Non-contraceptive Benefits of Hormonal Methods

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10.1 Introduction

The development of combined hormonal contraceptives is regarded as one of the most groundbreaking achievements in public health of the last century [1]. Initially introduced in the USA in 1960 to prevent unplanned and unintended pregnancies, combined oral contraception (COC) has been used by hundreds of millions of women [2], and it is estimated that nowadays 100–150 million women use them on a daily basis [3]. COC is the second most common method of reversible contraception and has the widest geographic distribution of all modern contraceptive methods [4].

In addition to combined oral contraceptives, which contain both estrogen and progestogen compounds, progestogen-only contraceptives have been developed, and many different formulations are available nowadays, including oral preparations, monthly injections, implants, and intrauterine devices (IUDs) [5].

Since their approval, a growing number of studies have demonstrated that hormonal contraceptives may have several additional health benefits for users (Table 10.1). In the short term, combined oral contraceptive pill reduces many troublesome side effects related to menses, whereas in the long term it reduces the risk of different type of cancers, most notably ovarian and endometrial cancer [6]. In particular, the extensive use of HCs has highlighted its positive effects on many health issues and diseases affecting women, such as [4, 7]:

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Table 10.1 Non-contraceptive benefits of hormonal contraceptives

Established benefits of hormonal contraceptives
• Menses-related – ↑ Menstrual cycle regularity – ↓ Menstrual blood flow – ↓ Iron-deficiency anemia – ↓ Dysmenorrhea – ↓ Premenstrual syndrome • Inhibition of ovulation – ↓ Ectopic pregnancy • Other – ↓ Acute PID – ↓ Endometrial and ovarian cancer
Emerging benefits of hormonal contraceptives
• Positive effects on bone mineral density • Acne, hirsutism, and hyperandrogenism • Colorectal cancer • Endometriosis • PCOS

- Ovarian and menstrual cycle:
  - Reduction of dysmenorrhea
  - Reduction of dysfunctional uterine bleeding
  - Improvement of premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS)
- Endometriosis
- Polycystic ovarian syndrome (PCOS)
- Hirsutism, acne, and hyperandrogenism
- Pelvic inflammatory disease
- Ectopic pregnancy
- Bone mineral density
- Gynecological and non-gynecological cancer incidence

On the other hand, HCs are not devoid of risks and side effects, and the lay press and media influence on this topic has been far-reaching, negatively influencing women's and in some instances general practitioners' ideas of hormonal contraceptives [8]. Common side effects are generally self-limiting and usually decrease with duration of use, whereas serious adverse effects, like venous thromboembolism, are rare among healthy users. Moreover, many false beliefs about hormonal contraception, particularly regarding weight gain, fertility impairment, and oncologic risk, have been proven wrong by several studies [2, 9, 10]. Additionally, no evidence of increased mortality in ever HC users was found by long-term follow-up studies [11, 12]. Also long-acting reversible contraceptives are highly effective in typical use and show a very low risk profile [5].

Patients who are well-informed about the efficacy of HC, its risks and side effects, and the additional non-contraceptive benefits are more likely to choose them, avoiding unplanned pregnancies and all the psychological, economic, and social burdens they carry [7].

10.2 Menstrual and Ovarian Cycle

The non-contraceptive benefits associated with HC, and in particular with COC, are mainly due to its mechanism of action: inhibition of ovulation and local progestin effects on the endometrium and other reproductive trait tissues [13]. One of the most frequent off-label indications for COC is the treatment of menstrual-related disorders. COC has proven itself effective in improving dysmenorrhea, irregular bleeding, and PMS [14].

10.2.1 Dysmenorrhea

Dysmenorrhea is the most common gynecological symptom, affecting up to 50–90% young women [15]. It is defined as severe cramping sensation in the lower abdomen, often accompanied by other disorders such as bloating, headaches, and nausea, all occurring before or during menses [16]. Primary dysmenorrhea refers to menstrual pain without an identifiable associated pathology, whereas secondary dysmenorrhea is caused by an underlying pelvic disorder. Dysmenorrhea has a considerable impact on women's quality of life, work productivity, and healthcare referral, being highly debilitating and accounting for an annual productivity loss of US $2 billion [17–19].

Dysmenorrhea seemly arises from the release of prostaglandins, which results in an augmented myometrial activity and an increased response to vasopressin and leukotrienes [20, 21]. Several studies documented that COC diminishes menstrual prostaglandin release, thus reducing uterine contractility and dysmenorrhea. Indeed, COC seems to be effective in relieving pelvic pain in up to 70–80% of women with primary dysmenorrhea [21–23].

