Effects Of Estrogen and Progesterone Used in Oral Contraceptive Pills: A review

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ABSTRACT:

Introduction Contraception is a method of avoiding unplanned pregnancy. Combined oral contraceptives (COCs) have become a prominent birth control method due to their contraceptive efficacy and acceptability profile. The use of oral contraceptive pills (OCPs) is linked to several health advantages as well as problems. Oral contraceptive pills can alter carbohydrate and lipid metabolism, including increased in blood glucose, triglyceride, low density lipoprotein LDL and total cholesterol. However, these changes may be affected by modification in type of progesterone used in oral contraceptive formulation.
Objective: the aim of this study is to evaluate the effect of oral contraceptives on glucose levels and lipid profile by emphasizing many studies that show the effect of oral contraceptive pills on the metabolic parameters such as (Fasting serum glucose, HbA1c%, total cholesterol, LDL, HDL and triglyceride level).

Keywords: oral contraceptive pills, lipid profile, glycemic control.

تأثير الاستروجين والبروجيستيرون المستخدمة في حبوب منع الحمل: بحث مرجعي

الخلاصة:
منع الحمل هو طريقة تجنب الحمل غير المخطط له, أصبحت حبوب منع الحمل وسيلة سائدة لتحديد النسل بسبب فعاليتها في منع الحمل وتقبلها . استخدام حبوب منع الحمل (OCPs) مرتبط بعدد من الفوائد الصحية بالإضافة إلى بعض التأثيرات الجانبية. يمكن أن تغير أقراص منع الحمل الفموية ايض الكابوهيدرات ومستوى الدهون، مما يؤدي إلى زيادة نسبة الجلوكوز في الدم, الدهون الثلاثية,والكوليسترول الضار (LDL) والكوليسترول الكلي. وهذه التغيرات ممكن ان تتأثر بتغير نوع البروجيستيرون المستخدم في تراكيب حبوب منع الحمل. الهدف: الهدف من هذه الدراسة هو معرفة تأثير حبوب منع الحمل على مستوى الكلوكوز وخصائص الدهون من خلال التأكيد من نتائج العديد من الدراسات التي تبين تأثير حبوب منع الحمل على العوامل الأيضية مثل (فحص السكر الصائم، معدل السكر التراكمي، نسبة الكوليسترول الكلي والدهون الثلاثية والكوليسترول المفيد HDL والكوليسترول الضار LDL.

الكلمات المفتاحية: حبوب منع الحمل، نسبة الدهون، مستوى الكلوكوز في الدم.

INTRODUCTION:

Oral contraceptive tablets contain hormonal compounds that a woman consumes to prevent unplanned pregnancy. These pills are separated into two sections, one containing simply the hormone progesterone and the other containing a complex including both progesterone and estrogen (1). Enovid 10 is the first type of pill, and it contains 9.85 mg of norethinodryl and 150 mcg of estrogen mestranol. The hormonal levels in today's pills are substantially lower, ranging from 0.1 to 3.0 mg of contemporary progestogen and 20 to 50 mcg of estrogen (2).
In recent years, the ethinyl estradiol EE dose has been reduced even lower, to 20 µg and even 15 µg. However, when compared to

higher doses of EE, these low levels have been linked to higher rates of withdrawal from clinical trials (primarily due to adverse effects such as bleeding) and bleeding abnormalities (amenorrhea/infrequent bleeding, irregular, protracted or frequent bleeding, spotting) (3).

The dangers and benefits of novel progestins used in contraception are determined by their molecular structure, the kind and dose of estrogen linked with them, and the method of administration (4). Lipoprotein alterations, insulin sensitivity to glucose, and coagulation variables have all been proposed as potential biomarkers of cardiovascular as well as venous risk generated by synthetic steroids being used contraception. As a result of these findings, the content of hormonal contraceptives has been altered to limit these alterations and so potentially reduce hazards (5).

Oral contraceptives (OCs), which include a combination of estrogen and progestin or solely progestin, are a safe, effective, and reversible method of controlling fertility. Since the 1960s, when the first steroidal oral contraceptive pill was approved, it has been the most often prescribed family planning technique, with 11.6 million women (or 19%) in the United States using it (6).

