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Hormonal contraceptives: pharmacology tailored to women's health

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BACKGROUND: In recent years, several new oral contraceptives have become available. In some ways, they represent an evolution in terms of individualization and compliance on the part of women. The new formulations make it increasingly possible to prescribe a specific hormonal contraceptive on an individual basis.

METHODS: A systematic literature search of PubMed was performed using the following combination of terms: 'oral contraceptives', 'estroprogestins' and 'combined oral contraceptive'. Only English-language papers published between January 2000 and July 2014 were included in our analysis. The present review analyzes all aspects of the choice of oral contraceptives in the different phases of a woman's life in detail.

RESULTS: Regarding the estrogen component, lowering the dose of ethinylestradiol (EE) helped reduce associated side effects. Natural estradiol is now available and represents a valid alternative to EE. And regarding progestins, the dose has changed over time, as well as the endocrine and metabolic characteristics. These are the fruit of much research into improvement of old products (19-nor-progesterone-derived progestins) with androgenic effects and testing of new molecules with improved metabolic neutrality in terms of insulin sensitivity and lipid parameters. New progestins were a genuine turning point because they greatly reduced major side effects, such as water retention, and their anti-androgenic properties made them indicated for all forms of hyperandrogenism associated with acne and mild hirsutism. The associations of estradiol/dienogest and estradiol/nomegestrol acetate are the most suitable contraceptives for women with abundant menstrual bleeding and can increase the number of potential users of hormonal contraception.

CONCLUSION: Progress in the provision of new oral contraceptives has improved the risk/benefit ratio, by increasing benefits and reducing risks. The present challenge is to tailor contraceptives to individual needs in terms of efficacy and protection of reproductive health.

Key words: combined oral contraceptive / oral contraceptives / estroprogestins / hormonal contraception / women's health

Introduction

The first combined oral contraceptive (COC) was introduced in 1960 (Enovid-Searle). Since then, use of the pill has spread exponentially, overtaking other reversible methods of contraception and providing simple, safe and effective protection against pregnancy (United Nations Department of Economic and Social Affairs, 2007). According to recent estimates, the pill is used by 9% of women of reproductive age and is the most common method of contraception in industrialized countries and the third most common in developing countries (United Nations Department of Economic and Social Affairs, 2007). The first COC contained higher concentrations of estrogens and progestins than today and was associated with intolerable side effects, such as irregular bleeding, nausea, headache, weight gain and episodes of venous thromboembolism (VTE) (Inman *et al.*, 1970). To reduce these effects, oral contraceptives underwent major changes in the quantity and type of hormones used, posology and routes of administration.

To reduce health risks and negative effects associated with COC, new administration regimes have been developed over the years. The first regimes were generally monophasic. In the 1980s, biphasic and triphasic formulations were introduced to reduce the total dose of steroids in each cycle, and also to mimic physiological fluctuations. Multiphasic contraceptives are highly effective when used correctly and provide excellent control of the cycle in most women. However, two studies comparing biphasic and triphasic with monophasic regimes found insufficient evidence of significant clinical advantages in terms of safety and efficacy of multiphasic pills. Moreover, bleeding seemed to depend more on the type of progestin than on the regime (Van Vliet *et al.*, 2006).

In recent years, many other substantial modifications have been made to COC regimes, with the aim of reducing the frequency and/or duration of menstruations and minimizing the risk of side effects such as menstrual or intermenstrual migraine and dysmenorrhea. Thus, the first COC with a reduced hormone-free interval (HFI) was introduced at the end of the 1990s. Regimes with 24 days of estrogens and progestins followed by 4 days of placebo (24/4 regime) were subsequently introduced with the aim of reducing HFI symptoms and allowing shorter and lighter suspension bleeding than with traditional 21/7 regimes. Another regime is the extended-cycle COC with 84 days of estrogens and progestins, followed by 7 days with placebo or only low-dose estrogens (84/7 regime) and therefore only four withdrawal bleedings per year. Clinical studies showed that these extended cycles are as effective in preventing pregnancies as traditional regimes and give better results in terms of menstrual symptoms (Nakajima *et al.*, 2007; Edelman *et al.*, 2014). However, women using the 84/7 regime reported frequent episodes of spotting after the fourth cycle (Anderson and Hait, 2003).

