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Review Article

ADVERSE EFFECT OF COMBINED ORAL CONTRACEPTIVE PILLS

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ABSTRACT

Oral contraceptive (OC) pills contain estrogen and progestin that are synthetic analogs of natural hormones. These synthetic hormones affect the hypothalamus-pituitary-gonadal axis of the female reproductive system. There are many types of contraceptives; most of the OC pills prevent pregnancy by inhibiting ovulation. Estrogen and progestin are two female reproductive hormones that are critical. Typically, estradiol is produced by growing follicle (ovaries) which stimulates the hypothalamus to produce the gonadotropin-releasing hormone, which further stimulates the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH production triggers the ovulation. Similarly, the progesterone is produced by corpus luteum (ovaries), which triggers the production of FSH and LH. There are many types of progesterone available. Long-term usage of synthetic estrogen and progesterone can disturb the balance between the level of these hormones in the body. This imbalance may lead to severe side effects such as breast cancer, cervical cancer, thrombosis, direct impact on the brain, and infertility.

Keywords: Estrogen, Progesterone, Contraceptives, Herbal contraceptives.

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INTRODUCTION

Contraception is a method to prevent unwanted pregnancy. Combined oral contraceptives (COCs) have become a popular method of birth control due to their contraceptive efficacy and good tolerability profile [1]. These pills contain hormones that act on the reproductive system of female leading to contraceptives such as estrogen and progesterone. OCs are the combination of estrogen and progestin or only progestin. Over the years, OCs have developed through gradually reducing the dose of ethinylestradiol (EE) and introducing 17-β estradiol, and various generations of progestin [2]. There are manytypes of estrogen and progesterone being used in pills like mestranol is a class of estrogen, and the 3-methyl ether of EE and norethynodrel is a type of progestin; its dose was 9.85 mg per pill initially. In clinical studies, the efficiency of contraceptive was excellent, but this drug caused many side effects such as nausea, dizziness, headaches, stomachaches, and vomiting; these are the symptoms that had presented by the 17% women undergoing the clinical studies. Though, the death of a female had been reported who was taking the contraceptive pills in 1961. Although after so many years, OCs have developed by reducing the dose of estrogen and by discovering a new generation of progestins, and other routes of COC administration have been developed [3]. The findings of the previous research show some severe side effects of these pills. Thus, this short study is focused on the overview of the female reproductive system and its regulation, hormonal contraceptive pills, mechanism of action of these drugs, and side effects of OC pills.

OVERVIEW OF FEMALE REPRODUCTIVE CYCLE

The balance between estrogen and progesterone handles the development and maintenance of the female reproductive system. Cellular differentiation is regulated by progesterone while estrogen controls cell proliferation. Thus, uterine endometrium has 3 phases (Fig.1)

1. The follicular phase (estrogen dominant) is a growth phase where uterine glands grow and proliferate
2. During secretory (luteal) phase, (progesterone dominant) glands get tightly coiled, and secrete
3. During menses, spiral arteries constrict, and endometrium sloughs.

REGULATION OF REPRODUCTIVE HORMONES IN FEMALE

The hypothalamus is responsible for the secretion of gonadotropin-releasing hormones (GnRH), which then stimulates the anterior pituitary to release follicle-stimulating hormones (FSH) and luteinizing hormones (LHs). FSH stimulates follicle growth, maturation of ovum leading to the release of estradiol from follicles. High levels of estradiol for a sufficient period stimulate sudden secretion of LHRH (GnRH-positive feedback), which induces a surge of LH (and FSH) secretes from the anterior pituitary (Fig. 2). LH surge leads to ovulation and assists the development of corpus luteum. Corpus luteum then releases progesterone. Increased levels of estrogen and progesterone will signal anterior pituitary and hypothalamus to stop the secretion of FSH and LH. The resulting negative feedback leads to deterioration of corpus luteum, which further decreases the amount of estrogen and progesterone [5].

The contraceptive pills work on the same hormonal axis mentioned above. These drugs modulate the normal condition of this hormonal regulation, which delays the follicle development in females. There are different categories of hormonal contraceptives and different mode of administration. Although, this study is focused only on COC pills and progesterone-only pills.

