

Special Report

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Women's Health

Oral steroid contraception

Oral steroid contraception is a popular method of family planning worldwide. Over the past several decades, this method of contraception has changed significantly by decreasing the estrogen dose, changing the progestin component, and reducing the hormone free interval. Despite the popularity of oral steroid contraception, there has been much criticism regarding the associated risks of venous thromboembolism and stroke. Despite these established, yet uncommon risks, oral steroid contraception has many important health benefits. This review highlights the available formulations of oral contraceptives along with their evidence-based associated risks and benefits. Highlights regarding future directions for development of novel oral contraceptives are also addressed.

Keywords: birth control • cancer risk • novel contraception • progestins • steroid contraception • venous thromboembolism

The number of women using contraception in developed countries has remained relatively constant since 1982 with approximately 62% of women of reproductive age using contraception in the USA. Oral contraceptive pills are the most common method used by 28% of contraceptive users [1]. Globally, oral contraceptive pills are used by 8.8% of contraceptive users [2].

Since the approval of the first oral steroid contraceptive in 1960, family planning options for women have changed and diversified dramatically. Despite novel developments for administration of contraceptive steroids in recent decades, oral steroid contraceptives are the most frequently used method of administering steroid contraception. The reported typical and perfect use failure rates of oral steroid contraceptives in the first year of use are 9 and 0.3%, respectively [3]. In this chapter, the pharmacology, formulations, side effects, health benefits and latest developments of oral steroid contraceptives will be discussed.

Pharmacology

Most oral steroid contraceptives are composed of both an estrogen and a progestin.

The progestin inhibits ovulation and thickens cervical mucus preventing sperm ascent into the uterine cavity and oviducts. The estrogen component inhibits follicular development and stabilizes the endometrium providing regular episodes of uterine bleeding during the 4–7-day interval without steroid use. The first oral steroid contraceptive pill, marketed as Enovid, consisted of 9.85 mg of the progestin norethynodrel and 150 µg of the estrogen mestranol (ethinyl estradiol 3-methyl ether). Since 1960, the composition of the oral contraceptive pill has changed significantly with dramatic reductions in the dose of mestranol in the 1960s and switching the estrogen component to ethinyl estradiol in the 1970s. Current formulations of oral contraceptive pills contain no more than 50 µg of ethinyl estradiol. The dose of ethinyl estradiol in one current formulation is only 10 µg. More recent compositions of oral contraceptive pills contain only 90 µg of progestin, a significant reduction from the original dose of 9.85 mg of norethynodrel in the 1960s.

Once oral steroid contraceptives are ingested, they are subject to extensive hepatic

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first pass metabolism. Following dissolution in the stomach, contraceptive steroids are partially metabolized in the small intestine by bacterial enzymes and enzymes within the small intestine [4]. A mixture of metabolized and unmetabolized steroids enters the portal venous system following absorption from the small intestine. The portal venous blood carries the contraceptive steroids and subjects them to numerous metabolic enzymatic actions of the liver. The amount of contraceptive steroid in the systemic circulation following first pass metabolism in the liver is known as its bioavailability.

Formulations

Ethinyl estradiol has remained the most widely used estrogen in combined steroid contraceptives since the 1970s. The wide variety of oral steroid contraceptives currently available is mainly due to the synthesis of newer progestins. Progestins in oral contraceptive pills used in the 1960s and 70s were mainly norethindrone and levonorgestrel which have been replaced by less androgenic progestins including desogestrel, gestodene, norgestimate and cyproterone acetate. Additionally, the spironolactone derivative drospirinone and the 19-norprogesterone derivative norgestrol acetate have been synthesized and approved for oral contraceptive use.

The classification of synthetic progestins is cumbersome and somewhat controversial. Although not particularly scientific, combination oral steroid contraceptives have been described in terms of 'generations'. First-generation oral steroid contraceptives contain 50 µg or more of ethinyl estradiol. Contraceptive pills containing levonorgestrel combined with less than 50 µg of ethinyl estradiol have been referred to as 'second-generation' formulations. Levonorgestrel is the active isomer of dl-norgestrel which was used initially. Newer formulations are referred to as 'third or fourth' generation pills. Third-generation formulations are those containing the less androgenic progestins desogestrel, gestodene or norgestimate. Fourth generation pills contain the progestins drospirinone and dienogest which are somewhat 'anti-androgenic'. The 'generation' classification system for oral steroid contraceptives is widely used yet incomplete. Despite the fact that norethindrone is an older progestin, it has never been classified within the 'generation system'. Similarly, cyproterone acetate is an 'older' progestin with anti-androgenic properties that has not been officially grouped within this classification scheme.