The impact of low-dose hormonal contraception on dysmenorrhea was assessed in a Swedish population in a longitudinal study, demonstrating that prevalence and severity of dysmenorrhea were significantly inferior in COC ever user, both at entry and after 5 years of use, compared to never user ($P < 0.001$ at a 5-year use) [23]. In 1992, Larsson et al. reported that low-dose COC significantly reduced dysmenorrhea: after 6-month treatment, only 4/20 women still complained of menstrual pelvic pain, compared to the 14/20 before the treatment ($P < 0.05$) [24]. More recently, a randomized controlled trial (RCT) compared an OC containing 20 μg ethinyl estradiol (EE) and 150 μg desogestrel, with an additional 20 μg EE in the last 5 days, to placebo for 4 months in 52 young women. Menstrual cramps were significantly reduced ($P < 0.001$) in OC users compared to placebo users [25]. Another RCT showed that dysmenorrhea prevalence decreased from 56% to 39% during 6-month use of oral contraceptives containing low-dose EE [26].

A recent RCT compared pain relief provided by estradiol valerate/dienogest and EE/drospirenone using uterine artery Doppler indices and visual analogue scale scores [27]. According to the authors, VAS score was significantly reduced in both treatment groups after a 3-month treatment ($P = 0.0001$), and the two groups were comparable in terms of mean percentage change of VAS score. Moreover, mean

value of uterine artery resistance index was significantly lower after therapy in both groups.

10.2.2 Heavy Menstrual Bleeding (HMB)

HMB is defined as a menstrual blood loss of >80 mL per cycle that cannot be explained by organic pathology or medical illness and affects approximately 10% of fertile women. Excessive blood loss may lead to iron-deficiency anemia and in some cases necessitate invasive surgical treatments, such as hysterectomy [14]. Early anecdotal evidence strongly supported the role of COC on reducing menstrual blood loss and irregular bleeding. This conclusion was based on studies performed several years ago, showing that high-dose COC reduced menstrual blood loss by up to 50% [28, 29]. Recent studies focused on low-dose COC. Larsson et al. documented a significant reduction in average blood loss in women treated with 30 μg EE/150 μg desogestrel, who passed from an average blood loss of 60.2 ± 3.2 mL to 33.7 ± 4.1 mL after a 6-month treatment ($P < 0.001$). Moreover, the mean duration of menses was significantly reduced during hormonal treatment [24]. Also Fraser et al. reported similar results from their randomized trial involving 45 menorrhagic women, demonstrating a significant reduction in blood loss in women receiving COC [30].

A more recent review by Hoaglin and colleagues compared several treatment classes, including levonorgestrel-releasing intrauterine device and endometrial ablation. Results showed that COCs were effective and comparable with long-term progestin therapy and danazol in reducing menstrual blood loss [31]. Newer estradiol (E2)-based COCs are also showing promising results in treating HMB. Results from some recent studies show that E2-based regimens lead to shorter and lighter withdrawal bleedings than those reported by women using the older and more conventional EE regimens. Moreover, this regimen seems to cause fewer overall bleeding and spotting days during the first 90 days of administration [32]. E2-based regimens were also superior to placebo in randomized, double-blinded controlled trials [33, 34]. To date, no head-to-head trial comparing different COC regimens with regard to their impact on HMB has been published, but evidence from recent well-designed clinical trials suggests that newer and lower-dosed COCs successfully reduce the volume of menstrual blood loss with conventional use.

As for the levonorgestrel intrauterine system (LNG-IUS), the treatment of women with HMB is perhaps its most important non-contraceptive benefit and has been observed since the first clinical trials [7]. LNG-IUS use can reduce uterine bleeding in up to 60% of women, in some cases leading even to amenorrhea, and also improves hemoglobin levels, iron stores, and anemia [35]. Moreover, the efficacy of this device is almost equal or superior to oral medroxyprogesterone acetate (MPA) and endometrial ablation, with an overall risk failure of 13.4% [36, 37]. LNG-IUS can be effectively used to treat HMB due to different causes, including hemostatic disorders, coagulation deficiencies, and anticoagulant drugs [38]. In a randomized controlled trial, Gupta and colleagues evaluated the efficacy of LNG-IUS in the treatment of HMB compared to usual medical treatment (tranexamic

acid, combined oral contraceptives, or progesterone alone) over a 2-year period. Despite observing an improvement in both groups, HMB was significantly lower in the LNG-IUS group and persisted through the period of evaluation [39].

10.2.3 Dysfunctional Uterine Bleeding

Low-dose hormonal contraceptives seem effective in treating dysfunctional uterine bleeding, such as metrorrhagia, menometrorrhagia, oligomenorrhea, and polymenorrhea. A recent randomized, double-blind, placebo-controlled trial demonstrated that more than 80% of women subjected to active treatment with low-dose COC experienced improved bleeding patterns and, more significantly, an improvement from baseline quality of life scores regarding physical functioning [40].

10.2.4 Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

During fertile years, 80–90% of women will experience troublesome symptoms (breast tenderness, bloating, acne, constipation) that negatively impact their quality of life [15], the so-called PMS. Premenstrual syndrome refers to the cyclic recurrence of emotional, physical, and behavioral changes in the luteal phase of the menstrual cycle that remit within 4 days following menses onset [41]. A more severe variant of this syndrome is PMDD, which comprehends serious, mostly psychiatric symptoms that cause major interferences with day-to-day activities and interpersonal relationships. It is estimated that 13–18% of women show evidence of cyclical patterns of distress, treatment-seeking, and life interference. Symptoms of PMDD can be similar to those found in major depressive disorder, panic disorder, and posttraumatic stress disorder [42]. Up to 40% of patients are unresponsive to the standard therapy with selective serotonin reuptake inhibitors [43].

