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INVITED MINI REVIEW

Evolution of Oral Contraceptive Pills

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Introduction

One of the first civilization to use birth control was Egyptian civilization. Various drawings from 3000 BC show men using condoms. However, the first and earliest depictions of the use of a condom by a man during sexual intercourse are portrayed on the wall of a cave in France which is almost 12,000 years old [1]. Various contraceptives such as vaginal pessaries/sponges were devised by Egyptians. They used pessaries which were made of honey, sodium bicarbonate, and crocodile dung [1].

The evolution of oral contraceptive pills (OCPs) is a significant landmark in the history of women's reproductive health. This revolutionary medicinal development has had a great impact on society, altering outlook toward sexuality, family planning, and women empowerment in the nineteenth century (Table 1).

The combined oral contraceptive (COC) pill is one of the maximally and habitually used methods of contraception universally since it was discovered in 1960. Early combined oral contraceptives were linked with substantial adverse effects and increased cardiovascular risks in spite of being highly effective. Without causing any concessions in the effectiveness, improvements in acceptability and safety have been made, mainly by causing a reduction in the dosages and the development of several new progesterone [2].

Margaret Sanger, a birth control activist in the early twentieth century, was a pioneer in the use of oral contraceptives. She fought for women's rights to control their fertility and laid the groundwork for the development of modern birth control methods. She wrote a series of articles called "What Every Girl Should Know." She also published a newspaper called the “Woman Rebel,” which had information about contraception. In 1921, Sanger was responsible for founding the American Birth Control League, which later came to be Planned Parenthood Federation of America in 1946. She was also responsible for funding research to develop a contraceptive pill. She said, "No woman can call herself free until she can choose consciously whether she will or will not be a mother."

However, it was not until the mid-twentieth century that scientists made significant breakthroughs in creating an effective oral contraceptive. The birth control pill was first developed by Dr. Gregory Pincus. Pincus and John Rock, a prominent Catholic Gynaecologist, were responsible for this phenomenon. The financial funding for this study was provided by Katharine Dexter McCormick at the recommendation of Sanger [3].

The first hormonal pill, called Enovid(®), was permitted by the Federal Drug Administration (FDA) in May 1960 which consisted of mestranol and norethisterone. The first oral contraceptive drugs contained 100–175 µg of estrogen and 10 mg of progesterone. Significant adverse reactions were seen at this dose; most important being an increased risk for venous thromboembolism [3]. In the past few years, oral contraceptives have lowered the dose of ethinyl estradiol

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Table 1 Compositions of various contraceptive preparations

(1) Standard dose
EE 0.05 mg, Levonorgestrel 0.25 mg
(2) Low dose
EE 0.03 mg, Norgestrel 0.15 mg
EE 0.03 mg, Desogestrel 0.15 mg
EE 0.03 mg, Norethisterone acetate 1 mg
EE 0.03 mg, Drospirenone 3 mg
(3) Very low dose
EE 0.02 mg, desogestrel 0.15 mg
EE 0.02 mg, Levonorgestrel 0.10 mg
EE 0.02 mg, Drospirenone 3 mg
(4) Ultra low dose
EE 0.01 mg, Norethindrone acetate 1 mg

(EE), introduced 17β-estradiol, and added many different progesterone in various doses.

A number of randomized control trials with one more combination comprising 50-mcg ethinyl estradiol and 4-mg norethisterone and were done in the UK and Belgium. This combination was introduced in the market as Anovlar. A company in the Netherlands introduced a similar product with another brand, Lyndiol, which consisted of 75-mcg mestranol and 2.5-mg lynestrenol; a 3-desoxo-derivate of norethisterone [4].

Although the mechanism of the use of oral contraceptive pills was not completely known, it was definite that estrogens by themselves were equally effective in ovulation suppression. This inspired Joseph Goldzieher, to develop a sequential pill whose dosage included estrogen alone for 2 weeks, followed by a combination of that same estrogen and a progesterone for another 6 days [5].

