk factors should be examined every 6 months; only breast and pelvic examinations should be conducted annually (9).

3. Results

The systemic effects of OCPs are described as follows:

1. OCP consumption increases the risk of cerebrovascular accidents in patients with defective genes, as factor V Leiden and prothrombin gene mutations are the main causes of deep vein thrombosis.

2. Cardiovascular diseases, caused by OCPs, result from acute conditions, especially thrombosis due to the presence of dose-dependent estrogens. Venous thrombosis depends on the estrogen level and is limited to current OCP consumers (11). Also, smoking increases the risk of arterial thrombosis, while it has no effects on venous thrombosis (smoking more than 10 cigarettes a day increases the risk of thromboembolism) (12).

Risk of venous thrombosis in new OCP types is almost twice higher than that of older generations. It usually occurs in the early years of consumption (4) and is more common among obese and older females. Arterial thrombosis is the main possible side-effect of OCP. Also, risk of myocardial infarction only increases in female smokers consuming OCPs (13).

Arterial thrombosis only affects female smokers and those with high blood pressure. In case of high blood pressure in nonsmoking women less than 35 years, low-dose OCPs can be administered by controlling blood pressure every 3 months (14). A limited increase in blood pressure occurs following the consumption of monophasic, low-dose OCPs, containing new progestins. Annual evaluation of blood pressure is still a significant factor in clinical assessments (15). Overall, in such methods, involvement of the renin-angiotensin system influences blood pressure.

3. Generally, OCP increases peripheral resistance to insulin; this effect is mostly attributed to progestins. Changes in the metabolism of lipids and carbohydrates do not increase the risk of cardiovascular diseases; also, OCP consumption does not increase the risk of diabetes mellitus (16).

4. Liver is more affected by steroids, compared to nongenital organs (17). Liver examination is part of assessment programs for OCP consumers. In case of liver enlargement, the OCP regimen should be discontinued and the necessary follow-ups should be performed (18). Estrogen affects the synthesis of liver DNAs, RNAs, enzymes, serum enzymes, and plasma proteins. Cholestatic jaundice and itching are among the benign and reversible side-effects of high-dose OCPs.

The only absolute contraindication for OCP use is acute or chronic cholestatic disease (19). Women can start OCP consumption right after the treatment of acute liver disease. The increased incidence of gallbladder stones due to the consumption of OCPs is mostly reported in the first year of consumption due to the increased cholesterol level, caused by estrogen; however, this effect has not been confirmed in all previous studies.

OCPs have no effects on the progression of acute or chronic hepatitis. In addition, these products do not influence the severity of cirrhotic fibrosis, risk of hepatocellular carcinoma (in women with chronic hepatitis), or risk of dysfunction in hepatitis B virus (HBV) carriers. Overall, there is no relationship between the consumption of OCPs and hepatic cancer. In general, liver lesions caused by estrogen and androgen components of OCPs are categorized in 3 groups: 1) adenoma associated with the risk of bleeding; 2) peliosis associated with dilated vascular spaces with no endothelial coverage (regressed by OCP discontinuation); and 3) focal nodular hyperplasia caused by OCP consumption.

5. Nausea and discomfort in breasts are reported following the consumption of OCPs, especially in the early months of use.

6. Weight gain is usually controlled by dietary restrictions; OCP discontinuation is rarely the only way to control weight (20).

7. There is a risk of oral contraceptive failure in patients with gastrointestinal malabsorption, although it rarely happens. In patients with inflammatory bowel diseases and gastrointestinal malabsorption, the vaginal route is ideal for delivering the drugs (21).

8. Chloasma gradually resolves by OCP discontinuation; nevertheless, in some cases, it may never completely disappear.

9. OCPs may influence sexual activity due to the effects of estrogen on increasing the level of sex hormone-binding globulin and free testosterones. In fact, oral contraceptives, containing drospirenone (new progestins) are reported to increase sexual performance and health (22).

