Review Article

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Low Dose Oral Contraceptives

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Abstract

Combined oral contraceptives (COCs) offer a convenient, safe, effective, and reversible method of contraception. While being highly effective, the early COC formulations were associated with significant adverse effects and cardiovascular risk. Reduction in the dose of estrogen is a commonly accepted approach to reduce the side effects of COC. Improvements in tolerability and safety have been achieved with similar effectiveness, mainly via hormone dosage reductions and the development of new progestins. Use of newer generation of progestins, such as gestodene, reduces the androgenic side effects generally associated with progestogens. A COC with gestodene 60 μg and ethinylestradiol (EE) 15 μg showed overall good contraceptive efficacy and cycle control. Patients experienced significant improvement in well-being with respect to pre-menstrual complaints and symptoms. This COC regimen was safe, well-accepted and well-tolerated, reduced both the intensity and duration of bleeding. With the progress of treatment cycles, the incidence of breakthrough bleeding reduces. Gestodene/EE low dose was associated with lower incidence of estrogen-related adverse events, such as headache, vomiting, pain, and nausea. Furthermore, COCs containing low dose of estrogen have not been associated with any adverse effect on haemostasis in healthy women. Ultra-low-dose COCs can be considered in women who are at risk of developing estrogen-related side effects. Patients with obesity, heavy smokers and who are at a risk of developing stroke or myocardial infarction should be given these Oral Contraceptive Pills (OCPs). These formulations maintained efficacy, safety, showed good cycle control with shorter periods and lesser withdrawal bleed and enhanced the quality of life of patients.

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Introduction

Contraception, defined as any method of preventing pregnancy by either hindering sperm from reaching a mature ovum or by inhibiting a fertilized egg from implanting in the endometrium, plays a major role in managing women's reproductive health [1]. It prevents pregnancies that are too early, too late, too many or too close.

In developing countries, the rising contraceptive use has reduced the number of maternal deaths by 40% over the past 20 years, by decreasing the number of unintended pregnancies [2]. In India, mostly abortions are responsible for 10–20% of all maternal deaths [3]. Thus, there is a need for awareness about effective contraceptive methods, their consistent and correct use.

Need for Combined Oral Contraceptives

Combined estrogen-progestin oral contraceptives (COCs) are among the most widely used modern contraceptive methods in many countries and are also extensively studied drugs in history. Their primary mode of action is to prevent ovulation by inhibiting gonadotropin secretion at both the level of the pituitary gland and the hypothalamus.

The estrogen component of OCPs directly inhibits follicle-stimulating hormone (FSH) secretion and thus limits the development of the dominant ovulatory follicle. The progestin component of the OCPs suppresses the luteinizing hormone (LH) secretion and thus prevents the LH surge which triggers ovulation [4].

The benefits of oral contraceptive pills are beyond pregnancy prevention. OCPs provide relief from menstrual symptoms and reduce the risk of developing endometrial or ovarian cancer [5]. They are used in the management of several conditions like abnormal uterine bleeding, heavy menstrual bleeding, dysmenorrhea, premenstrual syndrome, osteoporosis, endometriosis, ectopic pregnancy and functional ovarian cyst [6].

Evolution of Low-Dose Oral Contraceptives

The first hormonal pill, containing mestranol and norethisterone, was approved by the Federal Drug Administration (FDA) in May 1960. Mini pill was introduced in the 1970s. The pioneers of OCP development realized early that their new products were actually contaminated with up to 7% of the estrogenic mestranol, an intermediate step in synthesis of the progestogens. Mestranol was subsequently replaced with its active metabolite ethinyl estradiol (EE), a synthetic derivative of 17-β-estradiol, which has remained the predominant estrogen in OCPs for over fifty years, largely due to its high oral bioavailability [7]. While being highly effective, the early COC formulations were associated with significant adverse effects and cardiovascular risk. However, over the last five decades the dose of EE has been greatly reduced from doses of 50- 100 micrograms (μg) in the 1950s to low-doses of 30-35μg of EE in the 1970s and more recently to ultra-low doses of 10-20μg of EE. Improvements in tolerability and safety have been achieved with similar effectiveness, mainly via hormone dosage reductions and the development of new progestins [8].

This striking reduction in EE dose was prompted primarily by efforts to reduce the incidence of cardiovascular side effects & Venous Thromboembolism (VTE) risk [9].

