Chapter

Contraception and Family Planning: New Aspects Related to the Therapeutic Possibilities

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Abstract

The therapeutic use of CHC (combined hormonal contraception) is examined in healthy patients who accept this contraceptive method and in patients with specific problems (abundant menstrual flows, hyperandrogenism, chronic pelvic pain, PMS, disability, different lifestyles, etc.) who require contraception. Rational motivation for the non-only contraceptive use of this device is represented by their mechanism of action: antigonadotropic action with ovulatory block and reduced production of sex steroids, endometrial response with changes in menstrual bleeding, action on the progesterone receptor, downregulation of estrogen receptors, and anti-inflammatory action. The dosing regimen (continuous regimen) can also modulate the therapeutic response in relation to the utilization in pathologies with catamenial exacerbation. The metabolic response varies in relation to the characteristics of the association (synthetic or natural estrogen, progestin component) with possible hepatocellular action, characteristic for associations with EE. Numerous data on associations with EE, few data with natural estrogens are available; the assumptions of use in relation to particular therapeutic lines are examined.

Keywords: combined hormonal contraceptives, endometrium, bleedings, endometriosis, hyperandrogenism

1. Introduction

Today, the panorama of combined hormonal contraception includes association of ethinyl-estradiol or natural estrogens (estradiol valerate, estradiol, estetrol) with various progestogens. All the associations share the ability to inhibit ovulation by antigonadotropic action with reduction of follicular activity and, consequently, steroid production. This effect modifies endometrial response in variable ways depending on the characteristics of the estrogen and the type of progestogen used. The metabolic impact of CHC (combined hormonal contraception) is also different.

1.1 Associations with ethinyl estradiol (EE)

This synthetic estrogen (**Figure 1**) is delivered by oral, transdermal, and vaginal route, with rapid and complete absorption. Its half-life is 26 ± 7 hrs. Binding affinity

with Sex Hormone Binding Globulin is low; binding to albumin is 98.5% effective; bioavailability is 45–55%. The molecule's high metabolic stability is due to the presence of the C = CH group, which prevents the oxidation of 17β and the transformation into estrone. The oxidation of the C=CH group by cytochrome P 450 3 A 4 induces the formation of an intermediate metabolite capable of inhibiting the same cytochrome P 450 3 A 4. This results in accumulation that explains the greater biological potency of EE compared to E2 in all estrogen-related activities, in particular the synthesis of certain hepatic proteins, such as SHBG, the increase of which is dependent on the dose of EE and the type of progestin used. Metabolization at the gastric level is modest (0.44%); more than 30% of EE is sulfated in the intestine (during fasting), while endogenous estrogens are glucuronide conjugates [1].

It is known that progestogens stimulate endometrial 17-beta HSD2, which inactivates estradiol in the endometrial cell, reducing local estrogenic effect. This does not happen for EE, which inhibits the action of this enzyme [2]. This leads to relative endometrial stability for associations with EE. Concerning metabolic impact, EE is characterized by its dose-dependent hepatocellular action, which is modulated by the associated progestin (**Figure 2**). The progestogen component differs in half-life, progestogen potency, residual androgenic activity or antiandrogenic character, neuroprotective and anti-mineralocorticoid action, and glucocorticoid action with different metabolic repercussions [3].

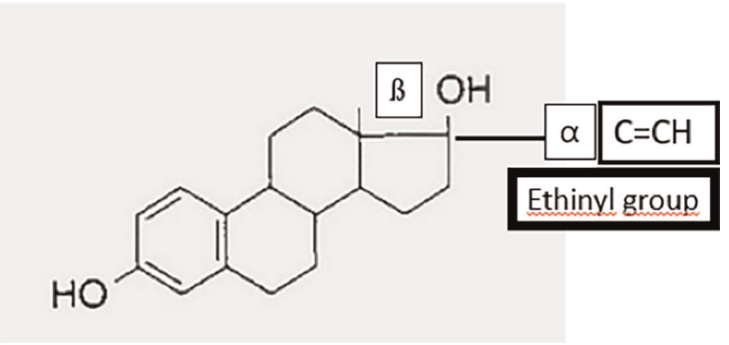

Figure 1.
Ethinyl-estradiol.

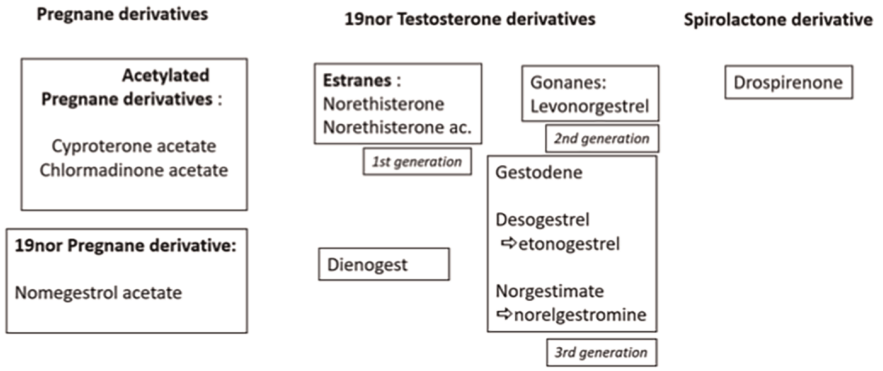

Figure 2.
Progestogens in contraceptive combinations with Ethynylestradiol.

Progestogens with residual androgenic activity moderate the prothrombotic activity of EE. Combinations with levonorgestrel (LNG) and norgestimate (NGS) are at lower VTE risk [4]. In particular, LNG has an androgenic activity of 3–4% and an anabolic activity of 20–30% that of testosterone. Its half-life (in association with EE) is 36 +/− 13 hours. The binding of LNG to SHBG is 50%. LNG does not induce a significant increase of SHBG when associated with EE. Norgestimate is a prodrug with rapid metabolism into Norelgestromin (NGMN), 39% in the liver and 49% in the intestinal mucosa. During hepatic first pass, 25% is metabolized to LNG, and at a later time, liver microsome activity produces a further 10% of LNG [5]. In a study [6] on 12 volunteers, about 22.6% of the dose of NGM administered in association with EE became systemically available as LNG. The progestogenic activity of norgestimate is marked, the androgenic activity minimal. There is glucocorticoid antagonist activity, albeit modest, and moderate mineralocorticoid antagonist activity. The binding of NGM to albumin is 99%, no binding to SHBG. From the point of view of therapeutic use, antiandrogenic activity of progestins, that is, the antagonism on androgen receptor (synergic with the inhibitory action of skin 5a reductase), is a relevant feature of biological action. This action is typical of cyproterone acetate, dienogest (40% compared to CPA), drospirenone (30% compared tp CPA), chlormadinone acetate, and, minimally, nomegestrol acetate (NOMAC) [7].

All the progestins used in contraception have a central action. They probably have an effect on the hypothalamic Kisspeptin-Neurokinin-Dynorphin neuronal system that regulates GnRH secretion and gonadotropin production. We do not know if the inhibitory action is direct or mediated by endogenous opiates. This effect requires estrogen priming and entails ovulation inhibition [8]. At the peripheral level, all progestins present in combined oral contraception (COC) induce decidualization of endometrium, albeit to different degrees. This effect is documented *in vitro* by morphological changes and is mediated by the interaction with progesterone receptors and enhanced, during COC use, by the progestin from the first days of intake of the combination drug. Progestins (LNG, NETA, DNG, DRSP, MPA) have been demonstrated to exercise anti-inflammatory activity, above all in the endometrium and peritoneum. Various studies have evidenced its ability to inhibit the production of prostaglandins, as well as to modulate pro- and anti-inflammatory cytokines, and regulate T-cell activation, resulting in reduced tissue production of nerve growth factors and vascular growth factors. The inhibition of proliferative signaling pathways mediated by estrogen receptor beta also plays a role [9]. These effects have been extensively documented in women with endometriosis as well as in healthy controls [10].