10. OCPs seem to be associated with the risk of gynecologic cancers. OCPs have protective effects due to the efficacy of progesteronic agents against endometrial cancer. At least one year of OCP use is associated with a 50% decline in the risk of cancer; this protection is maximized by 3 years of OCP use (the effects persist for 20 - 30 years)

(23). The protective properties of OCPs affect 3 types of endometrial cancers, ie, endometrioid carcinoma, clear cell endometrial cancer, and papillary serous endometrial cancer (24, 25).

The risk of epithelial ovarian cancer reduces by 40% in OCP consumers, and optimal effects can be obtained by 3 years of consumption; however, the risk reduces within 3 to 6 months of OCP consumption (25). This protective effect is especially evident in nulliparous women, breast cancer (BRCA) gene I and II carriers, and those with a positive family history. According to the conducted studies, the rate of epithelial cancer and borderline tumors reduces following the consumption of OCPs (26). However, the mechanism of oral contraceptives in the prevention of ovarian cancer is unknown, although induction of apoptosis may be one of the involved mechanisms (27, 28).

There is no definite relationship between cervical cancer and OCP use due to the presence of confounding factors (29, 30). The risk of cervical ectropion increases following the consumption of OCPs, and the relationship between OCPs and cervical adenocarcinoma has been confirmed. Also, impaired metabolism of vitamins following the use of OCPs (31) and reduced clearance of human papillomavirus (HPV) can increase the risk of adenocarcinoma (32).

If HPVs enter the body, the risk of cancer can be minimized by vitamins and a strong immune system. The risk of HPV infection increases in women who use OCPs and show high-risk behaviors. Moreover, OCP probably increases the risk of HPV establishment; in case of OCP use for more than 5 years, the interval between Pap smear tests should be reduced (33). Also, history of cervical intraepithelial neoplasia or cervical neoplasia surgery is not a barrier against the use of OCPs (34).

11. Use of high-dose OCPs has protective effects against benign breast diseases. This effect emerges after 2 years of consumption and significantly reduces the risk of breast cancer (40%). Moreover, OCPs have protective effects against benign proliferative diseases, and increased consumption is known to decrease the risk of disease. Full-term pregnancy at young age decreases the risk of breast cancer. Also, OCP consumption in BRCA carriers reduces the risk of ovarian cancer, while the effect on breast cancer is unknown.

12. Previous history and duration of OCP consumption have no effects on the reduction of risk for breast cancer. OCP consumption does not reduce the risk of breast cancer in women with a history of breast cancer or benign breast disease. In fact, after 5 years of OCP consumption, breast cancer is usually detected in the early stages (35).

13. The risk of colorectal cancer reduces in women with a continuous OCP regimen and those recently starting on OCP. Consumption of OCP is also recommended for women with a family history of colorectal disease.

14. The risk of partial molar pregnancy increases by the consumption of OCPs, while the risk of persistent gestational trophoblastic neoplasia does not increase.

15. Regarding the hematological effects of OCPs, the erythrocyte sedimentation rate and total iron-binding capacity increase by OCP use.

16. Depression occurs due to estrogen interference in the production of tryptophan; in these cases, it is better to discontinue OCP and treat depression. Also, this effect can be reduced by adding pyridoxine (36).

17. Voice changes occur following the administration of high-dose OCPs.

18. By increasing the level of circulating thyroid hormone-binding globulin, the level of total thyroxine increases, while the level of free thyroxine remains in the normal range.

19. The risk of pelvic inflammatory disease decreases in OCP consumers, which results from cervical mucus thickening and menstrual bleeding reduction. These changes protect the body against gonococcal infections, whereas chlamydial infections are intensified, according to different studies (37).

20. All OCPs can protect the body against functional ovarian cysts with different degrees, but are not useful for the treatment of large functional ovarian cysts. Also, they are effective in reducing the risk of ovarian neoplasms (37).