Another attempt to improve safety and tolerability of COC involved using natural estradiol instead of ethinylestradiol (EE). This estrogen allows good control of the cycle with limited metabolic effects (Endrikat *et al.*, 2008).

Methods

A systematic literature search of PubMed was performed using the following combination of terms: 'oral contraceptives', 'estroprogestins' and 'COC'. Only English-language papers published between January 2000 and July 2014 were included in our analysis. The present review analyzes in detail all aspects of the choice of oral contraceptives in the different phases of a woman's life.

Oral formulations: doses and regimes

Currently available oral contraception makes it possible to choose between formulations based on estrogens and progestins and those containing only a progestin. The former vary in dose and type of estrogen, dose and type of progestin, regime (monophasic, biphasic, triphasic or quadriphasic) and route of administration (pill, patch, vaginal ring or subcutaneous implant).

The metabolism of EE is similar to that of endogenous estradiol, i.e. it undergoes oxidation at various carbon atoms (De Leo *et al.*, 2013; Christin-Maitre, 2013): 2-α-hydroxylation is the most frequent, whereas 16-α-hydroxylation, just as important in the destablization of endogenous estradiol, seems impaired by the ethinyl group bound to the carbon in position 17.

The dose of EE has gradually been reduced over the years and pills are now available containing 35, 30, 20, 15 and 10 μg. Such reductions were enabled by the availability of progestins with high antigonadotrophic activity and partly thank to new regimes of administration. In other words, even extremely low doses of EE, such as 20 μg, can ensure excellent suppression of ovarian activity if associated with progestins having high antigonadotrophic activity. Fifteen micrograms of EE is the lowest dose of estrogen currently used in oral contraception. The contraceptive efficacy of this formulation is ensured both by association with gestodene (GSD) (60 μg), a progestin with high antigonadotrophic activity, and by the fact that it is administered for 24 instead of 21 days, and therefore with a shorter HFI. The reduction of this interval ensures excellent suppression of ovarian activity even with such low steroid doses. Contraceptive efficacy of COC with 15 and 20 μg EE, measured by the Pearl index, is in the range of 0.07–0.88, and is therefore similar to that of COC containing 30 μg EE (0.06–0.88) (Poindexter, 2001).

Estradiol undergoes an intensive first-pass effect in the cytochrome P450 (CYP)3A system of the liver, leading to the formation of its metabolites: estrone, estrone sulfate and estrone glucuronide (Hoy and Scott, 2009). Most of its destablization occurs in the intestinal mucosa. Approximately 95% of the oral dose is metabolized before going into systemic circulation. The half-life of estradiol in plasma is ~2.5 h, whereas the terminal half-life is ~13–20 h and depends on enterohepatic circulation and on circulating levels of sulfate and glucuronide metabolites. On suspension of treatment, estrogen concentrations return to basal levels in 2–3 days. Estradiol is mainly eliminated in the urine (Hoy and Scott, 2009), ~10% is eliminated in feces.

The first natural estrogen introduced into hormonal contraception was estradiol valerate (E2V) associated with dienogest (DNG) in a quadriphasic regime in which the dose of estrogen and progestin followed the physiological pattern of the ovarian and endometrial cycle for 26 days plus 2 days of placebo (E2V/DNG-containing COC). The four hormonal phases of E2V/DNG-containing COC extend over 28 days as follows: 3 mg E2V for 2 days; 2 mg E2V + 2 mg DNG for 5 days; 2 mg E2V + 3 mg DNG for 17 days; 1 mg E2V per 2 days and placebo for 2 days. The early dominance of estrogen in this formulation ensures good initial endometrial proliferation and prepares the