Progestins may also be classified into those chemically related to progesterone and those chemically related to testosterone. Progestins chemically related to progesterone are classified as pregnanes and 19-nor-

pregnanes. Examples of pregnanes include medroxyprogesterone acetate and megestrol acetate. 19-Norpregnanes include norgestrol acetate and nesterone. Those progestins more closely related to testosterone are further subdivided into those progestins with and without a 17-ethinyl group. Those with a 17-ethinyl group include norethindrone and levonorgestrel. Progestins without the 17-ethinyl group include dienogest and drospirinone [5].

The classification of progestins is really only important when discussing the clinical impact of these various formulations. Perhaps the most relevant component of the action of certain progestins relates to its androgenicity. Synthesis of less androgenic progestins has been the trend of contraceptive steroid development. Less androgenic progestins may improve acne and reduce weight gain. Their use may cause harm as the less androgenic progestins may not inhibit the procoagulant effect of ethinyl estradiol to the same degree as older, more androgenic, progestins. Less androgenic progestins may actually increase venous thromboembolic events (VTE) more than levonorgestrel containing agents.

Despite the possible increased relative risk of VTE with less androgenic progestins, steroid contraceptive experts have made a position statement addressing this issue. Although some case-control studies have demonstrated an increased risk of VTE among third- and fourth-generation progestin users, other cohort studies have not demonstrated this same effect. Until further prospective studies have been conducted addressing this issue, less-androgenic progestin combination oral contraceptive (COC) formulations should continue to be offered to women. Physicians should always screen women appropriately according to both the WHO and Centers for Disease Control (CDC) Medical Eligibility Criteria (MEC) for contraceptive use [6]. Furthermore, a systematic review of VTE and arterial thrombosis in drospirinone-containing contraceptive users reported that when compared with users of levonorgestrel containing pills, drospirinone users had a increased relative risk of VTE ranging from 1.0 to 3.3 compared with levonorgestrel. This same increased risk was not present for arterial thrombosis, however [7]. This highlights the fact that a VTE may occur in women without arterial risk factors but an myocardial infarction or stroke only occurs with increased frequency when risk factors such as smoking and hypertension are present.

In addition to changing the progestin component of the combination steroid contraceptive pills, the schedule of active/nonactive pills in the formulation has also changed. Oral steroid contraceptive formulations consist of 21 active/7 inactive, 24 active/4 inactive, 84 active/7 inactive and daily active monophasic

regimens. Triphasic and, more recently, quadruphasic regimens with different amounts of steroid also exist. While the contraceptive efficacy of these various methods appears unchanged, shortening the hormone-free interval does decrease serum levels of LH and FSH [8]. The reduction in serum LH/FSH levels may decrease follicular development and escape ovulation with the use of combination oral steroid contraceptives that contain a shortened hormone-free interval.

Side effects

Despite the utility of oral steroid contraceptives for prevention of unintended pregnancy, much like any exogenous drug, they are not without side effects. The side effects of oral steroid contraceptives may be divided into minor, more frequent and major, less frequent, health effects. Additionally, they may be classified into those related to the estrogen component and those related to the progestin component. Minor, more frequent, side effects attributed to the estrogen component include breast tenderness, bloating and fluid retention. Progestin minor side effects include headache, weight gain, acne and mood changes. Irregular vaginal bleeding is also a known side effect of steroid contraception. The impact of side effects such as bleeding irregularities may be lessened with adequate contraceptive counseling as well as switching to a higher dose formulation. Major, rare, side effects include venous and arterial thrombotic events caused by the thrombogenic effect of exogenous estrogen.

The overall incidence of VTE in women of reproductive age not pregnant or using combination oral contraceptives is 4/10,000 women/year. The risk of VTE is doubled with use of combined oral steroid contraceptive users to 9/10,000 women/year. This increased risk needs to be put into perspective, however. The incidence of VTE during pregnancy is 20/10,000 women/year, a fivefold increased risk [9–11]. Additionally, the rate of VTE in combination steroid contraceptive users is directly related to the estrogen dose [12]. The risk of VTE in pills containing greater than 50 µg of ethinyl estradiol is estimated to be 10/10,000 women/year and only 4.2/10,000 women/year in women taking pills with less than 50 µg of ethinyl estradiol.

Despite the increased risk of VTE in combination oral steroid contraceptive users, there is no increased VTE risk among users of progestin only oral steroid contraception [13]. A meta-analysis of six studies analyzing the relative risk of VTE with oral progestin only pill users when compared with a non steroid taking control was 1.03 and not found to be statistically significant. Thus, progestin only oral contraceptive pills are a reasonable option for women at risk for venous or arterial thromboses such as obese women or women

older than 35 who smoke cigarettes. Commercially available progestin only pills include formulations that contain 30 µg levonorgestrel (Norgeston), 350 µg norethindrone (Micronor) or 75 µg desogestrel (Cera-zette). The progestin only pill containing 500 µg of ethynodiol diacetate (Femulen) was recently discontinued by the manufacturer in March 2013. Progestin only pills are taken every day without a pill free interval and unscheduled bleeding is common. The contraceptive efficacy of each of these formulations is probably similar. While desogestrel users have greater inhibition of ovulation than levonorgestrel users, the frequency of irregular uterine bleeding was higher in women using a desogestrel progestin only pill and led to higher rates of discontinuation [14].