1.2 Associations with natural estrogens

Combinations of estradiol valerate with dienogest, estradiol with NOMAC, and estetrol with drospirenone are available.

17β Estradiol valerate (E2V) is the esterified form of 17ß-Estradiol (E2). E2V is rapidly and completely absorbed and hydrolyzed to natural estradiol during the first passage in the gastrointestinal tract. E2V is almost identical to E2 in terms of pharmacokinetics, and exactly identical in pharmacodynamics and clinic. The assessment of estradiol levels during E2V therapy puts in evidence that 1 mg of E2V is equivalent to 0.76 mg of E2 [11]. Regarding pharmacokinetics, 38% of estradiol is bound to SHBG, 60% to albumin, and 2–3% circulates in free form. The production of SHBG is increased by 150% after 28 days of intake. About 95% of estradiol undergoes metabolization before entering the systemic circulation. Its main metabolites are

estrone, estrone sulfate, and estrone glucuronide. Estradiol has a terminal half-life of 13–20 hours due to enterohepatic recirculation and the pool of circulating estrogen sulfates and glucuronides; its plasma half-life of estradiol is 90 minutes [12].

Estetrol (E4), a natural estrogen with four hydroxyl group, is synthetized by the human fetal liver only during pregnancy (**Figure 3**). Detectable blood levels are present at 9 weeks of gestation with exponential increase during pregnancy. The fetal exposure at term of pregnancy is about 3 mg/day, comparable with oral treatment with 50–60 mgE4 per day.

E4 half-life is 28–30 hours. The stimulus on liver SHBG synthesis is reduced. It also inhibits ovulation at a dosage of 5, 10, 20 mg due to a combination of central and peripheral action (given its suppressive effect on the ERα membrane). This effect is more pronounced using 20 mg doses [13]. E4 is able to block membrane ER and at the same time to activate nuclear ER exerting a strong estrogenic effect. E4 is an estrogenic agonist in the vagina [14], myometrium, endometrium, central nervous system, and bone. A dose-dependent proliferative effect has been shown in the endometrium in animal models [15] with increased cell differentiation, rather than mitotic activity [16]; dose-dependent increases in uterine weight were also seen. In combination with E2, estetrol has an anti-estrogenic action on breast tissue [17], and it exercises neuroprotective and antioxidant action in the CNS [18, 19] (**Table 1**).

Dienogest is a 19-nortestosterone derivative, that is, with 17a-ethinyl group (as in levonorgestrel) replaced by a 17a-cyanomethyl group. Despite limited *in vitro* binding affinity (approximately 10%) to the progesterone receptor in human uterine tissue, it is characterized *in vivo* by a potent endometrial activity, after oral intake. It follows that circulating dienogest levels are relatively high compared with those found with

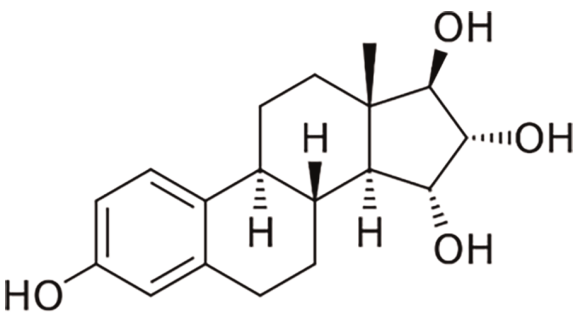

Figure 3.
Estetrol.

	E2V /DNG	E2/NOMAC	E4/DRSP
Half-life progestin (hours)	11	> 45	30
Antigonadotrope activity	moderate	strong	good
Progestational activity	strong	strong	good
Antiandrogenic activity	40% compared to CPA	15% compared to CPA	30% compared to CPA
Antimineralocorticoid activity	/	/	significant

Table 1.
Main characteristics of progestins in association with natural estrogens [20–22]. Half-life and biological activities of progestins used in COC with natural estrogens.

similar oral doses of others progestins [23, 24]. The endometrial action is carried out by blocking the aromatase, and by inhibiting COX_2 and the synthesis of PGE2, with consequent reduced production of estrogens, increased cellular apoptosis, and impaired angiogenesis [25–27].

Nomegestrol acetate NOMAC is a 9 norprogesterone derivate; it is devoid of estrogenic, androgenic, glucocorticoid, and mineralocorticoid activity but displays an anti-estrogenic activity on the endometrium and a moderate antiandrogenic activity [28]. It has a strong endometrial activity and a high contraceptive efficacy due to its high antigonadotropic effect and long elimination half-life [29].

Drospirenone (DRSP) is a spirolactone derivative with anti-mineralocorticoid activity. We remind that in addition to the kidney, there are several other cells and organs expressing mineral corticoid receptors, as blood vessels, inflammatory and immune cells, adipose tissue, and central nervous system [30]. So DRSP reduces differentiation of adipocytes, facilitates endothelial response to damage, and modulates inflammatory reactions. It also exerts neuroactive properties, balancing the negative effects of glucocorticoids on neurons and glia cells, and increasing the production of endogenous opiates [31, 32]. DRSP does not exert glucocorticoid activity as well as estrogenic activity. In ectopic endometrium, it shows anti-inflammatory effects [33].

The bleeding profile of the three associations with natural estrogens is presented in **Table 2** [34–39]. All of them induce a reduction of menstrual blood loss. Note that the association E4—DRSP seems favorable in terms of expected menstrual cycle and intermenstrual bleedings.

Concerning endometrial histology during the use of these combinations, a study on E2V/DNG put in evidence, after 20 cycles of use, only 11.4% of proliferative, and 16.9% of secretory endometrium vs. 64% of atrophic or inactive endometrium [40]. No specific data are available for E2/NOMAC association, even if clinical data support a strong endometrial activity. E4/DRSP induces, after 7 cycles, 81% of atrophic or inactive endometrium, 5% of secretory, and 22% of proliferative endometrium [41].

The pharmacological properties and the biological activities of these steroid combinations explain the possibilities of a therapeutic use.

	E2V /DNG	**E2/NOMAC [34]**	**E4/DRSP [35]**
Expected menstrual cycle	European Study: 77.7–83.2% [36]	82% 2nd cycle	76.5% 1st cycle
	North American Study: 76.5% [37]	68% 12th cycle	87% 12th cycle
			91–9 – 94.4%
Menstrual bleeding duration (days)	European Study:4.7–4	1.9–2.5	≤ 2 gg
	North American Study: 4.1–4-7	3.1–3.3	
Intermenstrual bleedings	European Study:28.8% (1st cycle)-11.25% (11th CYCLE)	> 20% reduction over time	13–17.4% (1st cycle)
	North American Study: 14%		16.2–19-8% (13th cycle)

Table 2.
Bleeding patterns during use of natural estrogen combinations.

2. Heavy menstrual bleeding (HMB)

We define excessive menstrual bleeding as blood loss of more than 80 ml (pad change every 1–2 hours, the presence of significant clots, and a duration of more than 8 days). Sometimes they represent a real clinical emergency. The rationale of using CHC is the association among the anti-ovulatory effect, with inhibition of follicular activity and ovarian steroid production, the suppression of endometrial proliferation, and the precocious decidualization, with reduction of menstrual flow.