CATEGORY OF HORMONAL CONTRACEPTIVES PILLS

Previously, administration of COCs used to deliver a dose of high EE or mestranol along with progestin, resulting in increased risk of cardiovascular disease. However, the therapeutic combinations of COC have substantially changed over the past few decades (Fig. 3). Current COCs contain a low dose of EE or estradiol (E2) combined with new progestins, and many alternatives or nonoral routes of administration have been evolved. Besides, progestin-only contraceptive pills are a contraceptive method that may be the better option for women with several routes of administration are available these days [6].

ORAL ROUTE OF ADMINISTRATION

OCs can be categorized into two main categories:

- COC pills and
- Progestin-only pills (POPs).

COCS PILLS

Synthetic estrogen (with high dose) and androgenic progestin like norethisterone acetate or norethindrone had been marketed as the first COC. The present COCs deliver low doses of EE every day. E2 valerate

and dienogest have been newly approved in Europe and the USA as quadriphase OC. Another monophasic COC that combines E2 with nomegestrol acetate, a progesterone-derived progestin, is now being marketed in several countries in Europe [7-9].

Estrogen in COC

The dose of estrogen has been decreased by drug companies to reduce the risk of cardiovascular disorders. The estrogen component, EE or 17α estradiol is used in COCs available these days (Table 1). Over the years, the dose of EE has reduced from 50 to 30-35 mg and gradually to 20-15 mg. Pills are now segregated into higher and lower than 30 mg dose of EE. This reduction has been made feasible due to the accessibility of new classes of progestin. In the 1970s, the concept arose to use the natural 17β estradiol in COCs, although no satisfactory formulations were available for years. In few cases, the pills containing 17β-E2 were contraceptive, but females showed low tolerance experiencing excessive bleedings. There are two combinations have been commercialized containing estradiol (E2). Selective estrogen receptor modulators are under development, which has estrogenic activity on bone and endometrium but antiestrogenic activity on the breast, e.g., estetrol [3].

Progestins in COC

In the different combined pills available nowadays, the progestin component in the pill inhibits LH peak, decreases ovarian sensitivity to FSH, and therefore, decreases estradiol production. The estrogenic component regulates endometrium proliferation and compensates estrogenic deficiency induced by the antigonadotropic effect of the progestin. Progestins are classically characterized according to their structural origins. They bind to progesterone receptors, but progestins may also bind to other steroid receptors such as androgen, glucocorticoid, and mineralocorticoid receptors. Most of the progestins contained in COCs were initially derived from testosterone and are called 19-nortestosterone derivatives. Norethisterone is an estrone, and norethisterone acetate and norethynodrel are gonanes. Few pills containing first-generation progestins are still available. Their side effects such as acne, oily skin, and decreased high-density lipoprotein, mainly due to their androgenic properties, are the primary cause for their progressive withdrawal. Over the years, progestins with less androgenic effects have been developed (Table 2). Levonorgestrel (LNG) and norgestrel are second-generation progestins. Third-generation progestin includes desogestrel (DSG), with its active metabolite 3-keto-DSG (also named etonogestrel), norgestimate (and its active 17-deacetylated metabolite, norelgestromin [NGMN]), and gestodene (GSD) [3].

Different progestins used in COCs are derived from progesterone. Molecules such as chlormadinone acetate, cyproterone acetate (CPA), and medroxyprogesterone acetate are called pregnane derivatives, as they are derived from 17-OH progesterone [10]. Some newer progestins have been available more recently in OCs such as drospirenone (DRSP). This progestin possesses antimineralocorticoid and weak androgen proprieties. Dienogest is a hybrid progestin, derived from the estrane group but does not exert the androgenic effects of the testosterone derivatives. A Cochrane review evaluated the effectiveness and side effects of different progestogens [11]. In this comparative study, 13,923 participants were included in a total of 30 trials enabling 16 comparisons. The conclusion of this Cochrane Review mentions that women using COCs containing second-generation progestogens may be less likely to discontinue than those using COCs containing first-generation progestogens. Based on one small double-blind trial, third-generation progestogens may be preferable to second-generation preparations concerning bleeding patterns, but further evidence is needed [3].