COC has been given to women suffering from PMS or PMDD for over 40 years, but the relief of PMS-related symptoms is apparently associated only with specific COC regimens. Since women with PMS demonstrate an abnormal emotional sensitivity to normal fluctuations of estradiol and progesterone [44], the stabilization of hormonal levels may represent a target for the treatment of this syndrome. Indeed, the suppression of ovarian function, as observed during pregnancy, lactation, hypothalamic amenorrhea, or using GnRH agonists leads to PMS disappearance [45, 46].

Several recent RCTs examined COCs containing EE and a progestin (drospirenone or levonorgestrel) to treat PMS. Typical 21/7 regimens were apparently ineffective compared with placebo [47], whereas two COC trials using 20 μg EE combined with 3 mg drospirenone in a 24/4 regimen have shown significant benefit compared with placebo [48, 49]. In particular, physical and emotional symptoms of PMDD were significantly reduced. On the other hand, Coffee et al. demonstrated a significant improvement in premenstrual symptoms among long-term users of a conventional 21/7 regimen of 30 μg EE and 3 mg drospirenone [50].

Recently Eisenlohr and colleagues reported no significant differences in terms of PMS-related symptoms improvement using either intermittent or continuous combination of 20 μg EE and 3 mg drospirenone. Both treatment regimens seem to lead to a significant decline in premenstrual symptoms. However, similar results were reached also in the placebo group, suggesting that further investigation is needed concerning the role of COC as a treatment for PMS [51].

10.3 Endometriosis and Adenomyosis

Endometriosis is defined as the presence and/or growth of endometrial tissue, both epithelium and stroma, outside the uterine cavity [52]. It affects 10–15% of reproductive-aged women and up to 50% of women with a history of infertility and 80–90% of women complaining of chronic pelvic pain [53]. A minority of patients is asymptomatic, but most are affected by pelvic pain, dysmenorrhea, dyspareunia, dyschezia, and dysuria, greatly reducing their quality of life [54]. Given its estrogen-dependent nature, hormonal contraceptives represent a potential treatment for endometriosis-related symptoms, especially dysmenorrhea, for women wishing to preserve their fertility and needing effective contraception. Progestogen-only methods may be generally preferable since they create a progestin-dominant hormonal environment that reduces nerve fiber density, inhibits angiogenesis, and possibly reduces inflammation in endometriotic lesions [55–57].

There has been debate in literature regarding the potential role of COCs in the development of endometriosis. In fact, it has been postulated that estroprogestins might lead to endometriosis progression, since they cause supraphysiologic levels of estrogens [58]. A large meta-analysis of 18 studies showed that the relative risk of endometriosis onset was 1.19 in ever users of COC, 0.63 in current users, and 1.21 in past users [55]. Furthermore, a cross-sectional study by Chapron et al. found that women who had previously used COC for the management of severe dysmenorrhea were more likely to be diagnosed with endometriosis at a later date [59], a result confirmed also by other authors [60].

On the other hand, according to some studies COC could positively influence endometriotic lesions; in particular, two studies found that size of endometriomas decreased with the use of combined oral contraception [61, 62]. Even so, the administration of conventional COCs in a cyclic regimen could expose women to the risk of experiencing dysmenorrhea and chronic pelvic pain during the hormone-free interval [63]. A recent meta-analysis by Zorbas et al. showed definite benefits of the continuous COC regimen: in particular, two studies by Seracchioli et al. found a positive trend toward favoring the continuous regimen regarding size and growth of endometriomas [64, 65], which was further confirmed by Vercellini et al. [66].

As for the recurrence rate of endometriosis after surgical treatment, a recent systematic review pooled the results of two RCTs, a prospective cohort trial and a prospective clinical trial employing different combinations of estroprogestins either used cyclically or continuously [67]. From the analysis of data, there seems to be a growing body of evidence supporting continuous COC regimes as a more effective

treatment for patients subjected to surgery. These findings appear in line with other studies available in literature, which show that the use of COCs reduces the risk of disease recurrence [64, 66, 68–70].

Regarding symptoms, the European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend to prescribe either progestins (level A) or hormonal contraceptives (level B), to reduce endometriosis-associated pain [71]. However, no clear data exist with regard to the best combination, based on the type of endometriosis and the age of the woman being treated [72].

To date, women have a wide choice of oral estroprogestin combinations, evolving from the predominant use of synthetic EE to estradiol-17β, the natural estrogen produced by the ovaries [73]. Moreover, several new progestogens have been developed, including dienogest, drospirenone, nomegestrol acetate, and desogestrel, to individualize contraception as much as possible.

