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REVIEW

Obesity and hormonal contraception: an overview and a clinician's practical guide

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Abstract

Background The growing prevalence of obesity among the fertile female population poses a considerable problem to contraceptive providers. Obese women, who are more at risk for venous thromboembolism and cardiovascular events due to their condition, might be at an even higher risk of developing thromboembolic events when on medical contraception. Combined hormonal contraceptives might be less effective in obese women and may lead to unacceptable metabolic side effects for this population. In addition, the lack of safety data for weight loss drugs and the higher risk for complications during and after pregnancy require a close surveillance of the fertility status of obese patients.

Objective The aim of this narrative review is to summarize the available medical contraceptive options and to give the readers a practical guidance for a wise contraceptive choice with regards to obesity.

Methods A general literature review of peer-reviewed publications on the topic "obesity and contraception" was performed using the PubMed database.

Results Nowadays, there are many useful tools that help clinicians in choosing among the wide range of therapeutic possibilities, such as the World Health Organization (WHO) Medical Eligibility Criteria for contraceptive use. Furthermore, the great diversity of hormonal contraceptive formulations (combined hormonal formulations; progestin-only methods) and active substances (different estrogens and progestins) allow physicians to tailor therapies to patients' clinical peculiarities.

Conclusion Long-acting reversible contraceptives [progestin-only implants, levonorgestrel-intra-uterine devices (IUDs) and copper IUDs] and progestin-only methods in general are excellent options for many categories of patients, including obese ones.

Level of evidence V, narrative review.

Keywords Obesity · Contraception · Contraceptive methods · Thromboembolic risk · Combined hormonal contraceptives · Progestin-only contraceptives

Introduction

An estimated 44% of pregnancies worldwide are unintended [1], and it has been assessed that many of these pregnancies are among obese women [2]. Obese women may avoid contraceptives because of fear that hormones may cause further weight gain. Therefore, it is extremely important for clinicians to address the contraception issue in this kind of patient, in order to prevent unintended pregnancies and the higher risk for gestational and obstetrical complications [3, 4]. Indeed, in early gestation, obesity can cause spontaneous pregnancy loss and congenital anomalies, as well as glucose intolerance and fetal overgrowth in late gestation. In addition, obese women have an increased risk of venous thromboembolism (VTE) and post-partum depression, difficulty with breastfeeding, and their offspring are more exposed to the risk of childhood obesity [4].

Furthermore, both medical and surgical treatments of obesity may face some limitations in obese patients planning a pregnancy or who are pregnant. Many obesity medications have not been tested in pregnant women, are teratogenic, or are not recommended in pregnancy/preconception

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period by the manufacturer, because weight loss is not advised during pregnancy. In particular, according to the "Pregnancy Categories" of the Food and Drug Administration (FDA), orlistat, phentermine–topiramate, lorcaserin, and phentermine belong to category "X" (contraindicated in pregnancy, because the risks involved in the use of the drug in pregnant women clearly outweigh its potential benefits); liraglutide is the only medicine assigned to category "C" (potential benefits may warrant the use of the drug in pregnant women despite potential risks) [5]. Also the novel combination therapy with naltrexone and bupropion is not authorized by the European Medicine Agency (EMA) for use in pregnancy or in women attempting to become pregnant [6]. Thus, contraception becomes a fundamental safety measure against potential teratogenic effects during medical weight loss therapy in obese, fertile women. In addition, according to American and European guidelines, reproductive-aged women are recommended to avoid pregnancy for 12–24 months after bariatric surgery. In fact, oral contraceptives may have reduced efficacy after malabsorptive bariatric procedures, and the weight loss occurring in the early months after surgery may lead to pregnancies with adverse effects and complications [7].

As the features of the obese population are changing, new health scenarios and therapeutic challenges are emerging. Indeed, while obesity was once considered as a male sex-specific disease, nowadays, its incidence is constantly on the rise in women, with a shift of the onset toward a younger age [8]. In this context, obese and overweight women seeking contraception pose a considerable challenge to the contraceptive provider. First of all, some methods of contraception may increase cardiovascular and thromboembolic risk in this population of women, who are already at risk for VTE due to their condition [9]. In addition, some methods may potentially cause women to gain more weight and some others may be theoretically less effective in the presence of obesity [10]. In this regard, a recent study reported lower total and bioavailable levonorgestrel (LNG) levels in obese and extremely obese women compared to normal body mass index (BMI) women taking a single dose of 1.5 mg LNG per os as emergency contraception. This may play a role in the reported reduced efficacy of this kind of contraception in obese users [11].

To summarize, the cumulative effects of obesity on the risks of contraception remain largely unexplored, as very little research has been conducted in this population of women. Furthermore, as the age of onset of obesity reduces, more obese and overweight women in their sexually active age range require contraception.

We, therefore, aim to review the different therapeutic contraceptive options available at the moment, along with risks and benefits, obese patients may be exposed to when undergoing contraceptive therapies.

Hormonal contraceptive methods

Hormonal contraceptive methods can be divided into two different groups, according to their composition, namely a combination of estrogens and progestins (combined hormonal contraceptives, CHCs) and progestin-only methods.