The pills combine a progestogen, which inhibits ovulation and improves overall contraceptive effectiveness, with an estrogen, which stabilizes the endometrium for better cycle control and overall contraceptive effectiveness. The first COC, Enovid-10, included 150 μg of synthetic estrogen mestranol and 10 mg of androgen-derived progestogen norethynodrel (7).

The goal of OCs is to prevent pregnancy by suppressing ovulation through modifying events during the ovulatory cycle. The progestin and estrogen components of OCs decrease the luteinizing hormone (LH) and follicle stimulating hormone (FSH) midcycle surge. The endometrial bed is decidualized and mitotic activity is suppressed as a result of the treatment. In the 1960s, early OC formulations attempted to replicate the natural cycle; however, using high dosages of estrogen instead of lower levels of combined estrogen and progestin resulted in a higher risk of major adverse events (8).

The first monthly dose routine of 21 active pills followed by 7 placebo pills or pill-free days remained consistent for decades, despite multiple changes in COC compositions. It was thought that a seven-day pause from active pill taking was required to elicit regular withdrawal bleeding episodes, which women referred to as 'menstruation.' This was recognized as crucial in the psychological acceptability of the pill in the beginning (7).

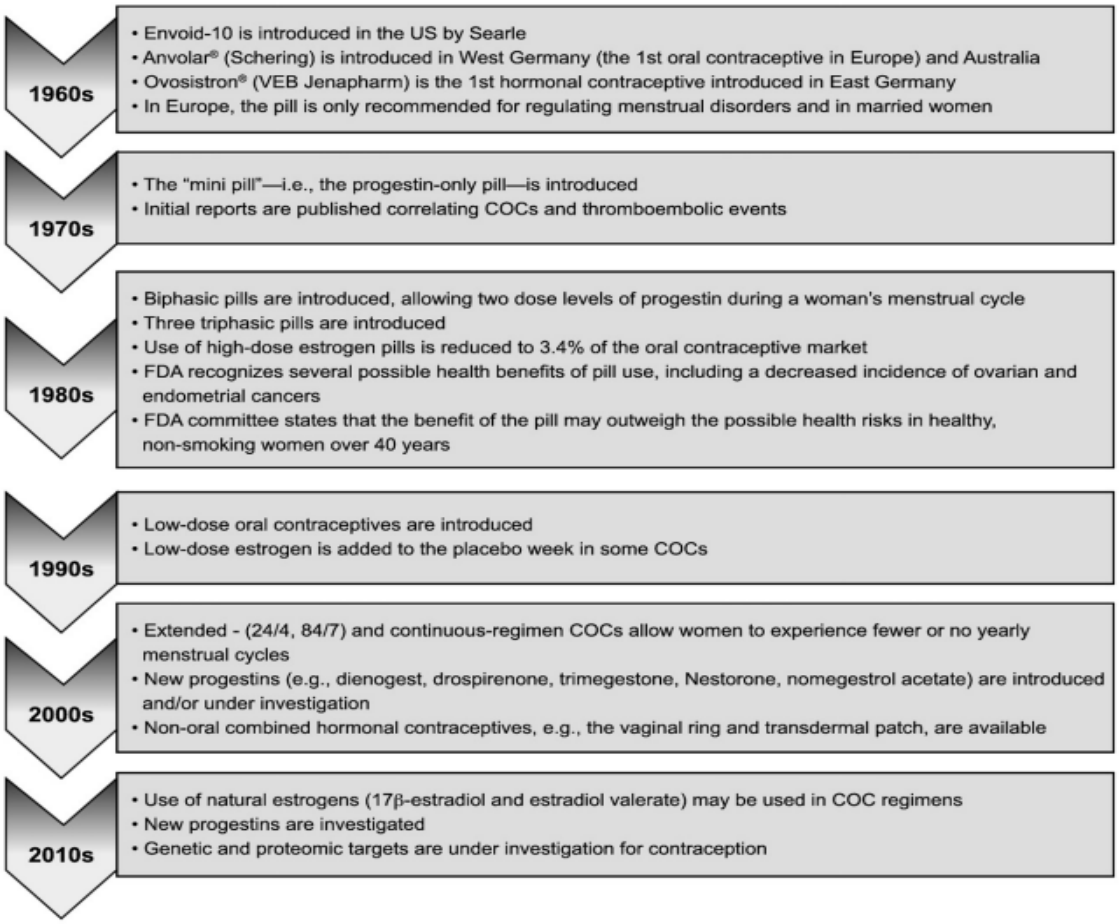

Figure (1): evolution of combined hormonal contraception (9)

The pill has gone through several stages in the 50 years after Enovid-10's introduction, including reductions in estrogen and progestogen doses, the creation of newer generations of progestogens, and changes in dosing schedules (Figure 1).