In acute HMB, the treatment must start after excluding pregnancy complications. When it is possible, an anamnestic and US evaluation to rule out organic pathology is useful. As we have explained in the previous paragraph, a more rapid cessation of bleeding and greater endometrial stability are ensured using combinations with EE. In hemorrhagic menarche with 8–10 g/dL of hemoglobin levels, the use of monophasic COCs containing 30–50 mcg EE, given once every 6 hours for 2–4 days, followed by the same dose given every eight hours for three days and then every 12 hours for the next 14 days, is recommended [42]. The extensive experience has been confirmed by a recent revision [43]. In clinical practice, the dosage of EE should be individualized in relation to symptoms, entity of bleeding, and patient BMI. The same therapeutic option is possible even in the presence of a hemorragic diathesis. The guidelines for the treatment in patients with von Willebrandt disease from the National Heart, Lung, and Blood Institute stated that the first choice of therapy for HMB should be COC, with LNG-IUs as the second choice [43].

In cases of contraindications to COC, MPA (150 mg im) followed by oral MPA therapy (20 mg 3 times daily X 1 week) or oral NETA (40 mg daily, in multi dose/week) are proposed. The response is slightly lower with progestins than with COC use. A recent study [44] has pointed out as the estrogen-containing treatment for HMB (20, 30, or 35 mcg of EE as monotherapy or in a COC) initiated within 3 months of menarche was associated with reduced growth at 24 months compared to progesterone-only or nonhormonal methods. Authors invited to a particular attention in case of subjects with short stature at baseline.

Regarding chronic HBM, there is strong evidence supporting the impact of COCs on reducing menstrual bleeding volumes and unscheduled bleedings [45]. A recent Cochrane review [46] from 8 RCT involving 805 women has demonstrated the varied but positive response to COC, with improvement in 12–77% of subjects compared to only 3% of those on placebo. The data regarding E2V/DNG association demonstrate a reduction of blood loss from 65 to 80% after only a single treatment cycle in women with HMB and in women with normal menstrual cycles [47–49]. The association E2/NOMAC is also characterized by a significant reduction in menstrual blood loss [39, 50].

3. Endometriosis

Endometriosis is an estrogen-dependent chronic inflammatory disease, related to the presence of ectopic endometrial glandular epithelium and stroma. The endometriotic tissue shows few differences from the eutopic endometrium. First of all, epigenetic modifications of estrogen receptor have been demonstrated with the reduction of ERα (physiological inductor of progesterone receptor) and increase in ERβ. The induction of progesterone receptor is reduced, with prevalence of PRA, which is less active than PRB. As a consequence, the production of 17βOH steroid

dehydrogenase type 2, which entails the conversion of E2 to E1, is reduced. Aromatase activity is enhanced, with increased production of estrogens from androgenic precursors. So, in endometriotic implants, hyper-estrogenism associated with resistance to progesterone is present [51]. The activation of inflammatory response and the dysfunction of immune response participate in the stimulation of angiogenesis, neurogenesis, and fibrogenesis, modulated by estrogens. As a consequence, the effects of COC on eutopic and ectopic endometrium, mainly the reduction of estrogen receptors induced by activation of PB receptors and increased metabolization of estradiol into estrone, are not the same in ectopic endometrium. In endometriotic implants, the predominant presence of βE receptors and the marked reduction of PB receptors counteract the decidualization.

The current Endometriosis Guidelines [52] recommend (as strong recommendation) hormone treatment with CHC (oral, vaginal ring, or transdermal) or progestogens to reduce endometriosis-associated pain. Various mechanisms explain the efficacy of CHC as a therapeutic intervention. The antigonadotropic effect reduces ovarian follicular activity and steroid production, containing menstrual bleeding, retrograde flux, and peritoneal inflammatory state. The absence of ovulation also plays a role, because we know that the follicular fluid of women with endometriosis contains elevated estrogen levels, which stimulate the proliferation of endometrial implants more than peritoneal fluid [53]. The CHCs demonstrate a dominant progestative effect on the endometrium, dependent on the length of use of the association. A downregulation of estrogen receptors with inhibition of cellular proliferation has been demonstrated, together with the stimulus of progesterone receptors [54]. The inhibition of endometrial metalloproteases and the anti-inflammatory action exerted by the progestogen component are complementary to the hormonal effects.

All the contraceptive associations with 20 or 30 mcg of EE associated with various progestins are effective for the relief of endometriosis-related dysmenorrhea, pelvic pain and dyspareunia, and improve quality of life, but the entity of the response is variable [55–57]. The vaginal ring that releases 15mcg of EE and 120 mg of etonogestrel (active metabolite of desogestrel) has also been used in the treatment of chronic pelvic pain of pre-surgical and post-surgical endometriosis. The rationale for use relates to the reduced steroid systemic concentrations compared with the oral route and the possible advantages of the drug prompt administration with direct effect on deep infiltrating endometriosis. One study involving 207 young women [58] compered 123 vaginal ring wearers and 84 patch wearers (EE 20 mcg and Norelgestromin 150 mcg). A reduction of symptoms was evident in both treatment groups, with greater efficacy in the use of the ring in patients with recto-vaginal lesions. A randomized, prospective study [59] on 60 women with chronic pelvic pain treated with vaginal ring in continuous regimen for 84 days or with COC with EE 30 mcg and LNG 150 mcg showed that the two treatments are equally effective. Compliance, satisfaction, and acceptance to use were higher in ring users (80%) than in COC users (70%).

According to a systematic review [60], a certain persistence of symptoms under estrogen-progestin treatment is present in 59% of cases, as well as the relapse of pelvic pain in 17% of cases at follow-up. The studies reported do not consent a specific correlation between type of endometriotic lesions and therapeutical results, although subjects with peritoneal endometriosis or ovarian endometrioma could probably be more easily treated than those with profound infiltrative lesions [61]. However, significant improvement in pain symptoms, menstrual bleeding, and sexual quality of

life was also reported in patients with deep-infiltrating endometriosis (DIE) with or without associated adenomyosis after treatment with EE 30 mcg/DNG 2 mg [62].

There is some debate about whether or not a more competent choice of the COC could give better results. Considering the characteristics of the associations, an elevated progestative activity and a reduced estrogenic stimulation have been proposed [63], because we know that estrogens promote inflammatory reactions, neurogenesis, and angiogenesis inside the endometriotic lesions. This could orient the choice versus low EE dosages or the use of natural estrogen associations. We note that, even if the differences in pharmacokinetic do not consent calculation of clear equivalence, in relation to various metabolic and hemostatic parameter, it has been proposed that 2 mg of estradiol should be considered similar to 5 to 10 mcg of ethynyl-estradiol. The interindividual differences in drug efficacy and metabolism must also be considered. Choice of associations with these characteristics is based on speculative consideration and not on specific clinical trials, but there are favorable data on the use of natural estrogen combinations. The combination E2V/DNG has also been used in the treatment of endometriosis, resulting in a better reduction of pelvic pain and an improvement of the QoL compared to NSAIDS [64]. Experiences involving small groups have been published also using estradiol/NOMAC association with reduction of painful symptoms and size of ovarian endometriomas; DIE lesions remained stable [65] and showed better results than using NSAIDs [66].