Combined hormonal methods

The evolution of contraception has mainly been aimed at reducing the dose of ethinylestradiol (EE), changing the route of administration, and finding new estro-progestin combinations containing 17β-estradiol (Fig. 1). Currently available CHCs differ enormously in terms of types and doses of active ingredient or routes of administration. Specifically, the progestinic component of CHCs is responsible for the inhibition of the luteinizing hormone (LH) peak with the subsequent block of ovulation. A parallel reduction in ovarian sensibility to the follicle-stimulating hormone (FSH)

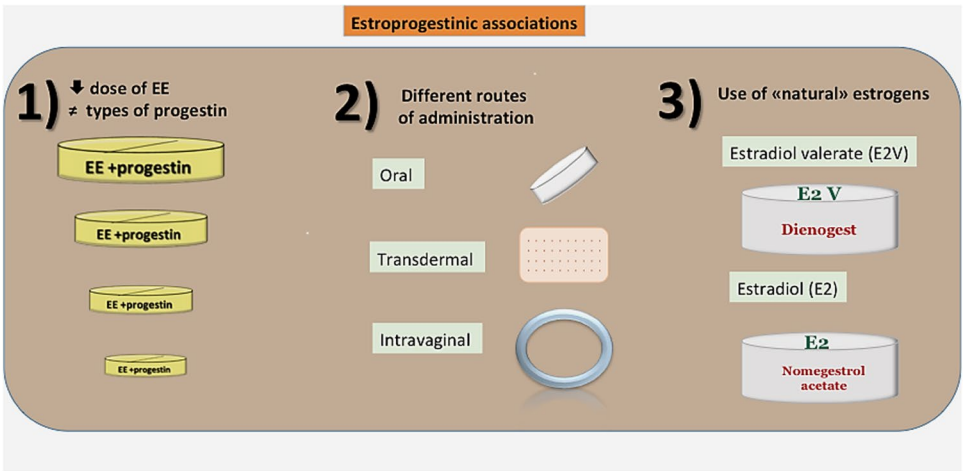

Fig. 1 Graphical representation of the main changes characterizing the evolution of CHCs

leads to a decrease in estradiol production. Therefore, the presence of the estrogenic component provides a more tolerable and acceptable bleeding profile; indeed, estrogens exert proliferating and stabilizing effects on the endometrium during the days of administration whilst sloughing the endometrium (i.e., withdrawal bleed) during the estrogen-free days. At the same time, the estrogenic component increases the contraceptive efficacy of the CHC potentiating the effect of the progestin on gonadotropins [12].

By now, the estrogenic components within commercially available CHCs are two: natural estrogens (NEs) and their derivates, or estrogenic synthetic products. Nevertheless, new formulations containing another estrogenic component, estetrol, are expected on the market in 2021. While the natural estrogen estradiol (E2) and its derivate valerate estradiol (E2V) have slight metabolic and thromboembolic effects, synthetic EE has a greater impact on metabolism (stimulating the hepatic synthesis of triglycerides and very-low-density lipoproteins, VLDLs) and thrombosis/thrombolysis balance [13, 14]. The ethinyl group of EE allows for high stability, long half-life, and high estrogenic potency [15]. In particular, EE has a greater impact on estrogen-dependent markers (such as liver proteins) than natural estradiol (E2), especially on sex hormone binding globulin (SHBG), angiotensinogen, and coagulation factors [13, 16]. SHBG is a carrier protein synthesized by the liver; it binds around 65–70% of circulating testosterone (T), which is, therefore, inactivated by SHBG [13]. E2 exerts a 500-fold lower effect on SHBG as compared to EE. The greater effect of EE on SHBG has been related to its 17α-ethinyl group, which prevents this kind of estrogen from inactivation, hence determining a longer tissue retention and a stronger hepatic effect [17]. Consequently, this chemical characteristic of EE can explain why its non-oral delivery would not avoid the first-pass liver effect, differently from E2 [18]. In particular, it has been demonstrated that users of CHC containing ≥ 35 µg of EE had higher SHBG levels than users of pills containing 20 µg EE, thus configuring a dose-dependent relationship between SHBG levels and EE [19]. This tight relationship is essentially due to the presence of an estrogen receptor-responsive element in the promoter region of the SHBG gene [20]. Conversely, EE inhibition on gonadotropins is more potent than that of NEs, allowing for the creation of CHCs formulations with decreased doses of EE and subsequently reduced estrogenic adverse effects (Fig. 2). Moreover, some evidence suggests that the known effects of combined hormonal contraceptives on hemostatic variables and estrogen-sensitive liver proteins are mostly related to EE and are independent of the route of administration [21, 22].

As mentioned above, the estrogenic component of CHCs has a strong impact on the production of liver proteins, including coagulation factors. In detail, a dose of 10 µg EE causes an increase in factor VII, factor VIII, factor von Willebrand, and β-thromboglobulin (+ 13%, + 17%, + 17%, and + 94%, respectively), which are all procoagulant proteins, and a decrease in antithrombin III (− 14%), which acts as an anticoagulant factor. On the other hand, a dose of 2 mg of E2V only produces an increase of 44% in β-thromboglobulin and a decrease of 9% in antithrombin III levels [16].