The estrogen utilized in nearly majority formulations is ethinylestradiol (EE), besides one that employs estradiol valerate. These are mixed with one of many synthetic progesterone. Only low-dose formulations, such as micro-pills with 15–35 μg EE, or the combination of estradiol valerate, should be provided routinely to reduce the risk of major adverse effects including thromboembolic events (10).

Biphasic or triphasic preparations have a daily dose that varies in a stepwise method, whereas monophasic combination pills have consistent daily doses of contraceptive steroids. Due to the reduction of pituitary suppression caused by the contraceptive drugs, follicular maturation begins during the pill-free time. During the first week of the next pill cycle, this is suppressed once more. The vaginal contraceptive ring and patch act similarly to oral combination preparations, with a 21-day hormone phase followed by a seven-day pill-free interval, during which a withdrawal bleed occurs. Their efficacy, adverse effect profile, and liver consequences are comparable to low-dose oral contraceptives (11).

Concerns about its negative cardiovascular (CV) effects led to changes in the composition of OCs with the purpose of lowering the risk of venous thromboembolism (VTE) and cardiovascular events, which have prompted public health concerns despite their rarity. Since its

introduction, the composition of OCs has undergone significant alterations in terms of both estrogen and progestin. First and second-generation OCs used progestins that were structurally linked to testosterone (19-nortestosterone derivatives; estrane and gonane families). This was linked to unfavorable androgenic side effects like acne and oily skin, as well as a negative impact on HDL cholesterol levels (12).

New progestins with improved specificity, derived from the progesterone structure or from spironolactone, have been created in recent decades to improve the safety profile (13).

Some estrogen-sensitive hemostatic variables and proteins generated in the liver are modified by the EE found in most combination hormonal contraceptives, and these estrogenic effects are controlled by the kind of progestin used. Despite the fact that none of the hemostatic changes could be linked to venous or arterial danger, it became evident that EE was also responsible for these occurrences, and a seek for natural estrogen combinations began. A novel oral OC formulation that delivers natural estrogen in the form of estradiol valerate (E2V) has recently become accessible globally (14).

Natural estrogens, such as 17b-estradiol (E2), have been linked to Nomegestrol acetate in monophasic contraceptives that have recently been licensed in Europe and are currently being assessed for approval in other countries. Estetrol (E4), a fetal estrogen produced from estriol (E3), is being studied in combination with other hormones for the development of innovative oral contraceptives with powerful antigonadotrophic progestins (15).

MODE OF ACTION AND EFFICACY OF ORAL CONTRACEPTIVE PILLS

The COCs' effect is essentially based on the reduction of gonadotrophin secretion. Follicular maturation, the preovulatory luteinizing hormone spike, and ovulation are all inhibited as a result. Most COCs contain a progestogen dose that is much higher than the ovulation suppression threshold therefore the contraceptive effect can be obtained even without the estrogen component. Progestogens' peripheral effects on cervical mucous, tube function, and the endometrium are also noteworthy. Cycle management, on the other hand, is dependent on the estrogen component's effects (16).

When pills are missed at the start of the first week of pills or at the ending of the last, the pill-free time during which follicular maturation resumes is extended, increasing the risk of conception. Figure (2) depicts the proper procedures for preventing undesired pregnancy when pills are missing. These restrictions only apply to monophasic combination preparations taken in the traditional manner, that is, for 21 days with a seven-day pill-free gap (17)

Because ovulation inhibition is mostly depended on the progestogen component, COCs containing 20 μg EE per day are as efficacious as those with 30 μg. Extending the pill cycle from 21 to 24 days (24/4) enhances follicular maturation suppression, allowing for a reduction in contraceptive steroid dose. Extended cycle regimens, such as 84 days with a seven-day PFI afterward (84/7), or continuous COCs usage, inhibit ovarian activity even more effectively. The amount of withdrawal bleeding is also reduced, which is something that many women like (18).