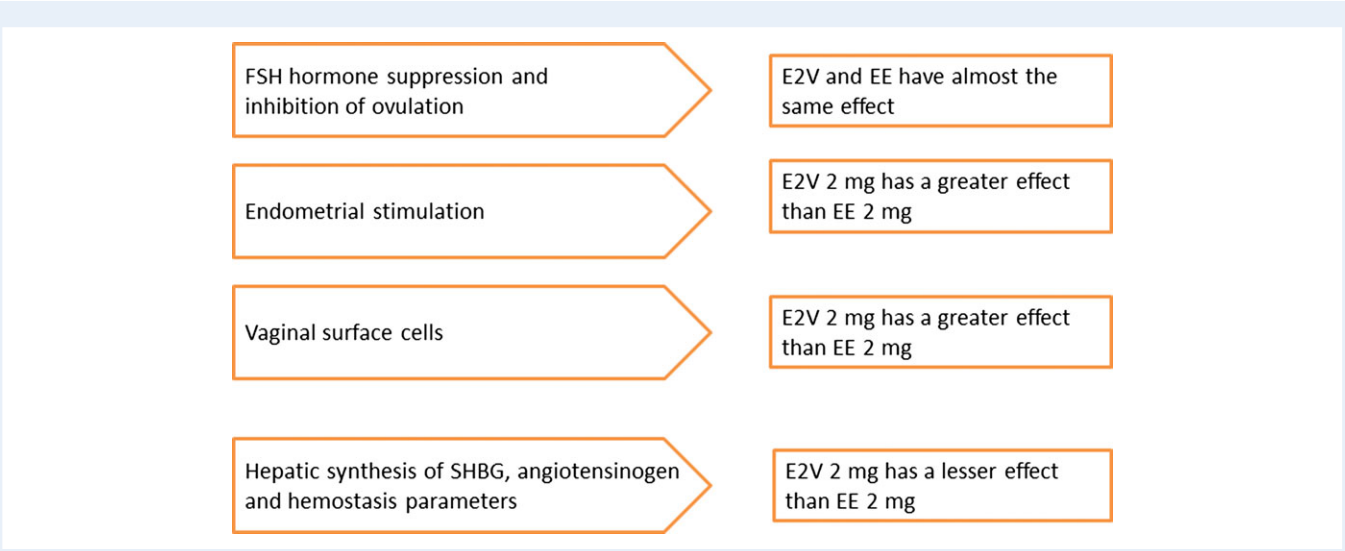

Figure 1 Comparison of the oral contraceptives (OCs) E2V and EE. SHBG, sex hormone-binding protein; E2V, estradiol valerate; EE, ethinylestradiol.

mucosa for the action of the progestin, while the association of E2V and DNG and the dominance of the latter in the middle to late part of the cycle, followed by modest estrogenic activity in the final phase, ensure satisfactory endometrial stability (Kuhl, 2005; Fruzzetti and Bitzer, 2010) (Fig. 1).

Recently, natural estradiol (1.5 mg) was associated with nomegestrol acetate (2.5 mg) in a monophasic formulation with a 24/4 day regime. This formulation, too, was better tolerated at metabolic level and with clotting parameters. It also provides good contraceptive efficacy and good control of the cycle, although there has been a little practical experience of its use.

Although EE and estradiol are the only estrogens used in COC, many progestins are currently available. These are the fruit of much research into improvement of old products (19-NOR derivatives) with androgenic effects and testing of new molecules with improved metabolic neutrality. The large range of active principles, each with its own characteristics, makes it possible to choose from a variety of pills, tailoring treatment to patient's needs (Table 1).

Levonorgestrel (LNG) is the hormonally active levorotatory enantiomer of the racemic mixture norgestrel (derived from nortestosterone). LNG binds to the progesterone receptor (PR) with high affinity but does not bind to estrogen receptors and has no intrinsic estrogen activity. It strongly inhibits gonadotrophin secretion. It binds to androgen receptors, and has negligible androgenic–anabolic activity but strong anti-estrogen activity. It has no glucocorticoid, mineralcorticoid or anti-mineralcorticoid effects, and as it is relatively unaffected by hepatic first-pass effect, it offers 100% bioavailability of the dose administered. It is hydrolyzed by the liver and eliminated after conjugation with glucuronic acid (Fotherby, 1995).

GSD, a third generation progestin, is a derivative of 19-nortestosterone. It is without significant residual androgenic effects but has slight mineralcorticoid activity and excellent anti-estrogen activity. As it is virtually without hepatic first-pass effect, GSD has a bioavailability of 100% (Grandi *et al.*, 2014). Desogestrel (DSG) is a highly effective progestin with low androgenic activity and high antigonadotrophic activity (De Bastos *et al.*, 2014). To act, it must first be converted into 3-keto-DSG.