Nowadays, most of the combined oral contraceptive (COC) pills contain EE at variable doses from 15 to 35 µg, while in the past, COCs used to contain relatively higher doses of EE. Several benefits of low EE dose pills have been acknowledged, including less procoagulative and metabolic effects than their high-dose counterparts. COCs containing EE are associated with a significantly increased risk of VTE with a step-wise increase as a function of the EE dose [23]. Regarding COCs containing NEs, the two available options are a quadriphasic formulation with E2V (1, 2 or 3 mg) and dienogest (DNG) and a monophasic formulation with 1.5 mg E2 and nomegestrol acetate (NOMAC). Albeit the two formulations contain different NEs doses, they are essentially bioequivalent, since 2 mg E2V and 1.5 mg E2 expose women to similar estradiol serum concentrations [24]. As previously mentioned, despite the reported weaker

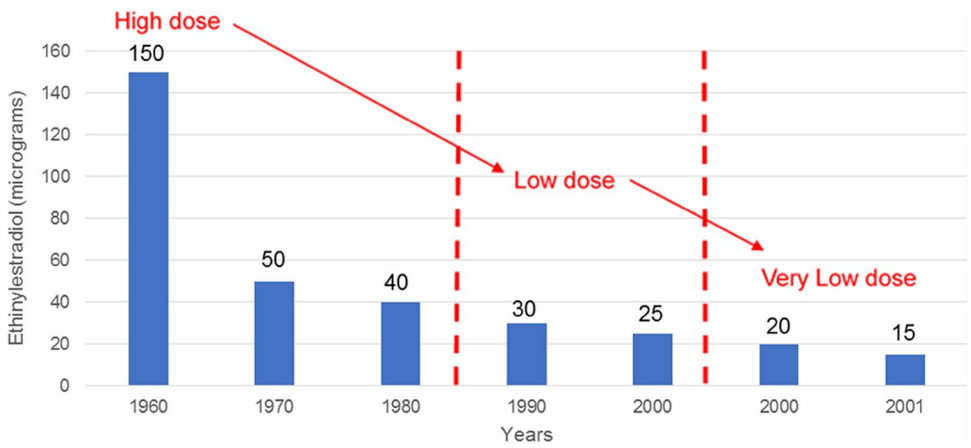

Fig. 2 Decrease in the dose of EE in CHCs over the years

impact of NEs on the coagulation cascade, no longitudinal studies have assessed the risk of venous thrombosis of DNG/E2V, thus challenging health professionals dealing with contraception. In addition, the thrombophilic effect of EE is significantly modulated by the progestinic component of the COCs: no statistically significant differences in resistance to activated protein C (a risk factor for venous thrombosis) and SHBG levels were found between DNG/E2V and LNG/EE, suggesting a comparable thrombotic risk of the two formulations [25]. In this regard, LNG is considered one of the safest progestins on thrombotic risk (see below).

In CHCs, progestins are the most effective component in ovulation inhibition, by inhibiting LH pre-ovulatory peak. Nowadays, several synthetic progestational agents are available (Table 1) and they vary in potency, affinity for steroid receptors, interaction with estrogens and physiological effects [26]. In particular, important differences can be observed in their androgenic activity. Proandrogenic compounds (mainly the gonans levonorgestrel, norgestimate, and the estrane norethisterone) bind the androgen receptor with great affinity, whereas predominantly anti-androgenic compounds (mainly the pregnane cyproterone, a derivate of 17OH-progesterone, the estrane dienogest and the spironolactone-derivate drospirenone) show a significant anti-androgenic activity (Table 2). Proandrogenic activity is advisable in attenuating the estrogen-induced risk of

Table 1 Synthetic progestins according to their structure and activities. Adapted from Sitruk-Ware and Nath [28]

Related to progesterone	Related to testosterone
Pure progestational: nestorone, nomegestrol acetate, trimegestone	Partly estrogenic and androgenic: norethindrone (norethisterone)
Anti-androgenic: cyproterone acetate, drospirenone, nomegestrol acetate, chlormadinone acetate	Partly androgenic: levonorgestrel, gestodene, desogestrel
Partly glucocorticoid: medroxyprogesterone acetate, anti-aldosterone, drospirenone	Anti-androgenic: dienogest, norgestimate

Table 2 Biological steroid receptor activities ("intrinsic activities") of progestogens. Adapted from Ruan et al. [84]