Millions of women have used estrogen and progestins as effective COCs. OCs modify surrogate markers such as lipoproteins, insulin response to glucose, and coagulation factors that have been associated with cardiovascular and venous risk. EE exerts a stronger effect that natural estradiol (E2) on hepatic metabolism. New progestins with high specificity have been designed to avoid interaction with other receptors and prevent androgenic, estrogenic, or glucocorticoid-related side effects. The risks and benefits of new progestins used in contraception depend on their molecular structure, the type and dose of associated estrogen, and the delivery route [3].

Progestin-only contraceptive pills (POPs)

POPs delivers a very low concentration of progestin every day (norethindrone, LNG, or DSG). While the developments of OCs pills are based on progestin-only components, recently POPs are less widely used than COC as a result of their negative uterine tolerance [12]. Though, POPs may be an attractive contraceptive choice for women with contraindications to COCs (Table 3).

ALTERNATIVE (NONORAL) MODE OF ADMINISTRATION

These types of contraceptives provide steady supplies of hormones. They can be delivered in a combination of estrogen and progestin or progestin only.

Combined contraceptives

There are two types of other (non-oral) mode of administration available: Patch and vaginal ring. The patch (transdermal) consists of EE along with NGMN and the vaginal ring consists of EE along with etonogestrel.

Progestin-only contraceptive

Currently, there are three major routes of nonoral administration of contraceptives which are frequently used in the USA and Europe [3].

Many synthetic hormonal contraceptives are available with different brand names, but these all contain synthetic estrogen and progesterone and having severe side effects. The details of few synthetic contraceptive drugs are mentioned in Table 4.

ADVERSE EFFECT OF SYNTHETIC CONTRACEPTIVE PILLS

It has been reported that OC pills may cause many side effects in a long run, and authors have discussed a few of those side effects in this article.

Table 1: Two type of combinations of estradiol [3]

Active ingredients	Classification of components
Quadriphasic COC-E2 valerate+dienogest	E2 valerate-synthetic estrogen, metabolized into 17 bE2
Monophasic COC-17b E2+nomegestrol acetate	Nomegestrol acetate-progestin

COC: Combined oral contraceptive

Table 2: Different generations of progestin used in COCs [3]

1st generation progestin	2nd generation progestin	3rd generation progestin
Norethisterone acetate	Norgestrel	NGM
Lynestrenol	LNG	DSG
Ethynodiol acetate		GSD
Norethynodrel		

COCs: Combined oral contraceptives, NGM: Norgestimate, DSG: Desogestrel, GSD: Gestodene, LNG: Levonorgestrel

Table 3: Mode of administration of progestin [3]

Mode of administration	Time duration
Injectable (intramuscular-medroxyprogesterone)	3 months
Single rod implant (LNG/etonogestrel)	3 years
Intrauterine device (low dose of LNG)	3-5 years

LNG: Levonorgestrel

Table 4: List of synthetic hormonal contraceptive pills available, their mode of action and their side effect