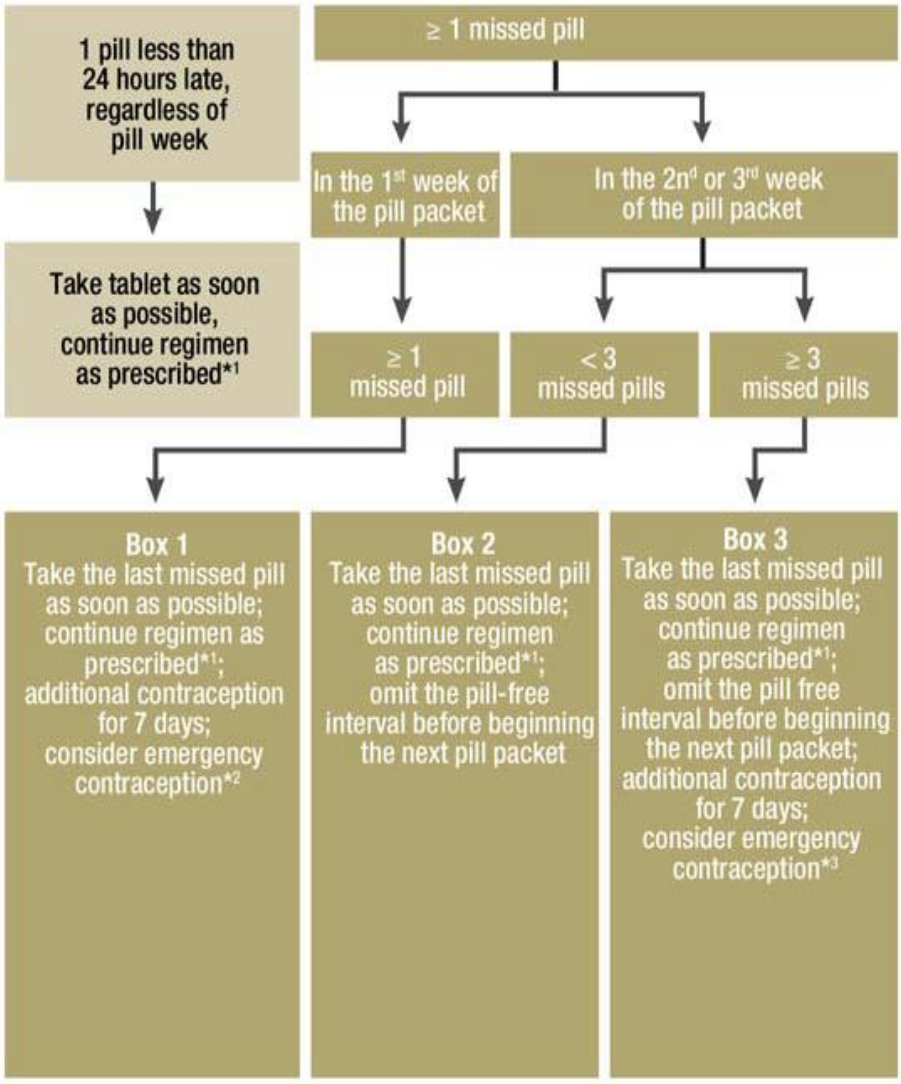

Figure (2) show the proper action to do after missing pills (19).

The COC's effectiveness can be compromised by gastrointestinal problems or antibiotic use. Despite the fact that a recent study demonstrated no effect of antibiotics, it is nevertheless recommended to utilize supplementary, alternative contraception (barrier methods) during antibiotic use and for a further seven days. The efficacy of hormonal contraceptives can be reduced if you use liver enzyme-inducing drugs like rifampicin or rifabutin at the same time. Oral contraceptives, on the other hand, can affect the efficacy of other drugs. As a result, COCs treatment can lower serum lamotrigine levels, increasing the risk of seizures and increasing the pill-free period. These swings can be avoided by using the COCs for a longer period of time or using it continuously (20).