Progestin	Progestogenic	Anti-gonadotropic	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Progesterone	+	+	+	–	–	±	+	+
Dydrogesterone	+	–	+	–	–	±	–	±
Medrogestone	+	+	+	–	–	±	–	–
17α-hydroxy derivates								
Chlormadinone acetate	+	+	+	–	–	+	+	–
Cyproterone acetate	+	+	+	–	–	++	+	–
Megestrol acetate	+	+	+	–	±	+	+	–
Medroxyprogesterone acetate	+	+	+	–	±	–	+	–
19-Norprogesterone-derivates								
Nomegestrol acetate	+	+	+	–	–	±	–	–
Promegestone	+	+	+	–	–	–	–	–
Trimegestone	+	+	+	–	–	±	–	±
Spironolactone-derivates								
Drospirenone	+	+	+	–	–	+	–	+
19-Nortestosterone derivates								
Norethisterone	+	+	+	+	+	–	–	–
Lynestrenol	+	+	+	+	+	–	–	–
Norethinodrel	±	+	±	+	±	–	–	–
Levonorgestel	+	+	+	–	+	–	–	–
Norgestimate	+	+	+	–	+	–	–	–
3-Keto-desogestrel	+	+	+	–	+	–	–	–
Gestodene	+	+	+	–	+	–	+	+
Dienogest	+	+	±	±	–	+	–	–

thromboembolism, while it may result in unwanted effects on androgen-mediated cutaneous disorders and lipid profile (i.e., increase in the levels of total cholesterol and triglycerides) due to the decrease in SHBG synthesis [27]. On the other hand, COCs containing second-generation progestins (norgestrel and levonorgestrel) and/or lower estrogen doses (20–25 µg EE) have a lower impact on SHBG concentrations [13]. Newer progestins with higher specificity, derived from progesterone and spironolactone (e.g., chlormadinone acetate and drospirenone), bind more selectively to progesterone receptors and exert fewer androgenic, estrogenic, and glucocorticoid side effects [28]. Interestingly, a recent review evaluating the efficacy of pharmacologic agents for the treatment of bulimia nervosa and binge eating disorder, conditions often associated with obesity, highlighted that, in empirical studies, the use of EE + drospirenone (DRSP) has been associated with a significant decrease in meal-related hunger and gastric distention after 3 months, as well as with a reduced frequency of self-induced vomiting and reduced total and free testosterone levels. Consequently, the authors suggest COCs containing DRSP as a useful treatment strategy for women with hyperandrogenic symptoms and bulimia nervosa [29].

Regarding the effect of oral contraceptives on the metabolic profile, a recent meta-analysis provides interesting insights into this issue [27]. A total of 831 women with polycystic ovary syndrome (PCOS) under OC treatment using EE combined with cyproterone acetate or third-generation progestins were included in the analysis. All these contraceptives were found to determine a worsening in the lipid profile, although with different timings, but no significant changes were observed in other metabolic outcomes, such as arterial blood pressure, BMI, fasting insulin, fasting blood glucose, and HOMA-IR (homeostatic model assessment of insulin resistance) Index. In particular, OCs containing DRSP or desogestrel (DSG) increased HDL-cholesterol (HDL-C) levels after just 3 months of use and triglyceride (TG) levels after 6 months. On the other hand, products containing cyproterone acetate (CA) required a longer time, 6 and 12 months, respectively, to raise HDL-C and TG levels. Finally, all the evaluated OCs led to an increase in LDL-cholesterol (LDL-C) after 12 months of administration. This meta-analysis shows that some of the most commonly used OCs have a significant impact on the lipid profile of women (in particular PCOS patients, who, however, often present as overweight or obese) using them, and this aspect has to be considered in the choice of the best suitable contraceptive for obese women.

Concerning thromboembolic risk, a Cochrane review published in 2014 found that COCs were associated with an increased risk of venous thrombosis: COC preparations considered in this analysis were associated with a more than twofold increased risk of venous thrombosis compared with non-use [23]. The effect size depended upon either the dose of EE or the progestin type. In particular, the risk of venous thrombosis for COCs progressively increased as a function of the dose of EE: the higher the dose of EE, the higher the risk of venous thrombosis. The highest risk was found among 50 µg EE COCs users [data available were in combination with LNG; RR 5.2 (CI 95% 3.4–7.9) vs non-users], while the same progestin combined either with 20 µg or with 30 µg of EE showed a significantly lower risk profile [RR 2.4 (1.8–3.2) for 30 µg + LNG vs non-users; 2.2 (1.3–3.6) for 20 µg + LNG vs non-users]. Similarly, COCs containing gestodene (GSD) showed a significantly higher risk in formulations containing 30 µg of EE as compared to those containing 20 µg [RR 1.7 (1.1–2.6)]. Moreover, when comparing pills containing the same dose of EE but different progestins, COCs containing 30 µg EE when combined with gestodene, desogestrel or drospirenone showed a similar risk [RR 3.7 (2.8–4.9), 4.3 (3.3–5.6) and 3.9 (2.7–5.5) vs non-users, respectively], and about 50–80% higher than COCs containing 30 µg EE but combined with LNG. To summarize, a higher EE dose in COCs is associated with a higher risk of venous thrombosis; among progestins, given the same EE dose (i.e. 30 µg), LNG has been reported to be the safest [23]. The peculiar safe profile of LNG is thought to be related to its androgenic activity, which is better able to counteract the promoting effect of EE on thrombotic factors within the liver [30, 31].

Combined hormonal contraceptives can be further stratified according to their route of administration in combined oral contraceptives and non-oral combined contraceptives (including transdermal patches and vaginal rings).