There are no data available on the use of the E4/DRSP combination in treatment of endometriosis, but some experimental data deserve a mention. A recent *in vitro* study [67] on the effects of E4 on epithelial and stromal endometriotic cells evidenced no modification of cell viability or proliferation at any concentrations. Considering steroid receptor effect, both the ratio ERα/ERβ and PR increased (further by activation of PR-related genes) with possible beneficial effect. In comparison, during 17β estradiol use, there is an increase of cell number and reduction in apoptosis, without modification of ERα/ERβ ratio. The association with drospirenone could also be beneficial. One study [33] demonstrated the anti-inflammatory effect of DRSP with DNA synthesis decrease in stromal cells and significant reduction of IL-6, IL-8, VEGF, and NGF mRNA expression in endometriotic tissues obtained from patients that had undergone laparoscopic surgery for endometrioma.

Studies comparing COC with EE and various progestins with dienogest alone showed that compliance and side effects were similar, but the improvement of pain symptoms resulted superior with DNG in all the studies (**Table 3**) [68–73].

It has been widely demonstrated that the use of COCs decreases the risk of disease recurrence after conservative surgery. In a randomized pilot study related to postoperative administration of DNG or COC (EE 30 μg/LNG 0.3 mg) compared to placebo, self-reported pain was found reduced in both treatment groups after 6 months of treatment [74]. In another trial, postoperative administration of E2V/DNG for 9 months or GnRH for 6 months seemed equally effective in preventing pelvic pain recurrence in the first 9 months of follow-up [75]. There is insufficient evidence, however, to reach definitive conclusions about the superiority of any particular treatment: all hormonal regimens (cyclic or continuous COC, GnRHa, DNG, LNG-IUS, GnRHa + OC, and GnRHa + LNG-IUS) given as long-term treatment tend to reduce the risk of endometrioma recurrence [76]. Similar results were obtained in another systematic review and meta-analysis [77]: Hormonal suppression immediately after surgery was able to reduce recurrence of pain. The study was related to monophasic and multiphasic COC use in cyclic or continuous regimen, LNG IUS, and Dienogest 2 mg.

Combinations	Design of the study	End points	Results	Ref.
EE 30 mcg/DRSP 3 mg (flexible extended regimen) compared to DNG 2 mg	Randomized clinical trial	Pelvic pain, QoL	DNG more effective	[68]
EE 30 mcg/DRSP 3 mg (24 weeks) compared to DNG 2 mg	Randomized clinical trial	Pelvic pain, dysmenorrhea, dyspareunia, QoL	No significant differences DNG fewer side effect	[69]
EE 20 mcg/LNG 100 mg (continuous regimen) compared to DNG 2 mg	Prospective cohort study	Size of endometriomas	DNG more effective	[70]
		DIE, pain, QoL		
EE 30 mcg/DNG 2 mg compared to DNG 2 mg	Multicentric case-control study	Size of endometriomas; pain	DNG more effective	[71]
			No statistical difference in reduction pain symptoms	
EE 30 mcg/DNG 2 mg compared to DNG 2 mg	Observational study	Pain, QoL, and sexual satisfaction	DNG more effective reduction over time.	[72]
E2 1.5 mg /NOMAC 2.5 mg compared to DNG 2 mg	Randomized study	Pain, QoL, and sexual function	DNG more effective	[73]

Table 3.
Overview of the available comparative data of using COC compared to DNG 2 mg.

The treatment choice should be individualized according to each woman's needs. One important issue regards the comorbidities associated with endometriosis. An observational study pointed out that women with endometriosis had an elevated prevalence of psychiatric disorders and significant association with pain severity [78]. A meta-analysis of 24 studies (99,614 women) showed, in particular, higher levels of depression among women with endometriosis compared to controls [79]. The association was largely determined by chronic pain [80] but was also modulated by individual and context vulnerabilities. The impact of COC and progestins on the risk of depression should be considered. The data in the literature are controversial [81]. A significant association [82–85], no association [86–89], or improvement of mood have been reported [90, 91].

Moreover, migraine may be associated with dysmenorrhea and endometriosis [92]. The prevalence of migraine especially in advanced stages of endometriosis is significantly higher compared with controls [93], and this is confirmed also in adolescents [94]. Thus, the presence of aura should be investigated, and an appropriate choice of COC is necessary. Hemorrhagic diathesis is a risk factor for endometriotic implants and could require a specific choice of COC or an extended regimen in order to avoid acyclic bleeding.

4. Adenomyosis

Adenomyosis is defined by the presence of endometrial implants inside the myometrium. The rationale for using COCs in adenomyosis is related to the induced

decidualization and subsequent atrophy of the endometrium, also in adenomyotic foci [95], reducing pain, abnormal bleedings, and uterine volume [96]. Abnormal uterine bleedings are not pathognomonic of adenomyosis, although an increased severity of the disease may increase the likelihood of this symptom [97]. COC is less effective in controlling pain and bleeding than LNG-IUS [98] or oral DNG [99].

5. Hyperandrogenism

Androgen excess can be characterized by specific clinical features associated or not with biochemical hyperandrogenism. A clinical evaluation is important to differentiate skin symptoms of androgen excess (hirsutism, acne, seborrhea, and female-pattern hair loss) from states of virilization (clitoris hypertrophy, voice modifications, increase in muscle mass, baldness, and mammary gland atrophy) related to more severe adrenal or ovarian diseases. Clinical hyperandrogenism is often associated with menstrual irregularities (chronic oligomenorrhea, amenorrhea, dysfunctional uterine bleeding) and metabolic dysfunction (as in polycystic ovary syndrome).

The motivation for therapeutic use of COC in hyperandrogenism is multifactorial: suppression of ovarian androgen production (and for few progestins also adrenal androgen production), SHBG increase, 5α reductase activity inhibition, and competition for skin androgen receptors with some combinations (**Table 4**).

The inhibition of ovarian steroid production is related to the anti-ovulatory effect, typical of all COCs. The circulating levels of SHBG, and consequently the amount of testosterone bound and inactive, are dependent on the type of estrogen and the progestogen present in the association. The liver production of SHBG is induced in a dose-dependent manner by EE, but it is also conditioned by the progestogen associated. COCs containing second generation progestins (with a minimal residual androgenicity) and/or the lower estrogen doses (20–25 μg EE) were found to have less impact on SHBG concentrations [100]. It is less evident with associations containing natural estrogens. For instance, SHBG plasma levels decreased with E4 (5, 10, or 20 mg) in association with LNG, while they showed a dose-dependent slight increase with 5 or 10 mg E4 in association with DRSP. This increase is considerably less than with the combination EE/DRSP [22, 101] (**Table 5**).

Concerning acne, it is a complex and multifactorial inflammatory disease involving excessive and altered sebum production, cutaneous dysbiosis, abnormalities of

Cyproterone acetate	**Dienogest**	**Norgestimate**	**Drospirenone**	**Chlormadinone acetate**	**Nomegestrol acetate**
Half-life 50 hrs	Half-life 11 hrs	Half-life 45–71 hrs	Half-life 30 hrs	Half-life 34–39 hrs	Half-life 50 hrs
CPA 2 mg/ EE 35 mcg 21 + 7	DNG 2 mg / EE 30 mcg 21 + 7; 24 + 4	NGM 250 mg/ EE 35 mcg 21 + 7	DRSP 3 mg/ EE 30 mcg 21 + 7	CMA 3 mg/ EE 30 mcg 21 + 7	NOMAC 2.5 mg/ E2 1.5 mg 24 + 4
	DNG 2–3 mg/ E2V 3–2-1 mg quadriphasic	NGM 180 mg-215 mg/ EE 35 mcg Triphasic	DRSP 3 mg/ EE 20 mcg 21 + 7; 24 + 4		

Table 4.
Progestins with antiandrogenic or non-androgenic activity in COC.