The other concern with combination steroid contraception has been the increased risk of arterial thrombotic events such as myocardial infarction and stroke. A large cohort study of combined contraceptive steroid users noted an increased risk of myocardial infarction when compared with non users. However, when adjusting for smoking status, there was only an increased risk in combined steroid contraceptive users who smoked more than 15 cigarettes/day [15]. Combination steroid contraceptives act synergistically with the effects of smoking to increase arterial thromboses. The WHO has issued a statement that nonsmoking, normotensive, nondiabetic women of any age using combination steroid contraceptives do not have an increased risk of myocardial infarction [16]. Additionally, since the reduction of the ethinyl estradiol dose to less than 50 µg in current formulations of combination steroid contraceptives, there has been no demonstrated increased risk of ischemic or hemorrhagic stroke in combination steroid contraceptive users without additional risk factors such as hypertension or smoking [17–19].

Given the adverse events of both venous and arterial thromboses associated with combination oral steroid contraceptive use, the WHO has published clinical practice guidelines for practitioners prescribing this contraceptive method to reproductive aged women. Depending upon a woman's medical, obstetrical or family history, the administration of combination hormonal contraception may be contraindicated. These clinical guidelines have been adapted by the CDC in the USA. The CDC Medical Eligibility Criteria for Contraceptive Use (CDC-MEC) has recommended that women with substantial risk factors for venous or arterial thromboses should not be prescribed a combination hormonal contraceptive method. These risk factors include <21 days postpartum, uncontrolled hypertension, personal history of VTE, age >35 and a smoker, migraine headaches with aura, known thrombophilias such as Factor V Leiden mutation,

or a history of ischemic or valvular heart disease [20]. Practitioners are encouraged to review the CDC-MEC document prior to prescribing any contraceptive method to ensure safety.

Not only do the WHO and CDC publish specific guidelines related to contraception for specific medical conditions, but necessary medical examinations, laboratory tests and routine follow-up required during initiation of hormonal contraception is provided in the Selected Practice Recommendations for Contraceptive Use. Aside from screening for medical and family health conditions that are contraindications for hormonal contraceptive use, healthy women of reproductive age only require a measurement of blood pressure prior to initiation of combination hormonal contraception [21]. Routine screening with blood pressure is necessary to screen for hypertension, and has been shown to reduce the incidence of cardiovascular events such as stroke and myocardial infarction in combined steroid contraceptive users. There are no necessary laboratory tests needed prior to initiation of hormonal contraception. If a family history of arterial or venous thromboses exist, testing for possible thrombophilias may be warranted prior to initiation of combined oral steroid contraception. One may wish to prescribe a progestin only pill if a woman has a family history of idiopathic VTE.

Health benefits

Much of the attention directed toward combined steroid contraceptives in the lay literature has been in efforts to dissuade their use by highlighting only negative side effects. The noncontraceptive health benefits of combined steroid contraceptives are widespread. These benefits include a reduction in menstrual blood loss, irregular menstruation, uterine cancer, ovarian cancer, benign breast disease, dysmenorrhea, functional ovarian cysts, pelvic inflammatory disease, premenstrual syndrome, ectopic pregnancy, acne and rheumatoid arthritis [22]. These health benefits have persisted despite the reduction in dose of both steroid components of combination oral steroid contraceptives [23].

Moreover, the Royal College of General Practitioners conducted a prospective cohort study from 1968 to 2007 of 46,112 women examining non-users versus ever users of oral contraception and associated all cause mortality. The results from this large prospective trial concluded that ever users of oral contraception had a 15% overall reduction in all cause mortality when compared with nonusers [24]. Additionally, mortality attributed to cancer was also reduced for ever users of oral contraception. The Oxford Family Planning Association examined cancer incidence in oral contraceptive users versus nonusers from 1968 to 2010 and included 17,032 women [25]. Ever use of oral contraception was

associated with a 50% reduction in both ovarian and uterine cancer. Breast cancer incidence was not found to be increased in oral contraceptive users when compared with nonusers. The relative risk of cervical cancer was increased to 3.4 (95% CI: 1.6–8.9) in oral contraceptive users compared with non-users. However, the nonuser group largely used diaphragms which may be protective against human papillomavirus infection.