Chlormadinone acetate (CMA) is a derivative of progesterone. It has anti-androgenic activity related to an increase in sex hormone-binding globulin (SHBG) and to inhibition of 5α-reductase, an enzyme that converts testosterone (T) into the more powerful 5α-dihydrotestosterone (Raudrant and Rabe, 2003), exercising a peripheral antagonist effect.

Drosperinone (DRSP), a derivative of 17α-spirolactone, has a very different molecular structure from other progestins. It is essentially characterized by strong affinity for PRs (like natural progesterone) (Huber *et al.*, 2000). It is an aldosterone antagonist and has a natriuretic effect, opposing the sodium-retentive effect of EE (Yding Andersen, 2002). That is why DRSP may help prevent the water retention, weight gain and increased blood pressure sometimes associated with oral contraceptive use (Oelkers, 2000). It is without androgenic, estrogenic, glucocorticoid and anti-glucocorticoid effects (Raudrant and Rabe, 2003).

DRSP is a progestin with strong anti-mineralcorticoid activity. Its affinity for mineralcorticoid receptors is five times greater than the affinity for aldosterone itself (Caprio *et al.*, 2011). This progestin maintains the anti-androgenic properties of progesterone without any androgenic, estrogenic, glucocorticoid or anti-glucocorticoid activity. It is used in hormonal contraception in monophasic formulations with 30 and 20 µg EE. It is also associated with 20 µg EE in a 24/4 monophasic formulation.

Metabolic effects and potential risks

COC can adversely affect different cardiovascular risk biomarkers and metabolic disorder risk factors and the effect on serum levels of adiponectin and leptin, and on insulin sensitivity and lipid profiles, is of particular importance (Shufelt and Bairey Merz, 2009). In particular, glucose intolerance and hyperinsulinemia may increase the risk of

Table I Effects of different progestins.

	Anti-estrogenic activity	Androgenic activity	Anti-androgenic activity	Anti-mineralcorticoid activity
Progesteron	+	–	(+)	+
Levonorgestrel	+	(+)	–	–
GSD	+	(+)	–	(+)
Desogestrel	+	(+)	–	–
Etonogestrel	+	(+)	–	–
Norelgestromin	+	(+)	–	–
Ciproterone a.	+	–	+	–
Clormadinone	+	–	+	–
Drospirenone	+	–	+	+
DNG	+	–	+	–
Nomegestrolo a.	+	–	–	–

Many progestins are currently available. These are the fruit of much research to improve old products (19-NOR derivatives) with androgenic effects and testing new molecules with improved metabolic neutrality (a., acetate).

arterial disease, especially in the presence of obesity, family history of diabetes, advanced age and history of gestational diabetes (Sirmans and Pate, 2013). It is therefore preferable to use a pill that has low effect on increased insulin resistance.

It has been known for more than 25 years that the use of high-dose COC increases the risk of anomalies of sugar metabolism, especially reduced tolerance to carbohydrates. The metabolic alterations induced by high-dose COC may be determined by either component, with effects that are often antagonistic and closely correlated with the chemical nature and dose of the compounds used. The reduced doses of both components in today's COC formulations are associated with a reduced incidence of glucose intolerance. The effects of different pills on sugar metabolism seem to be determined by the combination of insulin resistance induced by estrogens, which is dose-dependent, and by changes in the half-life of insulin induced by progestins (Sirmans and Pate, 2013). A progestin with androgenic properties causes a greater decline in insulin sensitivity than a progestin with anti-androgenic activity (Cagnacci *et al.*, 2009).

The use of oral contraceptives in diabetic premenopausal women does not affect levels of glycosylated hemoglobin, response to insulin therapy or progression toward vascular complications (Grigorian *et al.*, 2006). Thus, the World Health Organization (WHO) does not see contraindications for use of low-dose oral contraceptives in diabetic perimenopausal women who are non-smokers and without other cardiovascular risk factors (Stanback and Katz, 2002).

Oral formulations based on the progestin CMA and 30 μg EE have demonstrated metabolic 'neutrality' in terms of insulin sensitivity and lipid parameters (Cagnacci *et al.*, 2009).