Combined oral contraceptives

COCs are largely used among women of all ages, and there are many possible available dose regimens. COCs are categorized as monophasic or multiphasic, depending on the different levels of hormones contained in each pill per cycle. Common monophasic formulations, in which the doses of estrogen and progestin remain the same throughout the cycle, mainly consist in 21 or 28 pills. In the 28-pill formulations, the last 7 pills are inert (21 + 7), to increase the compliance of the patients. Recent studies have observed that a 7-day suspension time might put patients at risk for reactivation of the hypothalamic–pituitary axis (HPA), especially in pills with a low dose of the estrogenic component, thus reducing the contraceptive's efficacy [32, 33]. To minimize this risk, 28 dose regimens were formulated, in which 24 pills actually contain the active principles and only 4 are inert (24 + 4). In biphasic regimens, the dose of estrogen is greater in the first 7 days of the cycle, whereas the dose of progestin is higher in weeks 2 and 3. Triphasic formulations consist in three different combinations of doses of estrogen

and progestin, that vary throughout the cycle. Nevertheless, triphasic preparation regimens have not shown a higher clinical efficacy compared to monophasic regimens [34].

Non-oral combined options

Non-oral administration of EE provides a minor fluctuation in estrogen plasma concentrations.

Transdermal patch

Transdermal patches have been designed to deliver either 35 µg EE with 150 mg norelgestromin (the active metabolite of norgestimate) or 13 µg gestodene with EE per day. Although it was first developed to deliver a relatively low daily dose of EE, a recent study comparing serum EE levels in women using either a patch, vaginal ring or 30 µg EE pill, showed that the EE mean serum concentration in the patch group was 3.4 higher than in the ring group, and similarly 1.6 times higher compared to the pill group [35]. Two novel patches delivering lower estrogen doses and with different progestins are currently under investigation [36].

Vaginal ring

The combined hormonal contraceptive vaginal ring (CVR) inhibits ovulation by the continuous release of 15 µg EE and 120 µg etonogestrel (ENG) in the vagina [37], where they are absorbed through the vaginal mucosa. The device is designed to stay in the vagina for 3 weeks, followed by removal and replacement after 1 week. In two clinical trials, CVR users reported a high compliance with this contraceptive regimen (80–90%) [38, 39].

It has been hypothesized that parenteral route of estrogen administration may avoid the first-pass liver metabolism, determining a different effect on lipemic and proteinemic synthesis [40]. Nevertheless, switching from OC to a transdermal patch has been shown to increase SHBG, whereas no change followed when switching from OC to a vaginal ring [41]; therefore, this hypothesis has yet to be confirmed.

Progestin-only methods

The estrogen component is non-compulsory to achieve effective and safe contraception; in fact, patients at risk for complications with combined hormonal therapies are candidates for alternative regimens. Progestin-only contraceptives (POCs) containing high-to-ultra-low-dose progestins are currently available with different routes of administration (oral, injectable, implant, and intra-uterine; Fig. 3). Progestins provide effective contraception by suppressing gonadotropins secretion, thus subduing ovarian function, and by modifying cervical mucous viscosity, thus preventing sperm

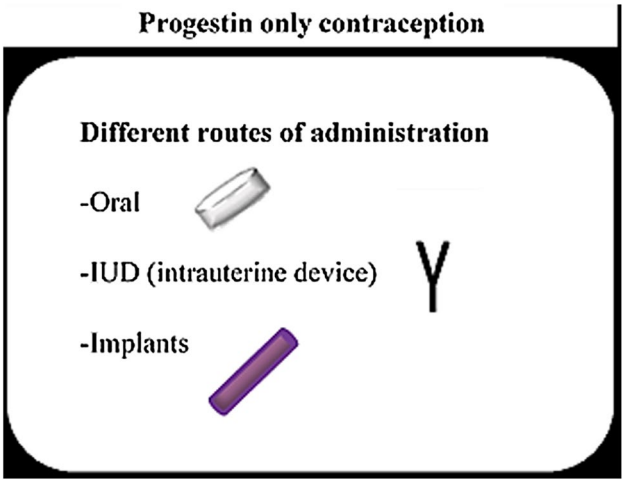

Fig. 3 Different routes of administration of progestin-only contraception

transport to the fertilization sites. Most POC users will experience irregular bleeding patterns in the first year of therapy, which usually resolve over time [42].

Progestin-only pills

Progestin-only pills (POPs) have a high contraceptive efficacy thanks to increased viscosity of cervical mucus, which inhibits sperm penetration along with thinning of the endometrium, reduced activity of the tubal cilia, and suppression of ovulation [43]. Available POPs contain either norethisterone, LNG, or DSG (28 pills with 75 µg DSG). Since POPs have a short duration of action and a short half-life, they are administered daily at the same time. This might help patients in maintaining a regular dosing regimen. Furthermore, POPs can be prescribed to breastfeeding patients, since they do not interfere with lactation [44]. Approximately 40% of women taking POPs have more frequent unscheduled bleeding (shorter, less predictable intervals between bleeding and/or longer episodes of bleeding), whilst 10% report amenorrhea. These differences are likely secondary to inter-individual differences of serum levels of progestins [45, 46].