The currently available OC pills now have a combination of 21 pills containing hormones and a 7-day pill-free interval consisting of placebo. Recently, both continuous and extended regimens have also been approved. Even other routes such as vaginal or transdermal routes of administration have been created mainly to aim at increasing compliance. In 2009, according to the United Nations, the mean global percentage of contraceptive use in women who either were married or were in a relationship was 62.7%. Contraceptive use in the form of COC was 8.8% and as high as 15.4% in developed countries. One hundred million women all over the world use COC's. However, each year, many unplanned pregnancies happen, demonstrating that contraception still needs to be promoted widely, and an awareness needs to be created across all social strata [1].

Journey of OC Pills Through the Ages

The dissimilarity between the original pills which was created and the existing formulations of hormonal contraceptive pills is huge. It has been mainly due to decrease in the dosages of hormones, introduction of new progesterone derivatives, development of various estrogen–progestin combination dosages, and alternative routes of administration. The need for this was mainly due to the requirement of OC's with less side effects, and this could only happen due to newer developments in the information regarding the mechanisms of action of the various hormones and their endocrine and metabolic effects [6, 7].

Reduction of the Dosage of Estrogen

In the estrogen dosage used in the initial formulations of contraceptives, there was high risk of thromboembolism [8]. This was the most important factor for the first wave of pill scare. Few years down the line, it was discovered that estrogens and ethinyl estradiol specifically are responsible for the synthesis of several clotting factors and the renin substrate angiotensinogen, which are responsible for causing pill-induced hypertension in women at risk. This first pill scare led to the gradual reduction in the dosage of ethinyl estradiol from 50 to 30, to 20, and to even as less as 15 μg. This reduction in dosage reduced side effects such as bloating, nausea, and breast tenderness. However, the prothrombotic effects were still significant at such low doses.

Different Regimes of Administration

Even though the sequential pill is no more available in the market, it was mainly responsible for the development of different combinations of estrogens and progesterone. These newer preparations could have better impact on the hormonal variations of the cycle of menstruation and hence decreasing the occurrence of irregular bleeding. The sequential pill was succeeded by the advancement of biphasic and triphasic oral contraceptive pills. The dose of progesterone was lowered per cycle with these pills. But this was made irrelevant with the new low dose combined monophasic pills. There was a dominant effect of progesterone seen on the endometrium even at low doses with biphasic and triphasic pills.

Second-Generation Progestins and Reduction in the Dose of Progesterone

LNG was a second-generation progesterone. At the end of 1960s, oral contraceptives with LNG in a dose with a range from 100 to 250 mg, combined with 20, 30, or 50 μg of

ethinyl estradiol, were on the market. Due to the reduction in the dosage of estrogens and progesterone, the lengthening on the duration of the pill intake to 24 days became mandatory to unable adequate suppression of follicular development. These are pills which are still marketed till today.

Extended/Continuous Regimens of Pill Intake

Pincus had been told that any cycle they planned could not deter away too much from the 28-day pattern of menstrual cycle. Thus, there was the creation of a dosage pattern of 21-day pill followed by a 7-day pill-free interval. There was a universal conviction that menstruation every 28 days is a sign of a normal reproductive female function. In fact, Enovid 10 mg was initially approved in 1957 by the FDA but it was for the treatment of only menstrual disorders. Its contraceptive use was approved only after 3 years. The main action of these pills is the suppression of ovulation. Promotion of extended regimens of the pill has been done only in the past 10 years. Initially, only women with perimenstrual symptoms were advised bi- and tri-cycling (i.e., taking the combined monophasic OC uninterruptedly for 42 or 63 days, respectively, before allowing withdrawal bleeding to take place). However, the current scenarios are that many women are taking their pill continuously for 1 year without a break [9, 10].

Third-Generation Progesterone and the 2nd Pill Scare Wave

Two new progesterone compounds, namely, gestodene and desogestrel, were derived two new progesterone derived from LNG. These drugs were invented mainly for the search for progesterone with no or minimum androgenic and metabolic effects. These were called the "third generation progesterone." These progesterone were combined with either 30 or 20 μg of ethinyl estradiol. In fact, these combinations almost replaced the second-generation hormonal contraceptives in the market. However in 1995–1996, there were three papers which were simultaneously published in The Lancet. These papers revealed that the risk of venous thromboembolism associated with the use of third-generation pills was as comparable as those with the second-generation pills [11–13]. These results were mainly responsible for the 2nd pill scare wave. Due to this, numerous women stopped using their hormonal contraception which resulted in greater number of unplanned pregnancies and abortions. However, the final opinion on the effects of these third-generation hormonal contraceptives on the clotting system is still a controversial matter [14–16].