21. The risk of leiomyoma decreases following the use of OCPs (38).

3.1. Contraindications for OCP Consumption

Contraindications for OCP consumption include (39):

- Age above 35 years and smoking more than 15 cigarettes a day
- Uncontrolled blood pressure (160 mmHg systolic and 100 mmHg diastolic blood pressure)
- Venous thromboembolism
- Identified thrombogenic mutations
- Ischemic heart disease and history of stroke
- Valvular heart disease (risk of arterial fibrillation and history of subacute bacterial endocarditis)
- Migraine aura at any age
- Hepatocellular adenoma, malignant hepatoma, and significant liver function impairments
- Hypercholesterolemia or severe hypertriglyceridemia
- Known or suspected pregnancy
- Abnormal vaginal bleeding with an unknown etiology
- Known or suspected breast cancer
- Diabetes mellitus in association with vascular disease

OCPs available in Iran's market

OCP on lactation (lynestrenol), also called minipil, is a white pill in a 28-tablet sheet with no estrogenic component. Since estrogen reduces milk production and may leave adverse effects on infants, it should not be used during the first 6 months after birth; besides, LD and HD are available. Use of new OCPs has a short history in the Iranian market, compared to older generations of these drugs. The difference between new and old generations of OCPs can be summarized by the addition of progesterones in the new generations, which have fewer side-effects and are authorized to be used under certain conditions for patients with underlying diseases (eg, acne). However, the mechanisms and failure rates are similar in the new and old generations of OCPs.

Rokin, Marvelon, Marolin, and Desoceptive comprise the new generation of OCPs. Desoceptive, Marvelon, and Marolin are similar contraceptives. It is noteworthy that in these medicines, desogestrel (0.15 mg) and ethinylestradiol (0.03 mg) are the progesteronic and estrogenic components, respectively. Desogestrel, as a progesteronic agent and a third-generation oral contraceptive, is useful in the treatment of diabetes and dyslipidemia. In addition, Rokin and Yasmin have similar compositions, including drospirenone (3 mg) as the progestin and ethinylestradiol (0.03 g) as the estrogenic component; these medicines are known to reduce edema in consumers.

Use of OCPs has other advantages in addition to contraception. They regulate the menstrual cycle and reduce menstruation bleeding and pain, as noticeable among women with such complications. Use of new OCPs sometimes promotes the hormonal balance in women's body and improves their mental and physical states; it also prevents the formation of new cysts in some patients with ovarian cysts (4).

4. Discussion

4.1. Common Questions Regarding OCPs

1. When can a woman who uses OCP as a contraceptive method stop the regimen and substitute it with hormone replacement therapy (HRT)? In other words, how can she understand that there is no need to use OCPs to prevent pregnancy?

When the FSH level reaches above 20 during menstruation bleeding, women can discontinue OCPs; however, if aged above 55 years during consumption, it is better to stop the regimen.

2. What does "rule 3" refer to in the consumption of OCPs?

In women with a miscarriage within 12 weeks, OCPs can be consumed as an oral contraceptive; however, in cases with miscarriage more than 12 weeks, it is recommended to delay the use of pills. Use of OCPs as oral contraceptives should be prevented in breastfeeding women for 3 months. However, in nonbreastfeeding women, OCP regimen can be started 3 weeks after delivery.

3. How are OCP consumption and HRT comparable regarding estrogen level?

Overall, 10 μg of ethinylestradiol in LD pills is equal to 0.625 mg of conjugated estrogen; therefore, the level of estrogen in LD pills is 3 times higher than that of HRT and 5 times higher than that of HD pills (containing 50 μg of ethinylestradiol). On average, estrogen in OCPs is 4 times stronger than other contraceptive methods.

4. Which ones are better, monophasic or triphasic pills?

In monophasic pills, estrogen and progesterone doses are the same, whereas biphasic or triphasic pills include different doses of hormones during the cycle (the dose of progesterone is usually different). However, no approved advantage has been reported for multiphasic regimens, and we recommend starting with a monophasic OCP (40).