Several studies suggest that desogestrel [66], gestodene [74], norethisterone [61], drospirenone [62], and levonorgestrel are all effective in reducing dysmenorrhea in the majority of women with endometriosis. In a recent systematic review, Grandi et al. analyzed the results of 17 studies, including more than 700 women [72]. The efficacy on endometriosis-related pain of almost all COCs containing EE combined with different generations of progestins, and of a COC containing E2, was demonstrated. However, a significant improvement in comparison with placebo was obtained only with EE and norethisterone acetate [61] and a flexible regimen employing EE and drospirenone [75]. In addition, the reduction of dysmenorrhea was usually associated with a decrease in chronic pelvic pain and dyspareunia, leading to an improved quality of life. Jensen et al. found similar results in another literature review [76].

Dienogest, a fourth-generation selective progestin, combines the pharmacological effects of 19-nortestosterone, having both an anovulatory and an antiproliferative effect on endometriotic lesions. A recent meta-analysis on the effects of different doses of dienogest (2 mg/day vs. 4 mg/day) showed a significant reduction in terms of severity of endometriosis evaluated by rASRM score for both doses, with no significant differences between them. Moreover, both groups showed a significant and comparable improvement in terms of clinical painful symptoms [77]. Furthermore, a recent retrospective study conducted on 116 women demonstrated the efficacy of dienogest-based hormone therapy in reducing endometrioma's volume, if administered for 1 year, both alone and combined with EE. In particular, all women who received only diegnost had a volume reduction >50%, 82.3% had a volume reduction >75%, and 76.5% had a volume reduction of 100% [78]. These encouraging findings appear in line with another two studies conducted on dienogest alone: the first one demonstrated a maximal endometrioma reduction of about 70% after a 15-month treatment period [79], while the second one showed a less pronounced but significant effect after 12 months, as well as a consistent reduction in terms of chronic pelvic pain, dysmenorrhea, and dyspareunia. Good results, both clinically and ultrasonographically, were also achieved by treatment with norethindrone acetate, but the decrease was significantly lower in the norethindrone group; moreover, women who received norethindrone acetate complained more frequently of uterine bleeding and spotting and weight gain [80].

Various studies have been conducted also on the effects of nomegestrol acetate (NOMAC), combined with EE. This progestin has a long half-life, up to 50 h, and is thus able to cover the 4-day hormone-free interval by its steroidal effects. Very recently, Caruso et al. compared a 6-month treatment with EE/NOMAC with no hormonal treatment, demonstrating that the combination of EE/NOMAC extraordinarily improved painful symptoms, in particular chronic pelvic pain, dysmenorrhea, and dyspareunia [81].

Upon the whole, the interpretation of these findings is complicated, due to many superimposed conditions that contribute to pelvic pain in endometriotic patients, such as PID, and the possibility that different lesions might respond differently to treatment. Despite this evidence, clinicians should bear in mind that almost all of the currently available hormonal drugs are suppressive and do not actually eliminate the disease, so the relapse of symptoms is fairly common at therapy discontinuation [82]. Furthermore, around 30% of women treated with hormonal contraceptives is unresponsive, probably due to an imbalance of estrogen and progesterone receptors, determining an intrinsic progesterone resistance [83].

To date, no definite evidence exists about the exact role of COC as a treatment option for endometriosis, even though results are encouraging [84]. Moreover, insufficient data are available to support the overall superiority of any given COC regimen and the relative benefit in comparison to other approaches [76]. The presence of a low-dose estrogen component may be advantageous in terms of bleeding control, thus maximizing therapy adherence. Preparations containing the lowest possible levels of EE or E2 should be the first-line choice, since the estrogenic content affects the risk of venous and arterial thrombosis and might lead to the progression of endometriosis itself [73].

As for LNG-IUS, many publications show its efficacy in alleviating endometriosis-caused dysmenorrhea, especially in women also presenting with adenomyosis. Results from some RCTs show that both LNG-IUS and GnRH agonists reduce pain scores measured on the visual analogue scale, without significant differences between GnRH users and LNG-IUS users. Also, both treatments improved staging scores and quality of life [85–87]. The mechanism of action of LNG-IUS on pain relief probably involves high intrauterine levels of levonorgestrel, a depletion of estrogen receptors, and a reduction of endometrial cell proliferation [88, 89].

Women with adenomyosis particularly benefit from the insertion of the LNG-IUS, since this device reduces the thickness of the junctional zone and total uterine volume, thus reducing menstrual blood loss and pain. Heavy menstrual bleeding is a key feature of uterine adenomyosis, and its improvement could be imputed to the direct effect of LNG on foci of adenomyosis with decidualization and hypotrophy of the endometrium [90]. The reduction of pelvic pain could be explained by the effect of levonorgestrel on the vascular supply to the pelvis, allowing relief from pelvic congestion. However, the efficacy of LNG-IUS apparently decreases after 2 years of placement, and some reports indicate that the intrauterine device should be replaced before its 5-year life span [91, 92].