Recent clinical studies show that the multiphasic association of E2V/DNG seems to have less impact on different metabolic and clotting parameters than EE. Changes in anticoagulant parameters also proved to be minimal but less pronounced with E2V/DNG than with EE/LNG. Comparison of E2V/DNG and a triphasic formulation (30–40 μg EE + 50–125 μg LNG) showed more significant increases in high-density lipoprotein and reduction in low-density lipoprotein with E2V/DNG. Carbohydrate metabolism remained stable in both groups (De Leo *et al.*, 2013).

In 1970, the Royal College of General Practitioners established that oral contraceptives containing more than 50 μg EE are associated with increased risk of cardiovascular and cerebrovascular events and are therefore contraindicated in all women older than 35 years of age (Cartwright and Waite, 1972). However, in 1991, the Food and Drug Administration (FDA) established that the risk is limited to smokers and that age itself cannot be considered a risk factor.

VTE is the most common serious complication associated with COC use. Its risk is an effect of the estrogen component. There is a clear relationship between risk magnitude and estrogen dose down to 20 μg EE. A number of studies have addressed differences in VTE risk between different formulations according to the progestin component of the pill. The risk seems to be higher for users of preparations with newer progestins, i.e. DSG, GSD and DRSP . This is most probably due to differences between the capacity of different progestins to balance estrogen-dependent risk of VTE and not an effect of the progestin by itself (Dinger *et al.*, 2010a; Brynhildsen, 2014).

For pills based on drospirenone, the FDA and European Medicines Agency (EMA) recently decided that the leaflet accompanying packets of this COC should include information on the associated risk of VTE. This decision was made on the basis of reports that women taking pills with DRSP are at higher risk of VTE than women taking pills without this progestin. However, the risk is still low, namely 6–10 cases in 10 000. The FDA and EMA underline, however, that the risk of VTE is much lower than that associated with pregnancy and post-partum (Gronich *et al.*, 2011).

The risk of COC-associated VTE is highest during the first 3 months of use (Dinger *et al.*, 2010b). Thus, there are both hereditary and acquired risk factors for VTE and they may enhance risk alone or in combination. These factors must be taken into account during contraceptive counseling and prescription of COCs. Positive family history has low predictive value (Grimes *et al.*, 2012) but can be used for preliminary screening.

The risk of VTE increases with age (Bergendal *et al.*, 2012). Healthy women of normal weight can be prescribed COC even at 40–49 years of age, but other potential risk factors must always be evaluated. A woman with a history of VTE should not use COCs because of the high risk of recurrence. Obesity is a well-known risk factor of VTE (Bergendal *et al.*, 2012).

Modern COCs containing less than 50 µg of EE do not increase the risk of myocardial infarction or stroke in healthy, non-smoking women of any age (Margolis *et al.*, 2007; Yang *et al.*, 2009), unless there is hypertension. COCs determine a slight reversible increase in systolic and diastolic blood pressure. This increase usually occurs in the first period of administration of the pill; it is self-limiting and not dose-related. Migraine is common in women and is associated with increased risk of ischemic stroke. For migraines with aura, the use of COC implies additional risk (Schürks *et al.*, 2009).

Although perimenopausal breast cancer is rather uncommon, it is the most common cancer in women of fertile age. A recently published systematic review and meta-analysis of 44 studies (Gierisch *et al.*, 2013) showed a borderline significant increase in risk of breast cancer during ongoing use of COCs [odds ratio (OR) = 1.08; 95% confidence interval (CI): 1.00–1.17]. No relation was found between risk and duration of use (OR = 0.95; 95% CI: 0.83–1.09). The risk vanished 10 years after cessation. Interpreted in absolute terms, this increase leads to a few extra cases as the incidence in this age group is very low.

A significantly increased risk for cervical cancer has been reported in association with COC use lasting more than 5 years. As in the case of breast cancer, the risk of cervical cancer disappears within 10 years of cessation. Recent analyses have not revealed an independent relationship between COC use and cervical cancer. The risk seems to be related to high-risk human papillomavirus (HPV) infection (Appleby *et al.*, 2007; Longatto-Filho *et al.*, 2011).