Intra-uterine devices

Levonorgestrel-containing intra-uterine devices (LNG-IUDs) mainly exert their contraceptional effects by thickening cervical mucus and determining endometrial decidualization, glandular atrophy, and increased production of the progestogen-dependent endometrial protein (PEP) [46, 47]. Three preparations with different LNG doses (52 mg, 19.5 mg, and 13.5 mg) are currently available. LNG-IUDs maintain LNG plasma concentration between 166 and 131 pg/ml during the first 18 months and between 101 and

74 pg/ml from month 24 to 60 [48]. They are, respectively, characterized by an average LNG release of 20 µg/24 h (LNG intra-uterine system = IUS 20), 12 µg/24 h (LNG IUS 12), and 8 µg/24 h (LNG IUS 8) over the first year. The 52 mg device is also used to treat atypical endometrial hyperplasia and menstrual-related disorders such as menorrhagia and dysmenorrhea [43]. Noteworthy, a recent case report focused on a patient with bulimia nervosa—the prevalence of which is higher among bariatric surgery candidates [49]—experiencing a relapse in nutritional restriction, increased anxiety, and a decline in outpatient program attendance after placement of a 52 mg LNG-IUD [50]. Although a link between IUD use and eating disorder symptoms relapse cannot be demonstrated, more rigorous research is needed on this understudied topic, and psychoeducation about the risks and benefits of contraception appears particularly important in patients with eating disorders [50]. Finally, LNG-IUDs can cause amenorrhea.

The main characteristics of LNG-IUDs are reported in Table 3.

Implants

Contraceptive implants are flexible plastic rods containing ENG or LNG inserted under the upper inner arm skin, providing a 3-year long-acting contraception. Those containing ENG (total content: 68 mg of the active compound) release 60–70 µg over the first 5–6 months, 35–45 µg over the first year, 30–40 µg over the second year, and then 20–30 µg until the end of the third year of therapy. Implants suppress ovulation and increase cervical mucus viscosity. After removal of the rod, ovulation resumes within the first 3 weeks in more than 90% of patients [51].

Injectables

Progestin-only injectables (POIs) contain either medroxyprogesterone acetate (MPA) or norethisterone enanthate. They are administered approximately every 3 months subcutaneously or intramuscularly. These compounds act by inhibiting gonadotropins secretion, thus preventing follicular maturation, and through a thinning effect on the endometrium [52]. Since they have been shown to cause amenorrhea in a considerable portion of users [53], they can be a valid option for those patients complaining of heavy menstrual bleeding.

A progesterone vaginal ring for contraception during breastfeeding (3 months) [54] and a POP containing only drospirenone 4 mg (24 + 4) are under development.

Following the review of the main medical contraceptive options available nowadays, it becomes clearer and fundamental to address the issue of weight gain due to hormonal contraception, especially with regard to obese women. So far, a causal relationship has not been established. In 2014, a Cochrane meta-analysis of controlled trials found that most comparisons of different CHCs showed no substantial difference in weight; the few trials with a placebo or no intervention group did not provide evidence supporting a causal association between CHCs (oral or patch) and weight change [55]. Furthermore, weight gain as a side effect of POCs has been debated; however, a recent review on the topic found limited evidence [56]. Nevertheless, weight gain is one of the most frequently cited reasons for contraceptive discontinuation [55]. The mechanisms underlying this possible effect are still under debate and include fluid retention, an increase in subcutaneous fat induced by the estrogen component, a stimulating effect on appetite, and an androgen-mediated increase in muscle mass [57]. As for fluid retention, synthetic estrogens contained in oral contraceptives have well-known effects on the renin–angiotensin–aldosterone system (RAAS) [58]. Indeed, a promoter region of the angiotensinogen gene is responsive to estrogens [59]; consequently, exogenous estrogen administration raises plasmatic, hepatic, and renal concentrations of angiotensinogen, leading to an increase in plasma concentrations of angiotensin II and aldosterone, which are the effector substances of the RAAS. Specifically, aldosterone, the main mineralocorticoid hormone, stimulates renal reabsorption of sodium and excretion of potassium, thereby indirectly influencing water retention, blood pressure, and blood volume [60]. In addition, the progestogen component of oral contraceptives per se can exert mineralocorticoid effects due to its affinity for the mineralocorticoid receptor (MR), contributing to fluid retention [28]. Differently, available evidence on the effect of contraception on body composition is scarce and lacks