10.4 Polycystic Ovarian Syndrome (PCOS), Hirsutism, and Acne

Polycystic ovarian syndrome is a heterogeneous disease involving reproductive and metabolic factors, with a worldwide prevalence of 7–14% [93]. According to the American Society for Reproduction Medicine, PCOS should be diagnosed if two out of three of these features are present: oligo- and/or anovulation, hyperandrogenism (HA), and polycystic ovaries [94]. Excessive androgen biosynthesis is a key pathogenetic mechanism of PCOS, along with insulin resistance and compensatory hyperinsulinism, with a tendency to favoring visceral fat deposition [95–97]. This in turn may lead to dyslipidemia, metabolic syndrome, hypertension, and endometrial cancer, due to the unopposed estrogen exposure caused by anovulation. In addition to lifestyle management, recommended for all patients with this syndrome, combined oral contraceptives, especially those with antiandrogen properties, can be helpful in reducing hirsutism and acne, by reducing testosterone bioavailability [98–100]. In fact, the progestin component of COCs suppresses the secretion of LH and decreases the ovarian androgen production, whereas the estrogenic fraction increases the levels of sexual hormone-binding globulin [101]. Moreover, the use of COC has been proven effective in protecting against endometrial cancer [102].

On the other hand, estrogens can worsen insulin sensitivity and increase the risk of thromboembolic and cardiovascular disease, particularly in women already at risk, such as those with PCOS [103, 104]. Recently, insulin sensitizers like metformin have been proposed as an alternative to COC, despite being ineffective for hirsutism. However, the evidence supporting their being safer than COC is limited [105, 106].

10.4.1 Impact on Acne and Hirsutism

Recent guidelines support the use of hormonal contraceptives as first-line management for concurrent treatment of menstrual abnormalities and clinical manifestations of hyperandrogenism [107, 108]. According to some authors, the use of third-generation hormonal contraceptives (containing gestoden or desogestrel) should be beneficial, as they are less androgenic. Also, the use of antiandrogenic progestins (dienogest, drospirenone, cyproterone acetate) may be recommended, since they directly antagonize the androgen receptor or inhibit the enzyme 5α-reductase activity [109]. A recent systematic review of RCTs comparing COC with different doses of ethinyl estradiol and different types of progestins demonstrated that the greatest improvements in the Ferriman-Gallwey score were obtained with COC containing cyproterone acetate [110]. Indeed after a 3-month treatment with cyproterone acetate, hirsutism subjectively improved in 83% of patients and acne in 40% [111]. Drospirenone was also shown to be effective after a 6-month course, improving acne [112], trunk acne [113], and significantly reducing skin

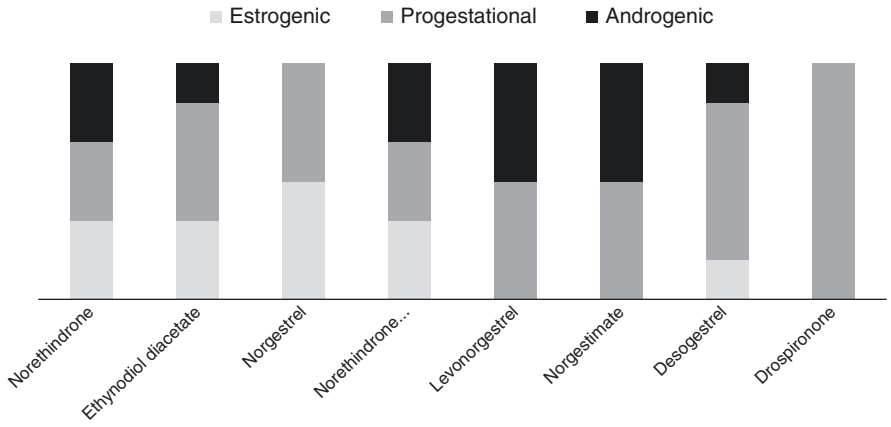

Fig. 10.1 Different hormonal effects (estrogenic, progestational, and androgenic effects) of common progestins

problem treatment costs [114]. Finally, a large meta-analysis of 56 clinical studies, including 2266 patients, reported the efficacy of dienogest on acne [115]. The different hormonal effects (estrogenic, progestational, and androgenic effects) of common progestins are reported in Fig. 10.1.

10.4.2 Impact on Metabolic Parameters and Cardiovascular Risk Factors

It has been postulated that the use of COC in women affected by PCOS may have a greater impact on cardiovascular disease risk, as explained above [116, 117]. On the other hand, some authors suggested that lowering serum androgens with COCs may provide a metabolic benefit, as androgens have been proved to reduce insulin sensitivity and adipocyte function [118]. World Health Organization and Centers for Disease Control and Prevention 2016 guidelines include obesity, hypertension, diabetes, and known dyslipidemia as relative contraindications to COC use (category 2), suggesting that the advantages linked to their use might be greater than their risks.

10.4.3 Impact on Glucose Tolerance

The use of COC in women with diabetes, either insulin or non-insulin-dependent, has limited effect on long-term control of the disease [119]. A recent Cochrane review concluded that COC had no significant effects on glucose metabolism and tolerance in women without diabetes [120]. Another meta-analysis including women with PCOS treated with COC for 3–12 months did not show any significant change in fasting glucose levels, insulin levels, and insulin resistance [121]. However, few studies have evaluated glucose metabolism after randomizing women

with PCOS to different types of COC. One RCT compared the effects of COC containing either drospirenone or desogestrel: women receiving drospirenone had a significant decrease in fasting glucose and insulin levels, whereas those receiving desogestrel showed a relevant increase of both.