CHARACTERISTICS OF ESTROGENS USED IN OCPs

The first generation of OCs contained mestranol, which was later replaced by ethinyl estradiol (EE), which was initially given in quantities as high as 150µg each pill, before being reduced to 50, then to 30 or 20 µg in today's OCs. In the gastrointestinal mucosa,

EE undergoes first-pass metabolism. 90 percent of the EE is absorbed from the upper gastrointestinal tract after oral administration, which can take one to two hours. It is subsequently subjected to oxidation reactions involving 2-hydroxylation and 16-hydroxylation at various carbons in the steroid nucleus. Following absorption, EE is converted to 3- and 17-sulfates, which are then partially deconjugated back to EE during enterohepatic recirculation (13).

When Steingold et al. measured the in vivo extraction of EE from the circulation, they discovered that oral administration of EE resulted in a greater delivery of circulating estrogens to the liver than to other tissues such as the brain or the uterus, explaining the estrogen's higher hepatic effects. On estrogen-dependent markers like liver proteins, EE has a higher effect than natural estradiol (E2). This higher hepatic action of EE has been linked to its 17a-ethinyl group, which prevents the molecule from inactivating, resulting in a sluggish metabolism and lengthy tissue retention, as well as a more pronounced hepatic effect of EE than estradiol. As a result, EE is 200–20,000 times more powerful than E2, based on the estrogenicity markers employed as end-points (21).

In addition, in contrast to E2, which has a short half-life, EE has a lengthy half-life, which increases its hepatic effects. In women who took an OC comprising 100 mcg LNG and 20 mcg EE, the elimination half-life was roughly 20 hours, but kinetics differed between fat and non-obese women. Furthermore, repeated EE delivery causes a rise in EE concentrations (22).

Endrikat et al. computed an approximate two-fold accumulation by comparing EE area under the curve (AUC) values obtained after the first and last pill administrations within a treatment cycle. Because of these qualities, there is no change in the mode of administration when EE is given orally, vaginally, or trans dermally, because the potency and long duration of action of EE still affects liver proteins (23).

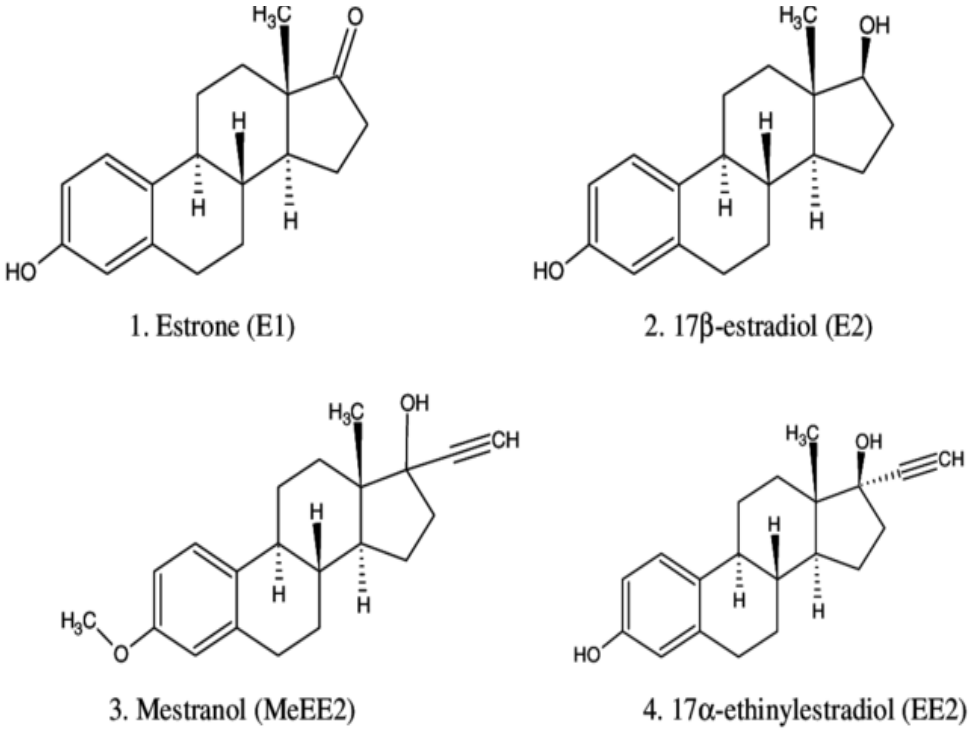

Figure (3): structures of estrogen used in hormonal contraceptive (13)