Oral contraceptives were classically given in a cyclic manner with 21 days of active pills followed by 7 days of placebo. However, this classical regimen may not suppress activity completely and follicular development. The ovarian follicular recruitment begins earlier in the 7-day hormone free interval (HFI). Hence if a woman missed the pill or started the next COC pill cycle late, it would result in contraceptive failure [10]. In the past few years, new oral contraceptives have been introduced which either shorten the placebo time, lengthen the active pills (extended cycle), or provide active pills every day (continuous). Studies of extended and continuous cycle OCPs showed that these regimens were as effective as cyclic administration. Their metabolic, hormonal, and endometrial effects are similar to cyclic OCP users. The most common side effects of continuous OCP dosing include irregular vaginal bleeding, but its incidence decreases over time. Women who prefer fewer menses, for occupational or personal reasons, may be considered for extended or continuous OCPs [11]. Alternative dosing regimens like the 24/4, which involves 24 days of active treatment followed by four days of inactive pills, was introduced as a means to reduce the HFI. This regimen

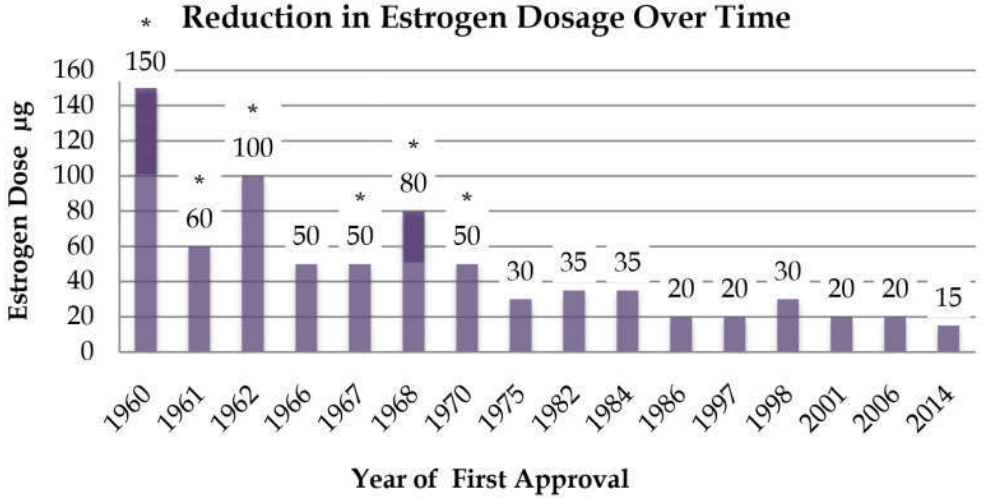

Fig. 1: Reduction in estrogen dosage over time

reduces the risk of escape ovulation, prevents hormonal fluctuations and has increased safety of contraceptives use [12].

Although EE and estradiol were the only estrogens used in COC, many progestins are currently available. The biological activity of a progestogen changes considerably due to its chemical structure. Levonorgestrel has no estrogenic but strong anti-estrogenic activity, along with no mineralocorticoid and glucocorticoid activities. Drospirenone has strong progestogenic and anti-aldosterone activity with natriuretic effect. It also has strong anti-mineralocorticoid activity [13]. Gestodene (GTD), desogestrel, and norgestimate are recently developed progestogens; exert a better selective progestational activity. This improves cycle control and minimizes metabolic changes and adverse effects while effectively preventing pregnancy [7].

Ultra-Low dose Contraceptives

The use of the lowest effective dose of hormonal oral contraceptives helps to prevent side effects such as nausea, headache, vomiting which in turn improves patient compliance. It is for this reason that the World Health Organization (WHO) recommends the use of the lowest effective dose of hormonal oral contraception [14].

Studies on COCs have focused on reducing the dose of estrogen and progestrogen with the objective of retaining contraceptive efficacy with the improved drug safety and acceptability. The dose of EE has gradually been reduced and pills containing 35, 30, 20, 15 and 10μg are now available. Progestins with high anti-androgenicactivity helped these reductions in dose along with new regimes of administration. Contraceptive efficacy of COC with 15 and 20μg EE, measured by the Pearl index, is in the range of 0.07–0.88, and is therefore similar to that of COC containing 30μg EE (0.06–0.88) [13].