The 'right' contraceptive for every woman

Age and family planning

Before prescribing contraception, it is always advisable to provide counseling on risks versus benefits of various contraceptive preparations, so that the woman can choose the product most suitable for her values and needs. This should lead to greater satisfaction and correct use. Family planning includes complete information on subjects such as sexual and reproductive health, prevention of sexually transmitted infections, the various contraceptive options available and how to use them correctly. The more fully the doctor personalizes the choice of contraceptive and shares the decision with the patient, the more she will follow instructions and accept advice. Women are more likely to continue use of a pill if it ensures perfect contraception while increasing a sense of personal well-being (Lopez *et al.*, 2008).

Contraceptive method is not ideal for all women. For adolescents, oral contraception is an option of preventing unwanted pregnancy, although adolescents should be encouraged to consider long-acting reversible contraceptive options such as intrauterine devices or contraceptive implants. These are the best reversible methods for preventing unwanted pregnancy, rapid repeat pregnancy and abortion in young women (Committee on Adolescent Health Care Long-Acting Reversible Contraception Working Group, 2012). In certain situations, the therapeutic role of the pill may be exploited, as in the case of young women with hyperandrogenism, dysmenorrhea or premenstrual tension desiring contraception. If we also consider ease of use, reversibility, low risks and low cost, it is evident why they are so popular (Agostino and Di Meglio, 2010).

In prescribing hormonal contraception for adolescents, it is also important to consider certain typical aspects of this age group, such as immaturity of the hypothalamo–pituitary–ovarian axis, the development of secondary sexual characteristics and bone development. That is why, it is not considered appropriate to administer hormonal contraception until 1–2 years after menarche, and then to prescribe a pill containing a low dose of EE or with natural estrogens that interfere less with the development of secondary sexual characteristics. As far as bone is concerned, we know that an adequate estrogenic milieu in the first 5–7 years after menarche is critical for good peak bone mass and that COC use is associated with stable circulating concentrations of estrogens that are below those typical of physiological cyclic variability (Cibula *et al.*, 2012). It is therefore preferable to use contraceptives with an estrogen content of 30 µg, especially if it is anticipated that contraception will be used for a long period (Agostino and Di Meglio, 2010), even if COC use is associated with a higher risk of VTE in young women. Adolescents also require reliable information on correct use of the pill, together with detailed information on how to avoid sexually transmitted diseases by combining pill use with a condom (Amy and Tripathi, 2009).

Use of the pill is also appropriate for perimenopausal women by virtue of the association of therapeutic and contraceptive effects. Perimenopause is a transition period lasting about 5 years and is characterized by menstrual irregularity because of a progressive decrease in follicular activity. Fertility is maintained, and indeed ~80% of women between the age of 40 and 44 years are still able to procreate. Pregnancy in perimenopause ends in miscarriage in 50% of cases. Moreover, with increasing maternal age, the increasing incidence of maternal and fetal pathologies associated with pregnancy includes extrauterine pregnancy, fetal malformations, chromosome abnormalities, intrauterine growth retardation, macrosomia, gestational diabetes, pre-eclampsia, early placental detachment and post-partum hemorrhage (Nybo Andersen *et al.*, 2000). These are good reasons for a practical and safe method of contraception.

In this period of life, imbalances between estrogens and progesterone leading to a condition of relative hyperestrogenism are common. This is associated with increased risk of estrogen-related pathologies involving the endometrium and the breast, as well as a higher frequency of dysfunctional menometrorrhagia.

The relation between oral contraceptives and breast cancer has long been debated and it is known that progestins, which are mitogens in breast tissue, should promote cell proliferation in breast tissue, after estrogen exposure. Among women from 35 to 64 years of age, current or former oral-contraceptive use is not associated with a significantly increased risk of breast cancer; the risk of breast cancer is not significantly related to the duration of oral-contraceptive use or to the dose of estrogen (Marchbanks *et al.*, 2002).

Perimenopausal women often complain of symptoms linked to estrogen deficit: hot flashes, emotional instability and sleep disturbances. Oral contraceptives have been demonstrated to significantly

reduce the number and severity of hot flashes (Kaunitz, 2001). There is also broad consensus in attributing a preventive role against osteoporosis to oral contraceptives (Pasco et al., 2000).

Thus, oral contraceptives are safe and valid therapy for perimenopausal women, who are non-smokers, enabling improved quality of life in terms of contraceptive safety, fewer vasomotor symptoms, prevention of osteoporosis, regularization of the menstrual cycle and prevention of endometrial, ovarian and colorectal cancer.