5. Which one is preferred, the new or old generation of OPCs?

Most of the available progestins have both progesteronic and androgenic activities. Progesterone with pure progesterone activity is ideal for this purpose, since there is no need for androgenic activity to induce contraceptive properties, and androgens increase the risk of side-effects and metabolic complications. There are new progestins, some of which can act as androgen receptor antagonists. However, no superiority has been reported regarding the consumption of these new products, compared to older progesterones; even some of them are associated with a high risk of venous thromboembolism (41).

4.2. Management of Complications Associated with OCP Consumption

If spotting is observed between 2 menstrual cycles during OCP consumption, the level of hormones in the body is probably insufficient and therefore, appears as bleeding. To prevent bleeding on days with spotting, it is better to take 2 pills a day. If bleeding increases to the level of menstruation, the OCP regimen should be discontinued. Bleeding while using OCPs is normal in the first 3 months of starting the regimen and consumers do not need to be concerned; nevertheless, women can use 1.25 mg conjugated estrogen pills, along with OCPs for a week.

If bleeding starts in the last week of OCP cycle, it is better to stop the regimen for 1 week and use a new tablet sheet. If bleeding starts in the middle of OCP cycle, conjugated estrogen (1.25 mg) or estradiol (2 mg) pills should

be used every day for 1 week; estrogen can be used for another week in case of recurrence. If bleeding occurs during continuous OCP consumption, the regimen should be discontinued for 3 or 4 days, but not more than once every 3 weeks.

4.3. Consumption of OCPs Along With Other Medicines

Rifampin is an antibiotic, which affects the metabolism of OCPs. In women who use anticonvulsants (such as phenobarbital, carbamazepine, phenytoin, oxcarbazepine, felbamate, and topiramate), OCP effectiveness reduces due to the induction of p450 liver enzymes; therefore, another contraceptive method, such as condoms, can be used. Also, there are some other anticonvulsants which have no effects on the serum level of contraceptive steroids, such as valproic acid, vigabatrin, gabapentin, lamotrigine, tiagabine, levetiracetam, zonisamide, ethosuximide, and benzodiazepines (42).

Moreover, antifungal agents, such as itraconazole, ketoconazole, and griseofulvin, induce liver enzymes and reduce the effectiveness of oral contraceptives. Ampicillin and tetracycline are also responsible for the failure of oral contraceptives due to the removal of intestinal bacteria, specifically Clostridium species, which hydrolyze intestinal steroid glucuronides.

Tetracycline and penicillin both reduce the serum level of ethinylestradiol (43). Therefore, effective contraception with condoms is recommended for women who are under antibiotic therapy. Ascorbic acid (vitamin C), acetaminophen, and antiviral medicines, such as efavirenz, atazanavir, and ritonavir, may increase the serum level of ethinylestradiol. Also, oral contraceptives reduce the metabolic clearance rate and increase the half-life of benzodiazepines (chlordiazepoxide, alprazolam, and diazepam), caffeine, and theophylline. Moreover, OCPs intensify the clearance of salicylic acid and morphine (44).

4.4. Fertility after OCP Consumption

The incidence of amenorrhea caused by OCPs is less than 2% in the first year of consumption and increases to 5% after several years (statistically insignificant) (45). A simple test for pregnancy is the measurement of the basal body temperature at the end of the no-OCP week or on the last day of stopping the active-pill phase (in the 24-day regimen). If the basal body temperature is below 36.7°C (98°F), the occurrence of pregnancy is impossible and OCPs can be continued.

After discontinuing OCPs, recurrence of cycles with ovulation may be delayed for several months. Women with amenorrhea should be fully examined for the high risk of prolactin-secreting pituitary tumors, even 6 months after the discontinuation of OCP regimen, since the presence of slow growing tumors, which can cause irregular menstruation, forces the patient to take OCPs. Women who do not have a normal menstruation up to 12 months after OCP discontinuation should be evaluated similar to patients with secondary amenorrhea (46).

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