Apparently, the use of COC does not seem to significantly influence carbohydrate metabolism; however, most evidence is derived from small studies including women with a normal BMI. Therefore, women with PCOS using COC should be screened for changes in glucose metabolism at regular intervals, especially if they present additional risk factors for diabetes [119].

10.4.4 Impact on Venous and Arterial Thromboembolism

As confirmed by a recent Cochrane review, the use of COC increases the risk of venous thromboembolism (VTE) in the general population (relative risk 3.5, 95% CI 2.9–4.3) [103]. This risk seems to be related to the dose of ethinyl estradiol and the type of progestin, being 50–80% higher with gestodene, desogestrel, cyproterone acetate, and drospirenone than with levonorgestrel. This might be due to the intrinsic ability of each progestin to modulate the effects of estrogen [122]. Evidence about the risk of venous thromboembolism is conflicting, with some studies reporting a lower incidence of VTE in women with PCOS using COC compared to nonusers [123] and others showing a twofold increased risk of VTE in women with POCS taking hormonal contraceptives [124]. However, the absolute risk of venous and arterial thrombosis is low in the young population. Women with PCOS assuming continued low-dose COC should regularly be assessed in order to identify potential associated risk factors.

Despite the little evidence about the optimal estroprogestinic combination, some authors suggest the use of COC with a lower dose of ethinyl estradiol combined with a less androgenic progestin or an antiandrogenic one [119]. It is arguable that the use of COCs in women with PCOS might augment the risk of cardiometabolic complications, compared to the general population. However, the lack of significant evidence on this and the fact that some authors found a reduced incidence of coronary artery disease and ischemic stroke cases in past COC users compared to neverbusers support the idea that benefits derived from COC use might be greater that their risks [125, 126].

10.5 Pelvic Inflammatory Disease (PID)

PID is an infection of the reproductive tract which is due to the ascent of bacteria from the cervix to the endometrium and fallopian tubes. The rate of sexually transmitted disease (STDs) is rapidly increasing, *Chlamydia trachomatis* being the most prevalent infection in Western Europe [15]. The influence of oral contraceptives on the risk of contracting *Chlamydia* is not yet well understood, since earlier studies suggested a decrease in hospitalization for pelvic infections, whereas in other

studies COC use was associated with an increased risk of chlamydial infection and gonorrhea [127]. A recent observational study conducted in the USA concluded that the use of COC did not have a significant impact on the risk of acquiring either chlamydia or gonorrhea, after adjusting for other risk factors [128], a result confirmed also by Ness et al. [129]. Other authors found that the use of COCs was 4.3 higher in women with asymptomatic endometritis [130]. Moreover, oral contraceptive use is associated with cervical ectopia, a recognized risk factor for *Chlamydia* infection [131].

In contrast with the evidence above, some authors suggest that COCs may reduce the risk of PID via progestin-induced thickening of the cervical mucosa and increased mucus viscosity, which in turn may reduce the risk of pathogens ascending the upper genital tract [132]. Also, the lighter menstrual flow quantity could be another possible protective mechanism, since it reduces the possibility for bacterial growth. Women using COC have been shown to have 50–80% lower risk of salpingitis compared with those using no contraception or a barrier method [133–135].

Three case-control studies found a reduced relative risk of hospitalization for PID among women using COCs, compared to women using no contraception or other contraceptive methods [133–135]. It is estimated that the control of PID with COC annually prevents 50,000 cases of PID and 12,500 hospitalizations in the USA [6]. A large, multicenter, case-control study showed that the relative risk of PID in COC users was 0.5 (95% CI 0.4–0.6), and the same degree of protection was also found by Wolner-Hannsen et al. [135]. An even larger reduction in risk of acute salpingitis in women taking combined oral contraceptives was noted by Eschenbach et al. [136]. Moreover, it was found that oral contraceptives are negatively associated with acute PID, even of chlamydial origin. In addition, among women with acute salpingitis, the occurrence of adhesions, tubal occlusion, and tubo-ovarian abscesses is less frequent in COC users compared to non-users [131], accounting for a decreased severity of the disease [134, 137]. Also, the risk of infertility in women with laparoscopically confirmed salpingitis appeared lower in COC users [138].

10.6 Ectopic Pregnancy (EP)

Ectopic pregnancy is one of the leading causes of maternal death during the first trimester of pregnancy, being responsible for up to 10% of pregnancy-related deaths [139]. Its incidence is rising over the decades, and recognized risk factors include age, previous EP, previous pelvic surgery, use of intrauterine devices (IUDs), tubal sterilization, and previous PID [140].

Even though all contraceptives should reduce the rate of ectopic pregnancy, by preventing conception and in some cases ovulation, women using OC have been shown to have one of the lowest rate of all, with an approximate 90% reduction in risk [141]. The risk of EP in COC users is estimated at 0.005 per 1000 women years, a value comparable to that of vasectomy and lower than that of barrier methods, diaphragm, copper IUD, and even tubal sterilization [6].