In the fertile period, personalization of hormonal contraception, as we shall see later, should also consider other parameters, such as BMI, menstrual bleeding characteristics and the presence or otherwise of other pathological conditions, such as polycystic ovary syndrome (PCOS) and endometriosis (Brynhildsen, 2014).

Benefits of oral contraceptives

Menstrual irregularity (rhythm, quantity and pain)

Disturbances of menstrual bleeding manifest in a wide range of ways. Abnormal uterine bleeding is the overarching term used to describe any departure from normal menstruation or from a normal menstrual cycle pattern. The key characteristics are regularity, frequency, heaviness of flow and duration of flow (Fraser et al., 2011).

During use of the pill, the menstrual cycle generally has a shorter duration and reduced bleeding. In some cases, the menstrual bleeding may be missed or followed by spotting at mid-cycle. Dysmenorrhea is also generally reduced (Rosenberg et al., 2000; Sulak et al., 2002).

With current low-estrogen or natural estrogen formulations, menstruation may not appear between one blister pack and the next. Return of the spontaneous cycle on suspension of the pill does not always occur after 25–50 days. This circumstance advises against unjustified periodic suspension of oral contraception. Cycles of pill use may be modified flexibly, reducing the number of menstruations (interruption after 2–8 months). In these cases, the number of days with endometrial bleeding is reduced, while the number of episodes of metrorrhagia increases.

The pill can also be taken continuously for months or years. Thus, many users become amenorrheic due to the prevalent progestin effect (Kwiecien et al., 2003, Edelman et al., 2006).

COCs can be used to reduce menstrual flow, as well as providing contraception, regularization of the cycle and decrease of dysmenorrhea. The combination of E2V with DNG is the only contraceptive indicated for the treatment of abundant menstrual flow. Its particular quadriphasic regime and the powerful uterotropic activity of DNG explain its optimal control of the cycle and briefer suspension bleeding with improved hemoglobin levels. However, unlike other contraceptive pills, this drug is often associated with an absence of suspension bleeding (Micks and Jensen, 2011).

One of the best known and documented non-contraceptive benefits of the pill is the reduction or elimination of dysmenorrhea, the pain associated with menstruation involving physical discomfort and with considerable psychosocial effect. The pathogenesis of dysmenorrhea depends on the arachidonic acid cascade, which by producing prostaglandins increases uterine contraction and pain. Besides, the arachidonic acid pathway, another factor influencing uterine musculature is nitric oxide, production of which increases muscle relaxation. Estrogens may act as nitric oxide donors. Dysmenorrhea is associated with an increase in menstrual flow requiring more contractile activity for expulsion. Heavy menstrual bleeding facilitates retrograde reflux of blood in the peritoneum, where it has an algogenic effect. Menstrual symptoms (lassitude, generalized pain and alteration of intestinal transit) are also linked to inflammatory mediators in menstrual blood that reach various organs and systems. Oral contraceptives (especially pills with uterotropic progestins) are particularly effective against dysmenorrhea because they reduce the thickness and maturation of the endometrium, decreasing menstrual flow, inhibiting prostaglandin production and interfering with cyclo-oxygenase 2 enzyme action. The combination E2V/DNG substantially reduces the abundance of menstrual flow with respect to other COCs and is therefore particularly effective in treating dysmenorrhea (Schindler, 2013).

Premenstrual syndrome and premenstrual dysphoric disorder

Premenstrual syndrome (PMS) is defined as the recurrence of psychological and physical symptoms from the end of luteal phase to menstruation in the absence of any organic pathology (Ussher and Perz, 2013). The incidence of PMS varies from 3% to 30% (Sadler et al., 2004) and seems to particularly affect women between 20 and 35 years of age, and those who are obese do not exercise and have a low socioeconomic level. The type and intensity of symptoms is variable, some women being affected by hormonal changes more than others. When psychological symptoms interfere with everyday life and relationships, the syndrome is called premenstrual dysphoric disorder (PMDD). The frequency of PMDD ranges from 2% to 5%. Symptoms often overlap with those of other mood disorders: mood changes, irritability, depression, apathy and anhedonia. Although mood changes and irritability are common to bipolar disorder, the onset of symptoms in relation to the menstrual cycle is fundamental for distinguishing PMDD from other mood disorders (Epperson et al., 2012).