Table 3 LNG-IUDs according to their pharmacokinetics and main characteristics

	LNG-IUD 13.5 mg	LNG-IUD 19.5 mg	LNG-IUD 52 mg
Duration	3 years	5 years	5 years
Average LNG release rate over the first year	8 µg/day	12 µg/day	20 µg/day
T frame size	28 × 30 mm	28 × 30 mm	32 × 32 mm
Improved visibility at ultrasound	Yes (presence of silver ring)	Yes (presence of silver ring)	–
Rate of amenorrhea	6% within 1 year	12% within 1 year	20% within 1 year
	12% within 2 years	23% within 5 years	50% within 2 years

standardized measurement procedures. In a prospective cohort study, changes in body weight and composition did not differ among copper IUD, LNG-IUS, and ENG implant users after 12 months, although lean body mass increased in LNG-IUS and copper IUD users but not in ENG implant users (with a mean increase of 0.5, 0.4, and 0.1 kg of body weight in the three groups, respectively) [61]. Conversely, a less recent study designed to elucidate the mechanism of weight gain frequently seen among depot MPA users, failed to demonstrate significant anabolic or fluid retention properties, suggesting that MPA-associated weight gain may be associated with fat deposition, as assessed by measuring skin-fold thicknesses [62]. With regard to oral contraceptives, in a trial on 150 obese and normal weight women randomized to treatment with EE/LNG at different doses, there were no clinically or statistically significant body composition changes evaluated by bioelectrical impedance analyzer, independently of BMI [63]. Similar neutral findings on body composition had been previously observed following treatment with 30 µg EE + gestodene (GSD) [64]. In conclusion, the risk of weight gain per se should not represent an obstacle to the prescription of contraceptive therapies for obese women, since strong evidence on the topic is lacking.

Obesity and contraception—how can I make the choice?

The incidence of VTE among fertile women in the general population is reported to be 2–4 per 10,000 women-years. This incidence has been estimated to be only slightly higher in women using COCs (5–7 per 10,000 users-years), while it rises dramatically during pregnancy (29 per 10,000 women-years) and puerperium (300–400 per 10,000 women-years) [65, 66]. As previously described, obesity represents a risk factor for VTE: Samama reported a doubled risk of deep venous thrombosis among outpatients with BMI greater than 30 kg/m^2 [67] and White et al. observed a relative risk of 2.5 for developing thrombosis among patients with a BMI greater than 25 kg/m^2 undergoing hip replacement surgery [68]. In this scenario, considering all the potential metabolic and thrombophilic effects of contraceptives, choosing the suitable contraceptive method for obese patients often represents a challenge. However, physicians who counsel women and couples about contraception today can rely on important tools to discern the most suitable choice among a broad range of methods. Namely, the US Medical Eligibility Criteria for contraceptive use, the World Health Organization (WHO) Medical Eligibility Criteria (MEC) for contraceptive use (Fifth Edition, 2015) and the UK Medical Eligibility Criteria for contraceptive use (UKMEC 2016) offer guidance in tailoring therapies according to the patient's profile [69–71] (Table 4). The WHO MEC identify four categories of recommendations in relation to medical conditions or medically relevant characteristics presented by the patient:

- 1: A condition for which there is no restriction for the use of the contraceptive method;
- 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks;
- 3: A condition where the theoretical or proven risks usually outweigh the advantages of using the method;
- 4: A condition which represents an unacceptable health risk if the contraceptive method is used.

The clinical judgements related to these four categories are the following (Table 5):

Table 4 Medical Eligibility Criteria for obesity-related comorbidities [70, 85]

WHO Medical Eligibility Criteria rating for obesity and related disorders									
Contraceptive method	Obesity	Age > 40	Hypertension[a]	Diabetes mellitus[b]	Hyperlipidemia	Cardiovascular disease (CVD)	Multiple CVD risk factors[c]	Bariatric surgery malabsorptive[d]	Bariatric surgery restrictive[d]
Combined hormonal pills	2	2	3	2	2/3	4	3/4	3	1
Patch/ring	2	2	3	2	2/3	4	3/4	1	1
Progestin-only pills	1	1	1	2	2	2	2	3	1
Depot-medroxyprogesterone acetate (DMPA)	1	2	2	2	2	3	3	1	1
Progestin-only implant	1	1	1	2	2	2	2	1	1
Copper IUD	1	1	1	1	1	1	1	1	1
Levonorgestrel IUS	1	1	1	2	2	2	2	1	1

[a]If blood pressure < 160/100 mmHg and can be assessed

[b]Without evidence of peripheral or vascular disease

[c]Such as older age, smoking, diabetes, hypertension

[d]Centers for Disease Control and Prevention MEC recommendations

Table 5 Practical use of WHO Medical Eligibility Criteria [70]

Category	With good resources for clinical judgement	With limited resources for clinical judgement
1	Use method in any circumstances	Yes (use the method)
2	Generally use the method	
3	Use of method not usually recommended unless other more appropriate methods are not available or not acceptable	No (do not use the method)
4	Method not to be used	

- Category 1: use the method in any circumstance;
- Category 2: generally use the method;
- Category 3: use of the method not usually recommended unless more appropriate methods are not available or not acceptable;
- Category 4: method not to be used.