A meta-analysis conducted by Mol et al. [142] compared ectopic pregnancy rates among women using different types of contraceptives. They concluded that all contraceptives protected against EP, the most probable mechanism involving ovulation inhibition. In line with these findings, a recent multicentric case-control study by Li et al. [143] found that current use of any type of contraceptive, with the exception of levonorgestrel emergency contraception, significantly reduced the risk of EP, with an adjusted OR for COCs of 0.14 (95% CI: 0.07–0.26). On the other hand, in case of contraceptive failure, current use of COCs and emergency contraception determined a fourfold increase of EP risk compared to women using no contraceptive method.

10.7 Bone Mineral Density (BMD)

COC effects on bone health are well documented and include the recognized influence of estrogens (increased calcium absorption and reduced loss, inhibition of osteoclasts) and the less established effects of progestins (decreased urinary calcium excretion, increased bone mass). Evidence in literature is encouraging but not completely conclusive, since the majority of studies have shown a positive effect on BMD associated with COC use, but many others have not found any relevant effect. Moreover, the longer women used COCs, the greater protection they gained [144, 145].

Early studies of pre- and postmenopausal women seem to highlight the bone-sparing effects of COCs. In fact, one of the first studies conducted on this topic found that a past history of COC use provided protection against low BMD (OR 0.4, 95% CI 0.2–0.5) [144]. A Swedish study showed that premenopausal women treated with COCs not only had higher BMD, but this translated also into protection against hip fracture [146], and this effect lasted over decades. The greatest benefit was noted among women having taken COCs after the age 40 and for at least 5 years. Another study involving women aged 20–69 revealed a 3.3% greater mean BMD at the lumbar spine among premenopausal women exposed to COCs ($P = 0.014$) [147], with a significant correlation with exposure duration. It is well established that estrogen replacement improves BMD in hypoestrogenic and postmenopausal women, but these results suggest that the use of COCs might improve bone mass even in patients with normal estrogen levels.

Despite this, many other studies have failed to find a positive association between oral contraceptives and bone mass, even if no detrimental effect on BMD has ever been shown [148].

As for adolescents, Polatti et al. found that while BMD in COCs users did not change significantly over 5 years of follow-up, but in controls receiving no treatment, this measure increased by 7.8% ($P < 0.01$) [149]. On the other hand, two cross-sectional analyses [150, 151] indicated no differences in BMD between low-dose COC users and non-users.

10.8 Prevention of Cancer

Considering the widespread and long-standing use of combined oral contraceptives, concerns have always been expressed about hormonal contraception's carcinogenic potential. Since their introduction, several studies have investigated the impact of COC on different types of cancer. Overall, the evidence seems to suggest that recent and current users of hormonal contraceptives have a reduced risk of endometrial and ovarian cancer, an effect apparently persisting for many years after therapy discontinuation [2, 7]. The most important study evaluating cancer risk in COC users in a large cohort of patients is the Royal College of General Practitioners' Oral Contraception Study, which has been recently updated [2].

10.8.1 Endometrial Hyperplasia

Although off-label in many countries, the use of LNG-IUS in the treatment of endometrial hyperplasia is effective and preserves fertility among young women. A meta-analysis by Gallos and colleagues evaluated the treatment of endometrial hyperplasia with LNG-IUS or oral progestogens and found higher regression rates with the intrauterine device, both for simple (pooled rate = 92% vs. 66%, $p < 0.01$) and atypical hyperplasia (pooled rate = 90% vs. 69%, $p = 0.03$) [152]. These results are similar to previous studies, which showed endometrial regression in 92% and 67% of cases with simple and atypical hyperplasia, respectively [153]. According to some authors, the main variable associated with failure of treatment with an LNG-IUS is a body mass index ≥35, which is also an independent predictor of relapse (hazard ratio = 18.93, 95% CI 3.93–91-15, $p < 0.001$) [154].

10.8.2 Endometrial Cancer

Estrogen normally exerts a stimulating effect on endometrial cell division, whereas progestins block cell proliferation, protecting from estrogen-induced hyperplasia and determining endometrial shedding during withdrawal bleedings [155]. The effects of COC on endometrial cancer risk have been extensively evaluated, and the first systematic review by Grimes and Economy seemed to indicate that COCs have a clearly protective effect against this type of cancer [156]. This tendency was confirmed by the RCGP Oral Contraception Study, which demonstrated that ever users have statistically significant lower rates of uterine body cancer, with an incidence rate ratio (IRR) of 0.72 (99% CI 0.51–1.13 and a RR of 0.58 (95% CI 0.42–0.79). The Cancer and Steroid Hormone (CASH) Study by Maxwell et al. focused on hormonal potencies and was able to conclude that both high-progestin and low-progestin OC users had a significantly reduced risk of endometrial cancer, but among women with BMI > 22 only high-progestin OC had a protective effect (OR 0.31; 95% CI 0.11–0.92) [157].