Androgen production suppression	**SHBG increase**	**5a reductase activity inhibition**	**Androgen receptor competition**
Specific types or doses of progestins, estrogens, or EP combinations	Higher increase in COCs with EE and non-androgenic progestins	Related to the type of progestins: *in vitro* evaluation compared to finasteride:	Anti-androgenic progestins
cannot currently be recommended → similar efficacy in treating hirsutism [102]	Moderate increase in COCs with natural estrogens	3-keto desogestrel cyproterone acetate dienogest levonorgestrel norgestimate [103]	(**Table 4**) Less metabolic impact

Table 5.
Rationale for the therapeutic effect of COCs on hyperandrogenism.

proliferation and differentiation of keratinocytes of the pilo-sebaceous unit, and activation of the inflammatory and the innate immune responses [104]. The influence of the hormonal milieu is relevant, but it is not the main cause, even if the androgenic effect on sebocytes differentiation and on lipogenesis has been well documented [105], and increased androgen production plays a recognized role in the pathogenesis of adult acne [104]. COCs are an important therapeutic aid in treating acne manifestations but in synergy with dermatological therapies.

A frequent and particular condition of hyperandrogenism is polycystic ovary syndrome (PCOS), an endocrinopathy characterized by irregular menstrual cycles, hyper-androgenism, characteristic ovarian morphology, systemic chronic inflammatory state, and dysmetabolism. A wide phenotypic variability is typical, ranging from mild hirsutism and anovulation to menstrual disorders, heavy signs of hyperandrogenism, and overweight. It is important to point out that the metabolic component worsens the androgen excess and should be investigated and treated, together with endocrine disorders.

In the report from the Multidisciplinary Androgen Excess and PCOS Committee [104], COCs in association with topical therapy are the first line of therapy in mild, moderate, or severe acne with hyperandrogenism. Estro-progestins may be used also in non-hyperandrogenic patients with moderate or severe adult acne as second-line therapy. Various combinations have been used: ethynyl-estradiol associated with acetylated pregnane-derivatives (CPA, CMA), 19 nor testosterone progestins (LNG, GSD, DSG/ETG, NGSM), and spironolactone derivative (DRSP). All COCs were effective on acne, but less androgenic progestins should be preferred. Moreover, a real therapeutic effect on hirsutism requires association with antiandrogens and, in some cases, esthetic procedures. Considering subjects with PCOS, COCs represent an effective and safe treatment in women with any PCOS phenotype. For patients with metabolic risk, overweight, or moderate insulin resistance that does not require insulin-sensitizer use, lifestyle changes should be promoted. The association with metformin has been widely used in subjects with relevant dysmetabolism [106]. A combination with natural estrogens [107] has demonstrated a positive influence on acne in a small number of patients (improvement in 52.8% and worsening 3.8% after 12 months of therapy).

Current guidelines [108] recommend the following:

- The COCs alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles.
- The COCs alone should be considered in adolescents with a clear diagnosis of PCOS for the management of clinical hyperandrogenism and/or irregular menstrual cycles.
- The COCs could be considered in adolescents who are deemed "at risk" but not yet diagnosed with PCOS, for the management of clinical hyperandrogenism and irregular menstrual cycles.

COCs as monotherapy are not very effective in arresting mild to moderate alopecia or hirsutism and are preferably combined with an anti-androgen to achieve a better response when targeting hirsutism and hair loss [109]. A longitudinal study [110] has documented the progressive reduction of Ferriman-Gallway score obtained with the association EE-35/CPA 2 mg > in 18% of cases after 6 cycles of treatment, in 55% of cases after 24 cycles, and in 72% of cases after 48 cycles.

6. Conclusion

The therapeutic use of COCs in various clinical conditions (not all specifically examined in this chapter) should always consider individual risk factors and the eligibility criteria for contraceptive use. The pharmacological knowledge, which motivates benefits, is also the prerequisite for understanding the eventual risks.

The thrombotic risk is linked to the hepatocellular action of EE; it is dose-dependent and limited by the association with progestins with residual androgenic activity (LNG). The combinations with Norgestimate, non-androgenic progestins (but to be considered a prodrug for its metabolization in Norelgestromin and LGN) are recognized in various systematic review and meta-analyses at low thrombotic risk [111–115]. Current epidemiological data on COCs with natural estrogens show a comparable risk to the association of EE-LNG [116, 117].

The choice of combination, even for therapeutic use, cannot disregard a careful familial and personal evaluation of the subject and, if possible, the correction of metabolic risk factors present.

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References

[1] Back DJ, Madden S, Orme EM. Gastrointestinal metabolism of contraceptive steroids. American Journal of Obstetrics and Gynecology. 1990;**163**: 2138-2145

[2] Gurpide E, Marks C. Influence of endometrial 17b-hydroxysteroid dehydrogenase activity on the binding of estradiol to receptors. The Journal of Clinical Endocrinology and Metabolism. 1981;**52**:252-255

[3] Kuhl H. Pharmacology of estrogens and progestogens: Influence of different routes of administration. Climacteric. 2005;**8**(Suppl. 1):3-63

[4] Martínez VF, Ramírez I, Pérez-Campos E, Latorre K, Lete I. Venous and pulmonary thromboembolism and combined hormonal contraceptives. Systematic review and meta-analysis. The European Journal of Contraception & Reproductive Health Care. 2012;**17**(1): 7-29

[5] Paris F, Balaguer P, Rimbault F, Gaspari L, Sultan C. Molecular action of norgestimate: New developments. Gynecological Endocrinology. 2015; **31**(6):487-490

[6] Kuhnz W, Blade H, Mahler M. Systemic availability of levonorgestrel after single oral administration of a norgestimate-containing combination oral contraceptive to 12 young women. Contraception. 1994;**49**(3): 255-263

[7] Kuhl H. Comparative pharmacology of newer progestins. Drugs. 1996;**51**: 188-215

[8] Moore AM, Coolen LM, Porter DT, et al. KNDy cells revisited. Endocrinology. 2018;**159**(9):3219-3234

[9] Fedotcheva TA, Fedotcheva NI, Shimanovsky NL. Progesterone as an anti-inflammatory drug and Immunomodulator: New aspects in hormonal regulation of the inflammation. Biomolecules. 2022;**12**: 1299

[10] Maeda N, Izumiya C, Taniguchi K, et al. Dienogest improves human leucocyte antigen-DR under-expression and reduces tumour necrosis factor-α production in peritoneal fluid cells from women with endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014;**177**:48-51

[11] Timmer CJ, Geurts TB. Bioequivalence assessment of three different estradiol formulations in postmenopausal women in an open, randomized, single-dose, 3-way cross-over study. European Journal of Drug Metabolism and Pharmacokinetics. 1999; **24**(1):47-53

[12] Stanczyk FZ, Archer DF, Bhavnani BR. Ethinyl estradiol and 17β-estradiol in combined oral contraceptives: Pharmacokinetics, pharmacodynamics and risk assessment. Contraception. 2013 Jun; **87**(6):706-727

[13] Duijkers IJM, Klipping C, Zimmerman Y, Appels N, et al. Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: Results of a phase II dose-finding pilot study. The European Journal of Contraception & Reproductive Health Care. 2015; **20**(6):476-489