Name	Active component	Mode of action	Side effects	References
Estradiol valerate	Estradiol valerate 2 mg	Estrogens diffuse into their target cells (i.e., cells in the female reproductive tract, mammary glands, hypothalamus, and pituitary) and bind to receptor proteins	Abnormal hair growth, Breast tenderness, changes in sex drive, cramps, dizziness, hair loss, headache, lightheadedness	[13]
Femilon	DSG BP 0.15 mg Ethinylestradiol IP 0.02 mg	Once bound to the receptor, progestins like DSG will slow the frequency of GnRH from the hypothalamus and blunt the pre-ovulatory LH surge Femilon contraceptive pill unleashes ethinyl estradiol and DSG into the blood stream	Vaginal infections, urinary tract infections, Breast pains and engorgement, auditory disturbances	[14]
CPA and ethinylestradiol	CPA 2 mg ethinylestradiol 0.035 mg	Binds to the progesterone and estrogen receptors slowers the release of GnRH from the hypothalamus and blunt the pre-ovulatory LH surge	blood clots cancers such as breast or cervical cancer	[15]
Estrogen and progestin	GSD BP 60 mcg ethinylestradiol 15 mcg	Estrogens increase the hepatic synthesis of SHBG and other serum proteins and suppress FSH from the anterior pituitary. The combination of an estrogen with a progestin suppresses the hypothalamic-pituitary system, decreasing the secretion of GnRH	Severe chest pain and cough of acute onset, severe headache, vision problems, dizziness	[16]
DSG and ethinylestradiol tablets	DSG 0.15 mg ethinylestradiol 0.03 mg	Binds the estrogen and progesterone receptor, inhibits ovulation	Severe allergic reactions, bloody diarrhea, breast lumps pain or discharge fainting, frequent or painful urination migraines, missed menstrual period	[17]
Ovipauz levonorgestrel	Levonorgestrel IP 0.15 mg ethinylestradiol 0.03 mg	It inhibits ovulation, prevents transport of sperm or eggs and thus prevents fertilization and alters the lining of the uterus to prevent	Ovipauz-levonorgestrel may cause thrombotic and thromboembolic disorders, vascular problems, hepatic neoplasia, carcinoma of breasts and reproductive organs, gallbladder disease, ocular lesions	[18]
Crisanta LS	Ethinyl estradiol 0.02 mg DRSP 3 mg	Progestins such as DRSP diffuse freely into target cells in the female reproductive tract and bind to the progesterone receptor. And block the GnRh release and LH surge	Darkening of facial skin, allergy, mood swings	[19]
Duoluton levonorgestrel	Levonorgestrel IP 0.25 mg ethinylestradiol 0.05 mg	Levonorgestrel tricks the body processes into thinking that ovulation has already occurred, by maintaining high levels of the synthetic progesterone. This prevents the release of eggs from the ovaries	Local skin reaction, depression, liver impairment, reduce menstrual loss	[20]
Ovral G	Norgestrel 0.5 mg ethinylestradiol 0.05 mg	The combination of an estrogen with a progestin suppresses the secretion of GnRH	Stomach cramping, Vomiting, dizziness	[21]

DRSP: Drospirenone, CPA: Cyproterone acetate, DSG: Desogestrel, GSD: Gestodene, SHBG: Sex hormone binding globulin, GnRH: Gonadotropin-releasing hormone

Effects on brain structure

Adult brain structure is subject to dynamic changes with age. These changes differentially affect brain areas, such as gray matter volumes in some regions, decline more strongly with age than others. An age-related strong decline has been demonstrated in the prefrontal cortex, as well as the hippocampus. Recent results showed that regional gray matter volumes in the prefrontal cortex, as well as the cingulate anterior gyrus, are larger in mixed samples of androgenic and antiandrogenic OC users compared to nonusers [22]. These regions are already larger in women when compared to men. However, regional gray matter volumes of OC users were also greater in the cerebellum, hippocampi, parahippocampus, and fusiform gyri [23]. Those regions are on the average larger in men compared to women. Results from rodent hippocampi suggest that these volume increase may be attributed to an increase in synaptic spin density mediated by estrogen receptors [24], but an increase in astrocyte volume in response to estradiol has also been suggested [13].

Hormonal contraceptives and risk of venous thromboembolism (VTE)

It has been reported that VTE risk is related to COC [25]. The risk of VTE is higher during the 1st year of use depending on the different combinations of COCs. Recently, new formulations of OCs and nonoral routes of administration have been evaluated in the context of VTE risk [26-28]. Based on the epidemiological findings, the risk of VTE is higher among those using 30-35 mg of within different types of progestin as compared to COC containing LNG [28]. With the same doses of EE (30-35 mg), the COC-containing DRSP, EE CPA, DSG, or GSD also increased the risk of VTE as compared to COC-containing LNG. It has also been reported that use of nonoral routes of combined contraceptives, patch, or vaginal ring is also associated with a higher VTE risk compared with the second-generation pills [28]. The changes found to be more deleterious to users of this new progestin than among LNG users. In combination with EE, these new progestin appears to induce resistance to activated protein C (APC), which is a surrogate marker of VTE risks. The effect on APC resistance of