Perhaps the most controversial aspect of combination steroid contraceptive use relates to its association with breast cancer. Concurrent with the publication of the Women's Health Initiative demonstrating an increased risk of breast cancer in postmenopausal women exposed to combination hormone replacement therapy, a case control study by the CDC showed no increased risk of breast cancer incidence among women aged 35–64 who were former or current users of combination oral steroid contraception [26]. These two articles were published in the same issue of the New England Journal of Medicine; however, the article showing no elevation in breast cancer risk among combination steroid contraceptive users did not receive much attention from the medical community. A recent case–control study of women aged 35–64 with exclusive use of one of ten formulations of combination steroid contraceptives demonstrated no increased risk of breast cancer irrespective of the formulation used [27]. Moreover, a comprehensive meta-analysis concluded that for *BRCA1* and *BRCA2* carriers, combination oral contraceptives significantly decreased the risk of ovarian cancer without increasing breast cancer risk [28]. Any past use of COCs was associated with a 40% reduction in ovarian cancer risk.

New oral steroid contraceptive formulations

A more recently developed oral steroid contraceptive consists of a quadruphasic dosing regimen consisting of estradiol valerate and the progestin dienogest [29]. This formulation is marketed as Qlaira in Europe and as Natazia in the USA. Estradiol valerate is rapidly hydrolyzed to estradiol after oral ingestion. Estradiol is less potent than ethinyl estradiol, and it does not increase the production of hepatic proteins as much as ethinyl estradiol. This may ultimately confer a reduction in VTE for users of this oral steroid formulation. Given the overall low rate of VTE in reproductive aged women, the reduction in VTE risk for women using this contraceptive regimen is only theoretical and has not been investigated in clinical epidemiologic studies.

Perhaps the best indication for use of this oral steroid contraceptive relates to its uterine bleeding profile. This formulation is currently approved in the USA for the treatment of heavy menstrual bleeding. Although

all combination oral steroid contraceptives are known to reduce menstrual blood loss, this particular formulation may provide a greater improvement in bleeding compared with older formulations [30]. The major criticism of the estradiol valerate/dienogest pill relates to its quadruphasic dosing regimen. This tedious dosing schedule makes counseling of women following missed pills cumbersome and may ultimately confer a reduction in contraceptive efficacy.

To circumvent some of the challenges of a multiphasic dosing regimen, the first ever monophasic COC using 1.5 mg estradiol with 2.5 mg norgestrel acetate in a 24/4 formulation was introduced to the European market in 2011 as Zoely. This novel COC has been compared in clinical trials to older formulations containing levonorgestrel-EE and drospirenone-EE. Contraceptive efficacy and safety profiles have been similar in estradiol-norgestrel acetate users when compared with older formulations [31]. Much like estradiol valerate, the utilization of estradiol in this new formulation should reduce the hepatic production of procoagulant proteins and reduce cardiovascular events. However, epidemiologic data for this rare event are not currently available. This novel COC is not currently available in the USA.

Although in developmental stages only, newer combination steroid contraceptives may utilize the natural human steroid estroestrol to replace the procoagulant effects attributed by ethinyl estradiol as well. Estroestrol is found in the maternal circulation during pregnancy and is secreted by the fetal liver. Animal studies have shown consistent ovulation inhibition in rats treated with oral estroestrol twice daily for 4 days [32]. In healthy, regularly cycling premenopausal women, a combination of 20 mg estroestrol/150 µg desogestrel ingested orally for 28 days demonstrated complete inhibition of ovulation in all treated women [33].

The development of novel steroid contraceptive methods using less potent estrogens such as estroestrol may provide women with adequate contraception without increasing their risk for development of the rare major side effects such as venous or arterial thromboembolic events. It is uncertain whether the new controversy surrounding third- and fourth-generation combination steroid contraceptive pills (both

which contain ethinyl estradiol and not the newer, less potent estrogens) will have an effect on the prescribing practices of physicians.

Conclusion

Combined oral contraceptive pills continue to be frequently used by women worldwide. There are many health benefits associated with the use of COCs. However, this method of contraception has also been associated with an increased risk of both arterial and thromboembolic events.

No method of contraception is without some risk; however, the most perfect method is one that is acceptable to women and decreases her chances of having an unintended pregnancy or developing a serious adverse event. Development of newer combination oral steroid contraceptives that maintain the health benefits of older formulations while decreasing the risk of VTE will remain an important aspect of oral steroid contraceptive development in the 21st century. Additionally, given the popularity of oral steroid contraceptives, development of a nonhormonal oral contraceptive pill should be pursued.

Future perspective

Over the course of the next decade, the future utilization of oral contraception will depend upon the development of novel approaches to reduce the known but uncommon adverse side effects of the estrogen component while highlighting the many important health benefits that these medications offer. Health practitioners that take care of women must be strong advocates for women's reproductive health by enhancing public awareness regarding the continued importance of oral contraceptives.

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