[14] Benoit T, Valera MC, Fontaine C, Buscato M, et al. Estetrol, a Fetal selective Estrogen receptor modulator,

acts on the vagina of mice through nuclear Estrogen receptor α activation. The American Journal of Pathology. 2017;**187**(11):2499-2507

[15] Abot A, Fontaine C, Buscato M, Solinhac R. The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor α modulation, uncoupling nuclear and membrane activation. EMBO Molecular Medicine. 2014;**6**(10):1328-1346

[16] Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: A unique steroid in human pregnancy. Journal of Steroid Biochemistry & Molecular Biology. 2008;**110**:138-143

[17] Coelingh Bennink HJT, Singer C, Simoncini T, et al. Estetrol, a pregnancy-specific human steroid, prevents and suppresses mammary tumor growth in a rat model. Climacteric. 2008;**11**(Suppl. 1):29

[18] Pluchino N, Santoro AN, Casarosa E, Giannini A, et al. Effect of estetrol administration on brain and serum allopregnanolone in intact and ovariectomized rats. The Journal of Steroid Biochemistry and Molecular Biology. 2014;**143**:285-290

[19] Tskitishvili E, Pequeux C, Munaut C, Viellevoye R, et al. Estrogen receptors and estetrol-dependent neuroprotective actions: A pilot study. The Journal of Endocrinology. 2017;**232**(1):85-95

[20] Endrikat J, Parke S, Trummer D, Serrani M, et al. Pituitary, ovarian and additional contraceptive effects of an estradiol-based combined oral contraceptive: Results of a randomized, open-label study. Contraception. 2013; **87**(2):227-234

[21] Christin-Maitre S, Laroche E, Bricaire L. A new contraceptive pill containing 17β-estradiol and nomegestrol acetate. Womens Health (Lond). 2013;**9**(1):13-23

[22] Klipping C, Duijkers I, Mawet M, Maillard C, et al. Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone. Contraception. 2021; **103**(4):213-221

[23] Stanczyk FZ. Pharmacokinetics and potency of progestins used for hormone replacement therapy and contraception. Reviews in Endocrine & Metabolic Disorders. 2002;**3**(3):211-224

[24] Sasagawa S, Shimizu Y, Imada K, Mizuguchi K. Pharmacological and clinical profile of dienogest. Nihon Yakurigaku Zasshi. 2009;**133**(1):32-40

[25] Shimizu Y, Mita S, Takeuchi T, Notsu T, et al. Dienogest, a synthetic progestin, inhibits prostaglandin E2 production and aromatase expression by human endometrial epithelial cells in a spheroid culture system. Steroids. 2011; **76**(1–2):60-67

[26] Yamanaka K, Xu B, Suganuma I, Kusuki I, et al. Dienogest inhibits aromatase and cyclooxygenase-2 expression and prostaglandin E_2 production in human endometriotic stromal cells in spheroid culture. Fertility and Sterility. 2012;**97**(2):477-482

[27] Miyashita M, Koga K, Takamura M, Izumi G, et al. Dienogest reduces proliferation, aromatase expression and angiogenesis, and increases apoptosis in human endometriosis. Gynecological Endocrinology. 2014; **30**(9):644-648

[28] Lello S. Nomegestrol acetate: Pharmacology, safety profile and therapeutic efficacy. Drugs. 2010;**70**: 541-559

[29] Ruan X, Seeger H, Mueck AO. The pharmacology of nomegestrol acetate. Maturitas. 2012;**71**(4): 345-353

[30] Jaisser F, Farman N. Emerging roles of the mineralocorticoid receptor in pathology: Toward new paradigms in clinical pharmacology. Pharmacological Reviews. 2016;**68**:49-75

[31] Armani A, Cinti F, Marzolla V, Morgan J, et al. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. The FASEB Journal. 2014; **28**(8):3745-3757

[32] Genazzani AR, Pluchino N, Begliuomini S, Pieri M, et al. Drospirenone increases central and peripheral beta-endorphin in ovariectomized female rats. Menopause. 2007;**14**(1):63-73

[33] Makabe T, Koga K, Miyashita M, Takeuchi A, et al. Drospirenone reduces inflammatory cytokines, vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) expression in human endometriotic stromal cells. Journal of Reproductive Immunology. 2017;**119**:44-48

[34] Archer DF, Mansour D, Foidart JM. Bleeding patterns of Oral contraceptives with a cyclic dosing regimen: An overview. Journal of Clinical Medicine. 2022;**11**:4634

[35] Gemzell-Danielsson K, Apter D, Zatik J, Weyers S, et al. Estetrol-Drospirenone combination oral contraceptive: A clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG. 2022;**29**(1):63-71

[36] Ahrendt HJ, Makalová D, Parke S, Mellinger U, Diana MD. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: A seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestre. Contraception. 2009;**80**(5):436-444

[37] Nelson A, Parke S, Mellinger U, Zampaglione E, Schmidt A. Efficacy and safety of a combined oral contraceptive containing estradiol valerate/dienogest: Results from a clinical study conducted in North America. Journal of Women's Health (Larchmt). Mar 2014;**23**(3): 204-210

[38] Jensen JT, Bitzer J, Nappi RE, Ahlers C. Pooled analysis of bleeding profile, efficacy and safety of oral oestradiol valerate/dienogest in women aged 25 and under. The European Journal of Contraception & Reproductive Health Care. 2020;**25**(2):98-105

[39] Mansour D, Westhoff C, Kher U, Korver T. Pooled analysis of two randomized, open-label studies comparing the effects of nomegestrol acetate/17β-estradiol and drospirenone/ethinyl estradiol on bleeding patterns in healthy women. Contraception. 2017; **95**(4):390-397

[40] Bitzer J, Parke S, Roemer T, Serrani M. Endometrial safety of an oral contraceptive containing estradiol valerate and dienogest. International Journal of Women's Health. 2011;**3**: 127-132

[41] Duijkers I, Klipping C, Kinet V, Jost M, et al. Effects of an oral contraceptive containing estetrol and drospirenone on ovarian function. Contraception. 2021;**103**(6):386-393

[42] Elmaoğulları S, Ayca Z. Abnormal uterine bleeding in adolescents. Journal

of Clinical Research in Pediatric Endocrinology. 2018;**10**(3):191-197

[43] Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): Evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia. 2008;**14**(2):171-232

[44] Nelson JM, Compton SD, Farahzad MM, Winfrey OK, Rosen MW. The relationship between estrogen and subsequent growth restriction among adolescents with heavy menstrual bleeding at menarche. Journal of Pediatric Endocrinology & Metabolism. 2023;**36**(3):255-260

[45] Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Human Reproduction Update. 2015;**21**(5):640-651

[46] Lethaby A, Wise MR, Weterings MA, Bofill Rodriguez M, Brown J. Combined hormonal contraceptives for heavy menstrual bleeding. Cochrane Database of Systematic Reviews. 2019;**2**(2):CD00015

[47] Jensen JT. Evaluation of a new estradiol oral contraceptive: Estradiol valerate and dienogest. Expert Opinion on Pharmacotherapy. 2010;**11**(7): 1147-1157

[48] Fraser IS, Römer T, Parke S, Zeun S, et al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: A randomized, double-blind phase III trial. Human Reproduction. 2011;**26**(10):2698-2708

[49] Rafie S, Borgelt L, Koepf ER, Temple-Cooper ME, et al. Novel oral contraceptive for heavy menstrual bleeding: Estradiol valerate and dienogest. International Journal of Women's Health. 2013;**5**:313-321