Briefly, category 3 and 4 represent, respectively, a relative or absolute contraindication to the use of the specific contraceptive method. According to the WHO MEC, class II and III (BMI ≥ 35 kg/m^2) obesity per se is considered to be a relative contraindication to the use of CHCs (category 3); on the other hand, the use is not contraindicated in class I obesity (30–34.99 kg/m^2). However, recommendations change when obesity is associated with specific cardiovascular risk factors. In particular, obesity of any class is labeled as MEC category 4 if combined with at least one of the following conditions (this counts also for non-obese women): multiple risk factors of coronary artery disease, hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), vascular diseases, history of or current deep vein thrombosis/pulmonary embolism, major surgery-prolonged immobilization, current or history of ischemic heart disease, stroke, age > 35, and smoking > 15 cigarettes/day. Conversely, obese patients may benefit from progestin-only methods, including POPs, intra-uterine devices (copper IUD and medicated IUS), implants and injectable methods, which are a MEC category 1, even in the case of class II (BMI 35–39.99 kg/m^2) and III (BMI ≥ 40 kg/m^2) obesity (Table 6).

As a practical matter, testing for thrombophilia before the use of oral contraceptives should not be performed on a routine basis, as recommended by the Centers for Disease Control and Prevention (CDC) of the United States [72]. However, testing for thrombophilia may be useful in asymptomatic relatives belonging to families with protein S, antithrombin or protein C deficiency, or for siblings of patients who are homozygous for factor V Leiden. Indeed, these subjects have a considerably increased risk of oral contraceptive-related VTE as compared to the general population (0.7% vs 0.04% per year of use) even in the absence of the specific genetic defect known in the family. This might indicate the presence of a notable thrombotic tendency in which as-yet-undiscovered thrombophilic defects have cosegregated [73]. Therefore, in these selected cases, thrombophilia screening would allow affected family members or affected young patients with a personal history of VTE (for whom the choice of a contraceptive method alternative to COCs should be recommended) to be identified [74].

In addition, it is important to briefly address two further points related to obesity. First, this condition has been associated with an altered pharmacokinetic profile and reduced efficacy of COCs in several studies [75–77] but not in some others [78, 79]. Therefore, controversy still exists regarding whether obesity adversely impacts the contraceptive efficacy of COCs, tipping the balance towards progestin-only contraception. Second, obesity is frequently comorbid with hyperandrogenism/hirsutism [80]. According to the 2018 Endocrine Society guidelines, all oral contraceptives are equally effective for the treatment of hirsutism [81]. For women with hirsutism at a higher risk for VTE (e.g., obese women), initial therapy with an oral contraceptive containing the lowest effective dose of EE (usually 20 μg) and a low-risk progestin is suggested [81]. Furthermore, lifestyle interventions are recommended for hirsute women with obesity, including those with PCOS [81]. Although it can be argued that oral contraceptives containing anti-androgenic progestins are more appropriate for the treatment of hirsutism, obese women are steeped in the risk of VTE, shifting the choice to the safest contraceptive method. Nevertheless, apparently less effective interventions (including

Table 6 Medical Eligibility Criteria for the use of different contraceptive methods related to obesity classes [70, 71]

	Copper IUD	IUS	Implant	Injectable	CHC	POP
BMI 30–34 kg/m^2	1	1	1	1	**2**	1
BMI ≥ 35 kg/m^2	1	1	1	1	**3**	1

Categories different from number 1 are marked in bold since they are referred to a method that should not be used in any circumstance

LNG-IUS, which has a lower systemic absorption than COCs) may result in a clinical improvement of hirsutism, due to their influence on gonadotropins and SHBG.

Finally, the literature is essentially in line with the WHO recommendations. In 2012, a meta-analysis by Mantha et al. demonstrated a relative risk of VTE of 1.03 for users vs non-users of progestin-only methods, suggesting the absence of a significant clinical risk for thromboembolic events with the use of these methods [82]. It follows that POCs (specifically, low-dose norethisterone pills, desogestrel-only pills, and LNG-IUDs) appear to be the safest contraceptive option when considering the risk of VTE, conferring no increased risk [83].

Conclusions

Nowadays obesity is a widespread condition and in some countries, e.g., in the USA, it is growing on an epidemic scale. Consequently, more and more obese women in their fertile age require contraception. Since different comorbidities can be related to this condition, such as hypertension, hypertriglyceridemia, as well as an increased risk of thromboembolic events, obesity can represent an absolute or relative contraindication to combined hormonal methods. The choice of a contraceptive method for obese women should consider its safety profile and particularly thromboembolic and cardiovascular risks. Long-acting reversible contraceptives (progestin-only implants, LNG-IUDs, and copper IUDs) and progestin-only methods in general are excellent options for this category of patients, since they offer reversible (long-term) contraception without the increased risk of thrombophilic adverse events related to estrogens. The WHO MEC can guide the contraception provider in this sometimes challenging choice.

Compliance with ethical standards

Conflict of interest Author Prof. Linda Vignozzi has received research grant fundings from Theramex and from Bayer. The authors Dr. Sarah Cipriani, Dr. Tommaso Todisco, Dr. Irene Scavello, Dr. Vincenza Di Stasi, and Dr. Elisa Maseroli declare that they have no conflict of interest.

Ethical approval This article does not deal directly with a study conducted on animals or humans by our research group.

Informed consent For this type of study formal consent is not required.

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