NATURAL ESTROGEN (ESTRADIOL)

Both cells and tissue are known to metabolize the natural estrogens 17b-estradiol (E2) and estrone (E1), with the interconversion of the two steroids and the creation of sulfo-conjugates. E2 has a very short half-life when taken orally, but this half-life is extended using micronized formulations. Hormone replacement therapy (HRT) and, more recently, contraception in combination with a progestin have both employed doses of 1–2 mg daily. Natural 17b-estradiol, unlike EE, has a substantially lower stimulatory effect on liver proteins when taken orally, and this effect is completely absent when E2 is applied trans dermally (24).

ESTRADIOL VALERATE

The combined oral contraceptives with dienogest (DNG) contain estradiol valerate (E2V), which is converted to 17b-estradiol and valeric acid, and E2, which is metabolized to estrone and estrone sulfate. Estradiol valerate is a synthetic version of the natural human estrogen estradiol (E2) that has been esterified with valeric acid at position 17. Given that 1 mg of E2V equals 0.76 mg of E2, the estrogenic effects of E2V and E2 are qualitatively and quantitatively comparable (3).

ESTETROL (E4)

E4 is an estrogen created by the fetus's liver from maternal E3 and is classified as an end product because it is not processed further. It has been synthesized, and it's being tested as a new estrogen for contraception and hormone replacement therapy. E4 is 18–20 times less active than EE and has a half-life of more than 24 hours when taken orally. It operates as an estrogen agonist in the bone, the brain, the vagina, the uterus, and the endometrium (25).

PROGESTIN USED IN ORAL CONTRACEPTIVE PILLS

Progestins generated from testosterone or 17-hydroxyprogesterone were the first generation of progestins, which were largely used in contraceptives. However, because of their nature, many compounds had undesired side effects, most of which were androgenic or glucocorticoid-like. The goal of the new progestins synthesized in the last two decades like drospirenone was to create the "ideal" progestin, with potent progestational and antiestrogenic effects on the endometrium, coupled with a strong antigonadotropic effect, but no androgenic or glucocorticoid effects, in order to produce the benefits of progesterone without undesirable side effects like acne, a decrease in high-density lipoprotein cholesterol (HDL-C) bloating and water retention (26).

The interaction of progestins with the progesterone receptor (PR), as well as the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR), and the mineralocorticoid receptor (MR), is responsible for the majority of their actions. Depending on the balance between the receptor coactivators and corepressors recruited by a progestin, a molecule could be agonistic or antagonistic, resulting in either promotion or avoidance of receptor transactivation (27).

The PR mediates progestational activity; the ligand causes a change in PR conformation, which is then converted into an active form that can bind to certain Deoxyribonucleic Acid (DNA) sites. By binding with coactivators, which act as bridging factors between the receptor and the general transcription machinery, the ligand-bound PR stimulates transcription. If corepressors are present, the DNA machinery is not transactivated once the hormone binds to the receptor, resulting in an antagonistic reaction (28).

By binding very selectively to the PR and not to other steroid receptors, the new progestins are designed to avoid androgenic, estrogenic, or glucocorticoid side effects. Some progestins are prodrugs that go through a metabolic process to become active. Progestin active metabolites including etonorgestrel (active derivative of desogestrel) and norelgestromin (active metabolite of norgestimate) have lately been chosen for use in non-oral contraceptive techniques. When taken orally, most progestins are well absorbed and undergo first-pass metabolism. The maximal concentration is attained in 1–3 hours, but pharmacokinetics shows a lot of inter-subject heterogeneity (29).

ESTRANES AND GONANES

Estrane-related progestins have a structural similarity to testosterone and can thus transactivate the androgen receptor. It may also have estrogenic properties (27).

It has been demonstrated that norethisterone acetate (NETA or NET-A) converts to EE. For the various doses, the conversion ratio of NET-A to EE ranged from 0.20 to 0.33 percent. Although the conversion rate is low, greater dosages of NET-A, as utilized in clinical trials, produce significant amounts of EE and may have an estrogenic impact. It has been proposed as an add-back regimen in the treatment of endometriosis without estrogen supplementation because of these estrogenic and androgenic properties (30).