Newer Progesterone [17, 18]

Several new progestins have been discovered over the period of past 10–15 years. Three of these newer progesterone have been included in newer oral contraceptive pill preparations. First is Dienogest which is a 19-nortestosterone derivative with the absence of androgenic, estrogenic, or mineralocorticoid properties, and with a strong anti-androgenic activity. Second of these is Drospirenone which is a spironolactone analog with anti-mineralocorticoid activity and moderate anti-androgenic effects. It also has an anti-aldosteronic effect which makes it useful as a contraceptive in women who complain of fluid retention and weight gain with the first- or second-generation pills. Third compound among these is nomegestrol acetate, which is a 19-norprogesterone derivative which binds only to the progesterone receptor. It is thus called as a pure progestational compound.

Natural Estradiol

Over the years, ethinyl estradiol has been causing a lot of issues, important ones being thromboembolism and others. Due to this, there have been several attempts to replace it with natural estrogen, i.e., estradiol. However, this has been associated with problems such as control of menstrual cycle and contraceptive ability. These issues were resolved by the development of a four-phase combination of estradiol valerate, which is broken down to estradiol, and addition of Dienogest as the progesterone in an extended cycle of 26 and/or 28 days. A new contraceptive containing 17b-estradiol and nomegestrol acetate, given according to a 24-day pill and a 4-day pill-free regimen, is going to be introduced in the immediate future [19].

One of the newer biological estrogens is estretol (E4) which is a natural estrogenic steroid produced by human fetal liver. It is a potent, orally bioavailable, natural selective estrogen receptor modulator. It has moderate affinity for both human estrogen receptor alpha (ERα) and ERβ. There is a high acceptability and tolerability for combined OCP's containing E4 and Drospirenone (DRSP). The above-mentioned combination effectively inhibits ovulation. There were good cycle control and positive effects on bleeding patterns with low doses (15 mg) of E4 with DRSP (3 mg) as compared to other COCs containing synthetic estrogens. Also, there were minimal effects on lipids, liver, SHBG levels, and carbohydrate metabolism. Therefore, there is a lower venous thromboembolism risk than ethinyl estradiol-containing hormonal pills [20].

Whether the use of a natural estrogen instead of the synthetic ethinyl estradiol will extend further advantages

as compared to the classical pill needs to be appraised with multicentric and randomized control trials over the next few years.

Discussion

Over the years, OCPs have undergone notable transformations in composition, dosage, and delivery methods. A good OCP should have good efficacy, reliable cycle control, a low incidence of adverse effects and should lead to non-contraceptive benefits. Beyond birth control, OCPs have found applications in managing various gynecological conditions such as polycystic ovary syndrome (PCOS), menstrual irregularities, and endometriosis. The versatility of these pills expanded their usage beyond contraception, benefiting women's health in multiple ways.

Ongoing research and innovation in hormonal contraception continue to this day. Newer developments aim to improve effectiveness, reduce side effects, and offer more tailored options for individual needs, such as extended-cycle pills that reduce the frequency of menstruation. In spite of their widespread use and benefits, oral contraceptives remain a subject of debate. Discussions persist regarding their safety, potential long-term effects, accessibility, and cultural implications. Efforts to address these concerns involve ongoing research, education, and initiatives to enhance access to reproductive health care worldwide.

Conclusion

In conclusion, the evolution of oral contraceptive pills represents a pivotal advancement in reproductive health care, granting women greater autonomy over their bodies and reproductive choices. The OC pills are the most extensively studied and researched drug formulations. The continuous development of safer and more effective contraceptive methods underscores the importance of ongoing research and innovation in improving women's health and well-being.

Declarations

Conflict of interest There are no conflicts of interest.

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