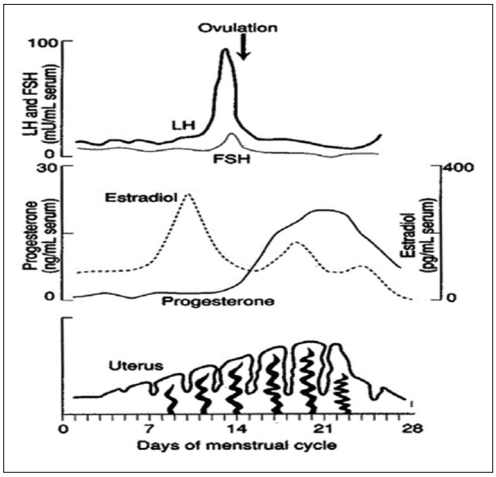

Fig. 1: Phases of female reproductive cycle without hormonal support [4]

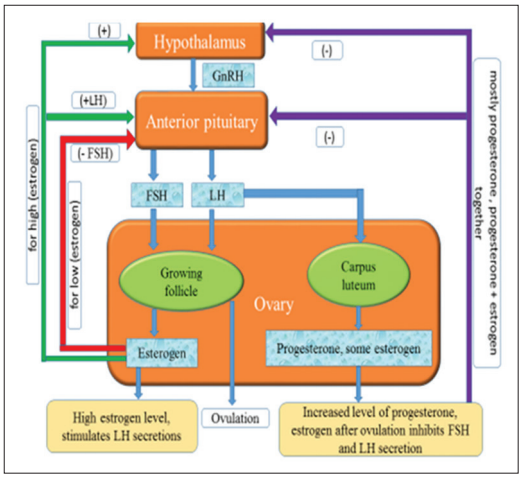

Fig. 2: Regulation of hypothalamus-pituitary-gonadal axis [5]

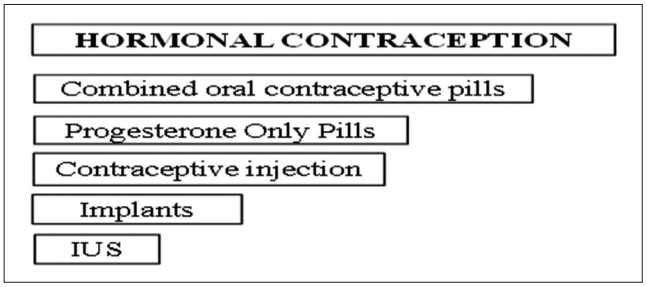

Fig. 3: Categories of hormonal contraception [3]

the different molecules of progestin associated with the same EE dose has been clearly investigated. It has been found that acquired APC resistance (measured as the effect of APC on thrombin generation) may be related to the thrombotic effect of hormonal contraceptives. Sex hormone binding globulin (SHBG), a carrier protein synthesized by the liver, has found to be positively correlated with APC resistance among pill users. It is, therefore, another useful pharmacological marker to predict the thrombotic venous safety of a combined contraception indirectly. Hence, SHBG appears to be higher among users of DSG, DRSP, and CPA containing pills as compared to those using LNG pills [29-31].

CONCLUSION

Contraceptive pills mainly work by inhibiting or delaying ovulation and up to some extent preventing fertilization and implantation. Several clinical studies have shown that COCs works primarily on either inhibiting or delaying ovulation. Millions of women in this reproductive age (14-45 years) are taking these medicines to delay pregnancy. Many of the women have experienced side effects after taking COCs or POPs such as spotting, weight gain or weight loss, nausea, breast tenderness, severe headache, depression, darkening skin, and vaginal infection. There is sufficient evidence in humans that combined oral estrogen-progesterone contraceptives are carcinogenic in nature. This assumption has made by increased risk for cancer of breast, cervical, and liver. However, experiments in animals have provided inadequate evidence for the carcinogenicity of progesterone, LNG, norgestrel, or progestin-derived contraceptive pills. These contraceptives act as LH receptor (LHR) and progesterone hormone receptor (PGR) inhibitors and thus in long-term usage interferes with the ovulation cycle which results in premature ovulation or delayed ovulation. However, herbal compounds have been found to work as partial inhibitors of LHR and PGR, and at the moment, they are being removed from the system, the ovulation cycle is retained. Collectively, there is a need to work for herbal analogs of these contraceptives which can be effective as well as safe.

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