The norethindrone (norethisterone) family of progestins includes norethindrone and its related estrange progestins (31).

Dienogest, a novel non-ethyl progestin, is an estrane like norethisterone but has a cyanomethyl group at Carbon 17 instead of an ethyl group. Hydroxylation and aromatization are used to break it down. Because it has a high oral bioavailability (>90%) and is rapidly absorbed, its pharmacokinetics make it appropriate for oral administration. After 2 hours, the peak level is attained, and the elimination half-life is roughly 10 hours. This molecule is extremely antiandrogenic and has no estrogenic or glucocorticoid activity, unlike the ethyl estranges (32).

The progestins that belong to the gonanes family, such as levonorgestrel (LNG), norgestrel, norgestimate, desogestrel (DSG), and gestodene, are better known as '13-ethyl gonanes.' Desogestrel is rapidly and completely converted to its active metabolite 3-keto-desogestrel in the liver and gut wall (etonorgestrel or ETG). Norgestimate is a highly selective progestational agent with low androgenic potential (31).

As they convert to LNG, levonorgestrel and structurally related progestins such as desogestrel, norgestimate, and gestodene belong to the levonorgestrel family of progestins. Although levonorgestrel and norethisterone are shown in second generation oral contraceptives, other less androgenic progestins in this family are included in so-called "third generation" oral contraceptives (32).

PREGNANES

When taken orally, the pregnanes (17hydroxy-progesterone) are structurally similar to progesterone and have significant action. The progestin medroxyprogesterone acetate (MPA) has been widely utilized in hormonal replacement therapy HRT and as a depot formulation in long-acting injectable contraceptives depo medroxyprogesterone acetate (DMPA). This chemical transactivates both the AR and the GR and, depending on the dose, causes associated adverse effects. Cyproterone CPA and chlormadinone CMA belong to the same class of pregnanes as medroxyprogesterone acetate MPA, but they react differently, with the first being the strongest antiandrogenic

molecule while the latter being somewhat antiandrogenic with no glucocorticoid activity (26).

SPIRONOLACTONE DERIVATIVE

Drospirenone (DRSP), a spironolactone-derived progestin, is rapidly absorbed after oral administration and achieves peak plasma levels in 1–2 hours. It has a bioavailability of roughly 76%. Its main antimineralocorticoid activity has the benefit of avoiding bloating, which might cause the slight weight gain associated with OCs and related to water retention. It also allows for a minor reduction in blood pressure, owing to the same mechanism that has been shown in postmenopausal women using natural estrogen for hormonal treatment (33).

The EFFECTS OF ORAL CONTRACEPTIVE PILLS ON LIPID METABOLISM

Increases in the LDL/HDL cholesterol ratio, especially in the apoprotein (apo)-B/apo-A1 ratio is regarded as important cardiovascular risk factors. Triglyceride levels may rise contribute to heart disease risk, but only when HDL levels are low (34).

The estrogenic component of OCs has been demonstrated to boost lipoprotein synthesis, particularly Very Low-Density Lipoprotein (VLDL) and High-Density Lipoprotein (HDL), while decreasing LDL levels. The magnitude of this effect is determined on the estrogen's potency and the progestin's androgenicity (35).

The influence of estrogens on lipid metabolism may be counteracted by progestins having androgenic characteristics. When hormonal contraceptives balance is oriented toward estrogen, the lipoprotein status is probably protective, but when the balance shifts toward androgens, it'll become neutral or pro-atherosclerotic (36). Indeed, estrogen therapy minimizes the likelihood of atherosclerosis in primates on a high-fat diet by 67 percent, but this benefit is reduced to 28 percent whenever the androgenic progestin LNG was co-administered with estrogens (37).

However, it is unclear whether HC-induced lipid metabolic changes have clinically meaningful implications on cardiovascular disease risk (38).

In comparison to levonorgestrel LNG-containing combinations that are more androgenic, OCs including novel progestins that are less androgenic, such as dienogest or nomegestrol acetate mixed with natural estrogen have been demonstrated to have a more beneficial effect on the lipid profile. The effects of a combination of nomegestrol acetate and 17b-estradiol (NOMAC/E2) on lipids and other metabolic variables were compared to levonorgestrel and ethinylestradiol LNG/EE oral contraceptive by Agren et al. During six treatment cycles, no clinically significant changes in total cholesterol, HDL-C, Low Density Lipoprotein-Cholesterol (LDL-C), or total triglycerides were seen in women receiving NOMAC/E2 (39).