[50] Weisberg E, Mc Geehan K, Hangan G, Fraser IS. Potentially effective therapy of heavy menstrual bleeding with an oestradiol-nomegestrole acetate contraceptive: A pilot study. Pilot and Feasibility Studies. 2017;**3**:18-25

[51] Marquardt RM, Tim TH, Shin Y, Jeong J. Progesterone and estrogen signaling in the endometrium: What goes wrong in endometriosis? International Journal of Molecular Sciences. 2019;**20**: 3822

[52] Dunselman GAJ, Vermeulen N, Becker C, et al. European Society of Human Reproduction and Embryology ESHRE guideline: Management of women with endometriosis. Human Reproduction. Mar 2014;**29**(3):400-412

[53] Somigliana E, Viganò P, La Sala GB, Balasini M, et al. Follicular fluid as a favourable environment for endometrial and endometriotic cell growth in vitro. Human Reproduction. 2001;**16**(6): 1076-1078

[54] Dinh A, Sriprasert I, Williams AR, Archer DF. A review of the endometrial histologic effects of progestins and progesterone receptors modulators in reproductive age women. Contraception. 2015;**91**:360-367

[55] Mabrouk M, Solfrini S, Frascà C, Del Forno S, et al. A new oral contraceptive regimen for endometriosis management: Preliminary experience with 24/4-day drospirenone/ethinylestradiol 3 mg/20 mcg. Gynecological Endocrinology. 2012;**28**(6):451-454

[56] Yoshino O, Suzukamo Y, Yoshihara K, Takahash N. Quality of life

in Japanese patients with dysmenorrhea or endometriosis-associated pelvic pain treated with extended regimen Ethinylestradiol/Drospirenone in a real-world setting: A prospective observational study. Advances in Therapy. 2022;**39**:5087-5104

[57] Caruso S, Iraci M, Cianci S, Fava V, et al. Comparative, open-label prospective study on the quality of life and sexual function of women affected by endometriosis-associated pelvic pain on 2 mg dienogest/30 μg ethinyl estradiol continuous or 21/7 regimen oral contraceptive. Journal of Endocrinological Investigation. 2016; **39**(8):923-931

[58] Vercellini P, Barbara G, Somigliana E, Bianchi S, et al. Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertility and Sterility. 2010;**93**:2150-2161

[59] Priya K, Rajaram S, Goel N. Comparison of combined hormonal vaginal ring and low dose combined oral hormonal pill for the treatment of idiopathic chronic pelvic pain: A randomised trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016;**207**:141-146

[60] Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: A systematic review. Fertility and Sterility. 2017;**108**(1): 125-136

[61] Vercellini P, Buggio L, Berlanda N, Barbara G, et al. Estrogen-progestins and progestins for the management of endometriosis. Fertility and Sterility. 2016;**106**:1552-1571

[62] Alcalde AM, Martínez-Zamora MA, Gracia M, Ros C, et al. Assessment of quality of life, sexual quality of life, and pain symptoms in deep infiltrating endometriosis patients with or without associated Adenomyosis and the influence of a flexible extended combined Oral contraceptive regimen: Results of a prospective, observational study. The Journal of Sexual Medicine. 2022;**19**(2):311-318

[63] Vercellini P, Buggio L, Frattaruolo MP, Borghi A, et al. Medical treatment of endometriosis-related pain. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2018;**51**: 68-91

[64] Grandi G, Xholli A, Napolitano A, Palma F, Cagnacci A. Pelvic pain and quality of life of women with endometriosis during quadriphasic estradiol valerate/dienogest oral contraceptive: A patient-preference prospective 24-week pilot study. Reproductive Sciences. 2015;**22**(5): 626-632

[65] Mariani LL, Novara L, Mancarella M, Fuso L, et al. Estradiol/nomegestrol acetate as a first-line and rescue therapy for the treatment of ovarian and deep infiltrating endometriosis. Gynecological Endocrinology. 2021;**37**(7):646-649

[66] Caruso S, Cianci A, Iraci M, Fava V, et al. Does Nomegestrol acetate plus 17β-Estradiol Oral contraceptive improve endometriosis-associated chronic pelvic pain in women? Journal of Women's Health (2002). 2020;**29**(9):1184-1191

[67] Patiño-García D, Palomino J, Pomés C, Celle C, et al. Estetrol increases progesterone genetic response without triggering common estrogenic effects in Endometriotic cell lines and primary cultures. Biomedicine. 2023;**11**(4):1169

[68] Harada T, Kosaka S, Elliesen J, Yasuda M, et al. Ethinylestradiol 20 μg/

drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: A randomized controlled trial. Fertility and Sterility. 2017;**108**(5):798-805

[69] El Taha L, Abu Musa A, Khalifeh D, Khalil A, Abbasi S, Nassif J. Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2021;**267**:205-212

[70] Piacenti I, Viscardi MF, Masciullo L, Sangiuliano C, Scaramuzzino S, et al. Dienogest versus continuous oral levonorgestrel/EE in patients with endometriosis: what's the best choice? Gynecological Endocrinology. 2021; **37**(5):471-475

[71] Angioni S, Pontis A, Malune ME, Cela V, et al. Is dienogest the best medical treatment for ovarian endometriomas? Results of a multicentric case control study. Gynecological Endocrinology. 2020; **36**(1):84-86

[72] Maiorana A, Alfano P, Mercurio A, Marcantonio S, et al. Quality of life and clinical factors in women with endometriosis, the role of dienogest vs EE/dienogest over time: A single-center study. Archiv Gynecol Obstet. 2023;**307**: 1503-1512

[73] Caruso S, Cianci A, Sareri MI, Panella M, et al. Randomized study on the efectiveness of nomegestrol acetate plus 17β-estradiol oral contraceptive versus dienogest oral pill in women with suspected endometriosis-associated chronic pelvic pain. BMC Women's Health. 2022;**22**:146

[74] Mehdizadeh Kashi A, Niakan G, Ebrahimpour M, et al. A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. International Journal of Gynecology & Obstetrics. 2021;**00**:1-9

[75] Granese R, Perino A, Calagna G, Saitta S, et al. Gonadotrophin-releasing hormone analogue or dienogest plus estradiol valerate to prevent pain recurrence after laparoscopic surgery for endometriosis: A multi-center randomized trial. Acta Obstetricia et Gynecologica Scandinavica. 2015;**94**(6): 637-645

[76] Wattanayingcharoenchai R, Rattanasiri S, Charakorn C, Attia J, et al. Post-operative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: A systematic review and network meta-analysis. BJOG. 2021;**128**(1):25-35

[77] Zakhari A, Delpero E, McKeown S, Tomlinson G, et al. Endometriosis recurrence following post-operative hormonal suppression: A systematic review and meta-analysis. Human Reproduction Update. 2021;**27**(1):96-107

[78] Vannuccini S, Lazzeri L, Orlandini C, Morgante G, et al. Mental health, pain symptoms and systemic comorbidities in women with endometriosis: A cross-sectional study. Journal of Psychosomatic Obstetrics and Gynaecology. 2018;**39**(4):315-320

[79] Gambadauro P, Carli V, Hadlaczky G. Depressive symptoms among women with endometriosis: A systematic review and meta-analysis. American Journal of Obstetrics and Gynecology. 2019;**220**(3):230-241

[80] van Barneveld E, Manders J, van Osch FMH, van Poll M, et al. Depression,

anxiety, and correlating factors in endometriosis: A systematic review and meta-analysis. Journal of Women's Health (2002). 2022;**31**(2):219-230