Gestodene-containing oral contraceptives inhibit ovulation similar to that of preparations containing other progestogens although the required dosage is lower [15]. The choice to combine EE with GTD relates to the fact that it is active per se and not a prodrug and hence has high bioavailability (approximately 100%) [7].

Modern COCs contain only 20 μg (low) or 15 μg (ultra-low dose) of EE combined with a selective progestin e.g. gestodene. These formulations are effective in inhibiting ovulation [7] and are administered for 24 day instead of 21 days hence shorter hormone free interval (HFI). The reduction of this interval ensures excellent suppression of ovarian activity even with such low steroid doses [13].

Some recent, an ultra-low dose contraceptive formulations contain only 15μg EE and 60μg gestodene. This combination results in a 25% reduction in the daily dose of the EE component and a 20% reduction in the gestodene componentcompared to the combined monophasic contraceptives that contain 20 μg EE [16].

Cycle control is also extremely important, as it is the strongest analyst in determining whether a woman will use the pill correctly and continue with their use. The combination of GTD 60 μg /EE 15 μg administered daily for 24 days followed by a 4-day hormone-free interval, showed better cycle control. Significant reduction in the length of withdrawal bleeding was observed after the sixth cycle compared to the first. This ultra-low dose COC showed highly acceptable cycle control, good tolerability, low side effects and high satisfaction rate [15].

Progestins: Focus on Gestodene

GTD differs from levonorgestrel by a double bond between carbons 15 and 16 in the D-ring. This variation in chemical structure causes a shift in the conformational location of the 18-ethyl group and accounts for differences in the pharmacokinetics of the two steroids [17]. GTD has a relatively high affinity for the androgen receptor, which is nearly twice that of levonorgestrel [17]. Approximately 75% of the total circulating GTD is bound to sex hormone-binding globulin (SHBG). GTD has a lower metabolic clearance rate and a greater concentration in the circulation due to its higher affinity for SHBG, which may be beneficial when pills are missed. Furthermore, the longer half-life and an alternative regimen contribute to the reduced failure rate of COCs [17].

Clinical Evidences

The Gestodene Study group evaluated the safety and efficacy of 24 day regimen of an oral contraceptive combination containing gestodene (GTD) 60 μg and ethinylestradiol (EE) 15μg in an open-label, multicenter study. The overall incidence of breakthrough bleeding and/ or spotting was 21%. The most frequent adverse events were headache (35%), absence of bleeding (16%), flu-like syndrome (15%), pharyngitis (15%) and abdominal pain (15%) Cycle control with this 24-day regimen was acceptable, and the incidence of discontinuation for

bleeding-related reasons was low. The overall incidence of absence of bleeding during an entire cycle was 7%. This combination offered adequate efficacy, tolerability and safety, and the potential for improved compliance [18].

Barbosa et al. conducted a prospective, open-label, non-comparative, multicenter study in 163 women who received an ultra-low-dose OCP containing GTD 60μg and ethinylestradiol (EE) 15μg for 6 months. This study evaluated the acceptability, safety, bleeding patterns and premenstrual symptomatology in these women. Results showed that the most frequent adverse event was breakthrough bleeding, which diminished, as the time of OC use increased. Cycle length and duration of bleeding decreased significantly with OC use. Patients experienced significant improvement in well-being with respect to pre-menstrual complaints and symptoms. This OC regimen was safe, well-accepted and well-tolerated, reduced both the intensity and duration of bleeding, had good cycle control and improved premenstrual symptomatology [16].

A study examined the effects of a 24-day regimen containing 15μg ethinyl estradiol (EE) plus 60 μg gestodene on cycle control and on hemostasis, in 58 healthy women. The overall incidence of irregular bleedings was 19.3%. A slight increase in thrombin-antithrombin III complexes was observed after 6 and 12 months of oral contraceptive use. Antithrombin III activity increased after one-year of pill intake.The moderate pro-coagulant activity of this formulation may be balanced by a compensatory increase in anticoagulation activity. Results show that low doses of EE, such as 15μg, do not impair hemostasis in healthy females but may be responsible for some effects on cycle control [19].