The LNG/EE therapy had no effect on total cholesterol, but it did lower HDL-C, raise LDL-C, and raise total triglycerides.

Other novel combinations, such as drospirenone and desogestrel, have been shown in clinical studies to enhance mean HDL levels, indicating that non-androgenic progestins do not block the EE action on that estrogen-dependent lipoprotein (40). It's unclear whether this lipid impact is related to atherogenesis. Preclinical evidence suggests that androgenic progestins like LNG can partially counteract the inhibitory impact of less strong estrogen on atherogenesis, which is dependent on the relative balance of estrogenic potency, estrogen–progestin dosage, and progestin androgenic activity (37).

Natural estrogens, such as 17b-estradiol, have been recommended in recent studies because they raise HDL levels without raising VLDL levels, which is a common side effect of EE. A new oral contraceptive (OC) including estradiol valerate (E2V) and dienogest DNG was discovered. A study comparing the effects of a four-phasic regimen comprising E2V/DNG to a tri-phasic regimen containing ethinyl estradiol and levonorgestrel EE/LNG in a randomized clinical trial of 58 patients across seven cycles provides preliminary information on lipid alterations. From baseline through cycle 7, increases in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured (41).

The estradiol valerate /dienogest oral contraceptive E2V/DNG OC resulted in an increase in HDL-C, whereas the EE/LNG OC resulted in a decrease in this estrogen-sensitive protein, and the difference was statistically significant ($p = 0.055$). E2V/DNG increased LDL cholesterol levels compared to EE/LNG, which decreased them, however the results were not statistically significant ($p = 0.46$) (42).

THE EFFECTS OF ORAL CONTRACEPTIVE PILLS ON CARBOHYDRATE METABOLISM

The impacts of various HC components on glucose metabolism are likely to vary according to estrogen type and dose, progestin type and method of delivery.

Reduced insulin sensitivity and/or decreased insulin secretion cause abnormal glucose regulation. Using OCs can cause glucose intolerance by altering both routes, although the effects on insulin sensitivity appear to be the more important. The mechanism by which OCs cause insulin resistance is not fully understood. The estrogen component appears to be the main cause of decreased insulin sensitivity, and this effect can be modified by gestagens (43).

A study made in Ethiopia to evaluate effect of OCPs on glucose metabolism, according to findings of this study, fasting blood glucose level increased in women who use OCPs than those who not use OCPs (44).

Studies on the effects of mestranol or EE on glucose metabolism found no significant differences (45, 46). Different estrogen formulations, given for 6 months (1.25 mg of conjugated estrogens,.08 mg mestranol, or either.05 mg or.5 mg EE) or even for 2 years (mestranol), did not appear to affect carbohydrate metabolism consistently.

When progestins bind to and transactivate the progesterone receptor (PR), they alter insulin half-life, which is linked to insulin resistance. This action is determined by the molecule's structure, particularly its androgenic potency (47).

The effects of formulations containing the same dose of EE (20μ g) and then either LNG or its derivatives, DSG and GSD, which have a lower androgenic effect, were compared in trial (48). Following administration of either DSG or GSD, fasting glucose levels and OGTT glucose response increased between 10 to 12 percent (for fasting glucose), but the impacts were less than those seen with LNG.

The effect of OCPs on glycated hemoglobin were studied in group of women using combined oral contraceptive pills (COCPs) and another group using progesterone only pills (POP) the percentage of glycated hemoglobin remain constant in users POP while it increased in users of COCPs (49).

DRSP in various formulations has no effect on OGTT glucose, insulin, or C-peptide responses (50). Another two non-androgenic progestins, including such NOMAc and DNG linked with either E2 or E2V, respectively, had a neutral effect on

insulin sensitivity or an OGTT (51).

CONCLUSION

Finally, various estrogens and progestins have varying metabolic effects. Progestins' metabolic effects appear to be linked to their androgenic or glucocorticoid characteristics. Nonandrogenic or anti-androgenic progestins have a minor effect on lipid profile and carbohydrate metabolism, which may minimize the risk of coronary heart disease in principle

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