[81] McCloskey LR, Wisner KL, Cattan MK, Betcher HK. Contraception for women with psychiatric disorders. The American Journal of Psychiatry. 2021;**178**(3):247-255

[82] Borgström A, Odlind V, Ekselius L, Sundström-Poromaa I. Adverse mood effects of combined oral contraceptives in relation to personality traits. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008;**141**(2): 127-130

[83] Skovlund CW, Mørch LS, Kessing LV, Lidegaard O. Association of Hormonal Contraception with depression. JAMA Psychiatry. 2016; **73**(11):1154-1162

[84] Zettermark S, Perez Vicente R, Merlo J. Hormonal contraception increases the risk of psychotropic drug use in adolescent girls but not in adults: A pharmaco-epidemiological study on 800 000 Swedish women. PLoS One. 2018;**13**(3):e0194773

[85] de Wit AE, Booij SH, Giltay EJ, Joffe H, et al. Association of use of Oral contraceptives with depressive symptoms among adolescents and Young women. JAMA Psychiatry. 2020; **77**(1):52-59

[86] Schaffir J, Worly BL, Gur TL. Combined hormonal contraception and its effects on mood: A critical review. The European Journal of Contraception & Reproductive Health Care. 2016;**21**(5): 347-355

[87] Pagano HP, Zapata LB, Berry-Bibee EN, Nanda K, et al. Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: A systematic review. Contraception. 2016;**94**(6):641-649

[88] McKetta S, Keyes KM. Oral contraceptive use and depression among adolescents. Annals of Epidemiology. 2019;**29**:46-51

[89] Robakis T, Williams KE, Nutkiewicz L, Rasgon NL. Hormonal contraceptives and mood: Review of the literature and implications for future research. Current Psychiatry Reports. 2019;**21**(7):57

[90] Young EA, Kornstein SG, Harvey AT, Wisniewski SR, et al. Influences of hormone-based contraception on depressive symptoms in premenopausal women with major depression. Psychoneuroendocrinology. 2007;**32**(7):843-853

[91] Toffol E, Heikinheimo O, Koponen P, Luoto R, et al. Hormonal contraception and mental health: Results of a population-based study. Human Reproduction. 2011;**26**(11):3085-3093

[92] Jenabi E, Khazaei S. Endometriosis and migraine headache risk: A meta-analysis. Women & Health. 2020;**60**(8): 939-945

[93] Wu Y, Wang H, Chen S, Lin Y, et al. Migraine is more prevalent in advanced-stage endometriosis, especially when co-occuring with Adenomoysis. Frontiers in Endocrinology (Lausanne). 2022;**12**: 814474

[94] Miller JA, Missmer SA, Vitonis AF, et al. Prevalence of migraines in adolescents with endometriosis. Fertility and Sterility. 2018;**109**(4):685-690

[95] Maia H Jr, Casoy T, Correia T, Freitas L, et al. Effect of the menstrual

cycle and oral contraceptives on aromatase and cyclooxygenase-2 expression in adenomyosis. Gynecological Endocrinology. 2006; **22**(10):547-555

[96] Vannuccini S, Luisi S, Tosti C, Sorbi F, et al. Role of medical therapy in the management of uterine adenomyosis. Fertility and Sterility. 2018;**109**(3):398-405

[97] Naftalin J, Hoo W, Pateman K, Mavrelos D, et al. Is adenomyosis associated with menorrhagia? Human Reproduction. 2014;**29**(3):473-479

[98] Benetti-Pinto CL, Mira TAA, Yela DA, Teatin-Juliato CR, et al. Pharmacological treatment for symptomatic Adenomyosis: A systematic review. Revista Brasileira de Ginecologia e Obstetrícia. 2019;**41**(9):564-574

[99] Cope AG, Ainsworth AJ, Stewart EA. Current and future medical therapies for Adenomyosis. Seminars in Reproductive Medicine. 2020;**38**(2–03):151-156

[100] Zimmerman Y, Eijkemans MJC, Coelingh Bennink HJT, Blankenstein MA, et al. The effect of combined oral contraception on testosterone levels in healthy women: A systematic review and meta-analysis. Human Reproduction Update. 2014; **20**(1):76-105

[101] Mawet M, Maillard C, Klipping C, Zimmerman Y, et al. Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. The European Journal of Contraception & Reproductive Health Care. 2015;**20**: 463-475

[102] Teede HJ, Misso ML, Costello MF, Dokras A, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction. 2018; **33**(9):1602-1618

[103] Rabe T, Kowald A, Ortmann J, Rehberger-Schneider S. Inhibition of skin 5 alpha-reductase by oralcontraceptive progestins in vitro. Gynecological Endocrinology. 2000; **14**(4):223-230

[104] Carmina E, Dreno B, Lucky WA, Agak WG, et al. Female adult acne and androgen excess: A report from the multidisciplinary androgen excess and PCOS committee. Journal of the Endocrine Society. 2022;**6**(3):bvac003

[105] Ju Q, Tao T, Hu T, Serap Karadağ A, et al. Sex hormones and acne. Clinics in Dermatology. 2017;**35**(2): 130-137

[106] Cibula D, Fanta M, Vrbikova J, Stanicka S, et al. The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids in PCOS patients. Human Reproduction. 2005;**20**(1):180-184

[107] Di Carlo C, Gargano V, Sparice S, Tommaselli GA, et al. Effects of an oral contraceptive containing estradiol valerate and dienogest on circulating androgen levels and acne in young patients with PCOS: An observational preliminary study. Gynecological Endocrinology. 2013;**29**(12):1048-1050

[108] Teede HJ, Misso ML, Costello MF, Dokras A, et al. International PCOS network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertility and Sterility. 2018;**110**(3):364-379

[109] Goodman NF, Cobin RH, Futterweit W, Glueck JS, et al. American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); androgen excess and PCOS society guide to the best practices in the evaluation and treatment of polycystic ovary syndrome -part 1. Endocrine Practice. 2015;**21**(12): 1415-1426

[110] Falsetti L, Gambera A, Platto C, Legrenzi L. Management of hirsutism. American Journal of Clinical Dermatology. 2000;**1**(2):89-99

[111] Plu-Bureau G, Maitrot-Mantelet L, Hugon-Rodin J, Canonico M. Hormonal contraceptives and venous thromboembolism: An epidemiological update. Best Practice & Research. Clinical Endocrinology & Metabolism. 2013;**27**(1):25-34

[112] de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, et al. Combined oral contraceptives: Venous thrombosis. Cochrane Database of Systematic Reviews. 2014;**3**(3): CD010813

[113] Hugon-Rodin J, Gompel A, Plu-Bureau G. Epidemiology of hormonal contraceptives related venous thromboembolism. European Journal of Endocrinology. 2014;**171**:R221-RR23

[114] Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: Nested case-control studies using the QResearch and CPRD databases. BMJ. 2015;**350**:h2135

[115] Dragoman MV, Tepper NK, Fu R, Curtis KM, et al. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. International Journal of Gynaecology and Obstetrics. 2018; **141**(3):287-229

[116] Dinger J, Monher S, Heinemann K. Combined oral contraceptives containing dienogest and estradiol valerate may carry a lower risk of venous and arterial thromboembolism compared to conventional preparations: Results from the extended INAS-SCORE study. Front Womens Health. 2020;**5**:1-8

[117] Reed S, Koro C, DiBello J, Becker K, et al. Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-oestradiol (1.5mg) (PRO-E2 study): Risk of venous and arterial thromboembolism. The European Journal of Contraception & Reproductive Health Care. 2021;**26**(6): 439-446