The protective effect seems to increase with duration of OC use, as found by most studies. Moreover, protection from endometrial cancer risk seems to persist for at least 15–20 years after cessation of use [157–161]. According to most studies, the beneficial effect of COCs is independent of their formulation and of modulating or known risk factors for endometrial cancer, although in high-risk patients OC formulations with higher progestin potency seem to be more beneficial [155].

As for LNG-IUS, its use has been recently associated with a protective effect against endometrial cancer. A recent study by Soini and colleagues demonstrated that women aged 30–49 years who used an LNG-IUS due to HMB had an observed-to-expected ratio for endometrial adenocarcinoma of 0.50 (95% CI 0.35–0.70) after the first use of LNG-IUS and 0.25 (95% CI 0.05–0.73) after the second use [162]. The possible mechanism associated with this protective effect for endometrial cancer could be the downregulation of estrogen receptors, reducing endometrial cellular proliferation and inducing amenorrhea [7].

10.8.3 Ovarian Cancer

Similar to endometrial cancer, a comparable reduction in the risk of epithelial ovarian cancer (EOC) has been observed among users of COCs. The first to demonstrate a significant risk reduction of ovarian cancer in OC users were Winer et al. [163], using source data from 45 studies. The degree of risk reduction is associated with duration of COC use [164]. According to Beral et al. [165], the worldwide use of COC prevents an estimated 30,000 deaths from ovarian cancer annually. These authors conducted the broadest meta-analysis to date, analyzing data from more than 100,000 women. Apparently, the RR of EOC decreased by 20% for each 5 years of COC use, ranging from 0.69 to 0.81, depending on the study design. A recent meta-analysis showed a clinically relevant reduction in ovarian cancer incidence in ever users compared to never users (OR 0.73, 95% CI 0.66–0.81) [166]. This response was also characterized by a significant duration-response relation, since an incidence reduction >50% was observed among women using COCs for 10 or more years. Many other studies confirmed these findings, in particular by the RCGP's Oral Contraception Study, which found an IRR of 0.67 (99% CI 0.46–0.97) in ever users [2, 159, 167, 168].

COCs might interfere with ovarian cancer development through several ways: inhibition of ovulation, reduction of gonadotropin levels, prevention of the invagination of cells from the Mullerian duct, and regulation of oncogenes [155]. A distinct biological mechanism explaining the risk-reducing effects of COCs however has not yet been identified. Recent data suggest that many high-grade serous EOCs do not arise from the ovarian epithelium, but from the distal fallopian tube, whose epithelium is also influenced by ovulatory cycles [169].

Regardless of the mechanism of action, the benefit effect of COCs on ovarian cancer has made this treatment a staple of the management of reproductive-aged women at high risk for developing EOC, especially those with BRCA-1/2 mutations [170]. However, it should be taken into account that the use of COC in BRCA-1/2

mutation carriers increases their risk of developing breast cancer although the risk is small and barely statistically significant [166, 171].

The protective effects seem greater for serous cancers although Beral et al. observed a risk reduction of >20% per 5 years of use for endometrioid cancers and 12% for mucinous cancers. On the other hand, data concerning the protective effect of COC on borderline ovarian tumors are more heterogeneous, since many studies failed to find a significant decrease in RR [172–174]. Notably, the reduction in RR is maintained for several decades after COC discontinuation, but diminishes in postmenopausal women. The protective effect of OC diminishes slowly 10 years after cessation, although a protective effect has been observed after >20 years or even 30 years. Beral et al. found a RR reduction for ovarian cancer by 48%, 38%, and 31% in women who used COC for 5–9 years and ceased <10 years, 10–19 years, or 20–29 years previously, respectively [165].

10.8.4 Colorectal Cancer

Few studies have examined the influence of COC on colorectal cancer (CRC), but literature is consistent in demonstrating a reduced risk of this type of cancer among COC users.

In a meta-analysis of epidemiological studies on CRC, the pooled RR of CRC for ever users was estimated to be 0.82 [175], although no relationship with COC use duration was noted. The pattern of risk was similar for colon and rectal cancer. Similar RR was also observed in studies conducted afterwards [167, 176–178]. Some authors also noted a greater risk reduction for current users (RR 0.38) compared to former users (RR 0.89) [179, 180]. As for recency of use, evidence is scant but seems to indicate that protection is stronger for recent COC users [167, 176].

As for ovarian cancer, the association between COC and CRC risk reduction lacks a definite mechanism of action, with possible hypothesis ranging from a direct effect of hormone on colorectal mucosa to genetic and epigenetic phenomena [181].

10.9 Conclusion

Over the last decades, hormonal methods have demonstrated their efficacy and safety as a valid contraceptive option for women wishing to avoid unwanted pregnancies. Since their introduction, many studies have first observed and then confirmed the presence of many different non-contraceptive health benefits, finding new therapeutic roles for estroprogestins and progestins. However, many women and many practitioners still remain unaware of this and instead focus only on health risks. Continuous education of patients is imperative, in order to involve women in an informed, conscious choice of the most adequate hormonal method, based on their needs, anamnestic characteristics, and preferences.

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