The Jaithivit et al. study that assessed the ultra-low dose COC (15 μg EE and 60 μg GTD) in Asian women, 93.6% were found to be satisfied or very satisfied physically at the end of the study and 95.8% reported emotional satisfaction or high satisfaction. The high satisfaction was echoed by majority of the subjects stating that they would continue the medication if it was available [15].

Safety

Cycle control can be classified as normal, or having breakthrough bleeding or spotting, or an absence of bleeding during the entire cycle. Any bleeding that started during the first 3 tablet-taking days of the following cycle and ended before day 7 of the cycle was classified as withdrawal bleeding. Any bleeding that began after the first 3 days was classified as breakthrough bleeding and/ or spotting. Spotting was defined as bleeding that required no sanitary protection, whereas breakthrough bleeding required sanitary protection [18]. Lowering the dose of EE in OCPs may compromise cycle control. A Cochrane review compared 20μg EE versus >20μg EE OCPs and found that low dose estrogen OCPs resulted in higher rates of bleeding pattern disruptions (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting). The ultra-low dose 15μg EE combination study in 94 Asian women for 6 cycles showed bleeding as 2.1 % in the first cycle and 4.3% in the second cycle. It then reduced until 0% through the sixth cycle. The percentage of spotting was 6.4%, 5.3%, and 4.4% in the first, second, and third cycle, respectively, then decreased until it disappeared after the third cycle. The study concluded that the ultra-low dose combination of EE 15μg and GTD 60μg has highly acceptable cycle control, good tolerability, low side effects and high satisfaction rate [15]. Although bleeding irregularities do not threaten health, sub-optimal cycle control may jeopardize the acceptance of and adherence to the OCP [20].

The use of lower doses in COC has the potential to reduce common side effects associated with oral contraceptive use, such as nausea and breast tenderness. Gestodene/EE low dose OC showed lower incidence of estrogen-related adverse events, such as headache, breast tenderness, and nausea [18]. Most frequent side effects in ultra- low dose OC were headaches, nausea, vomiting, pain etc. No changes in body weight, blood pressure or any laboratory evaluations were observed with these OCs [15,16]. Significant improvement in quality of life and premenstrual symptomswas noted, in terms of improvement in total Moos Menstrual Distress Questionnaire (MDQ) score [20].

Benefits of an Ultra-Low Dose Oral Contraceptive Pill

The American College of Obstetricians and Gynecologists guidelines recommend the use of combined oral contraceptive (OCPs) formulations containing less than 50μg of EE with the lowest progestin dose [21]. For prescribing OCPs, the common guiding principles for individual woman recommend an OCP with the lowest dose of estrogen and progestogen while providing good cycle control and effective contraception, is well tolerated, has the best safety profile, is affordable and offers

additional non- contraceptive benefits if desired [7]. Potential risks and benefits should be considered while prescribing OCPs. Currently, the ultra-low dose OCPs offer combination of attributes to most patients.

Advantages & Disadvantages

- Efficacy similar to low dose OCPs Higher rates of bleeding pattern disruptions
- Less estrogen related side effects More breakthrough bleeding
- More safety- lower incidence of myocardial infarction and thrombotic stroke Decreased vaginal lubrication

Women suffering from the side effects associated with estrogens (nausea, headache, breast tenderness etc.) should be recommended ultra-low dose OCPs. Patients with obesity, heavy smokers and who are at a risk of developing stroke or myocardial infarction should be given these OCPs. Women with a history of nausea, edema or hypertension during pregnancy, migraines, fibrocystic breasts and uterine fibrosis benefit from the use of ultra-low dose oral contraceptives [7].

Conclusion

Oral contraceptives are popular and highly effective. Apart from contraception, these offer various non-contraceptive benefits, including better control of menstrual symptoms, decrease in the incidence of iron-deficiency anemia, decrease in dysmenorrhea and decrease the incidence of endometrial and ovarian cancer. The ultra-low-dose combined formulations especially those containing gestodene and 15µg EE in a 24 day regimen were introduced with the lowest available daily dose regimen in an oral combined contraceptive. These formulations maintained efficacy, safety, showed good cycle control with shorter periods and lesser withdrawal bleed and enhanced the quality of life of patients.

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Author Contributions

All authors were involved in conception, design, analysis and interpretation of data. All authors were also involved in preparation of the manuscript, revising it for important intellectual content and final approval before submitting for publication.

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