As the symptoms of PMS and PMDD are closely correlated with ovulatory cycles, they may be treated by inhibiting ovulation. One of the possible treatments for PMS is a COC. Although the standard 21/7 regime ensures contraception and suspension bleeding, mimicking a standard menstrual period, it may have side effects such as pelvic pain, headache, bloating and breast tension. This is due to the estrogen deficit during the 7 days of interruption (Sulak, 2005). A 24/4 regime, on the contrary, has a smaller hormone-free window with consequently fewer related symptoms (Sulak, 2005). Continuous use of the pill may be a valid option to control symptoms.

The choice of progestin is also relevant for PMS. Different studies have shown that pills containing DRSP are useful for attenuating PMS. Indeed, DRSP's anti-mineralcorticoid properties inhibit water retention, reducing correlated premenstrual symptoms. A recent review in the Cochrane database suggests that a pill containing 3 mg DRSP and 20 μg EE may be a valid solution for women with PMDD (Lopez et al., 2012).

Suspension symptoms

Fluctuations in hormone levels occurring during the menstrual cycle are known to be associated with significant physiological effects. In particular, the drop in estrogen levels before the menstrual period is associated with headache, mood changes, bloating, cramps, nausea and breast tension.

It is now well known that administration of oral contraceptives decreases the incidence and severity of symptoms associated with the menstrual cycle (Oinonen and Mazmanian, 2002). However, certain menstrual symptoms may continue as side effects of the pill and occur particularly in the week of interruption. These symptoms are a result of the HFI, i.e. lack of ovarian suppression and consequent hormonal fluctuation.

In a prospective observational study on 262 women taking a pill with a 21/7 regime, it was found that menstrual symptoms (headache, bloating, cramps, pelvic pain and breast tension) were more frequent in the HFI than in the 3 weeks in which the pill was taken, irrespective of whether the patient was a new or a long-term user (Sulak *et al.*, 2000). In a recent study, our team demonstrated a significant reduction in catamenial headache in a group of women treated with EE 20 μg + DRS 3 mg with a 24/4 regime than in a group treated with a 21/7 regime of the same hormones (De Leo *et al.*, 2011).

In an attempt to reduce symptoms associated with the HFI, the FDA has approved different administration regimes for contraceptives: 24/4, 84/7 and continuous for 365 days. The efficacy of these new regimes is practically identical to the traditional 21/7 regime, with the advantage of having a smaller HFI. Extended regimes have been associated with high patient satisfaction due to decreased bleeding and consequent improvement in menstrual symptoms (Cremer *et al.*, 2010). These regimes may be used by any women and the type of regime can be determined on the basis of patient preference and experience with different regimes. In general, younger women tend to prefer four cycles per year, while adult women prefer to completely eliminate menstrual bleeding.

In any type of extended regime, breakthrough bleeding or spotting may occur and women should be informed of this fact. If bleeding should become unacceptable to the patient, a suspension of 3 days is advisable (Sulak, 2008).

A review conducted in 2006 (Edelman *et al.*, 2006) compared the contraceptive efficacy, satisfaction, bleeding and menstrual symptoms of two contraceptive regimes: 21/7 versus 28/0. No significant differences were found in bleeding or spotting; however, symptoms during HFI were much fewer in the group taking the contraceptive continuously.

Comparisons of different formulations indicate that pills containing DRSP meet better compliance regarding HFI symptoms. The use of a pill containing 3 mg DRSP and 20 μg EE was in fact associated with a low incidence of side effects typical of low-dose contraceptives, with good control of HFI symptoms.

Acne and hirsutism

Hyperandrogenism may manifest with hirsutism, acne and alopecia. Hirsutism consists of the presence of terminal hair on the face and/or body in an androgynous pattern and is the most common symptom in women with PCOS, present in ~60% of patients.

Acne occurs in 12–14% of PCOS patients, although the prevalence varies with race. This condition is characterized by the formation of comedones, consisting of accumulations of sebum and discarded epithelial cells that are colonized by the bacterium *Propionibacterium acnes*. Inflammation of these comedones may lead to the development of papules, pustules and nodules.

Alopecia consists of hair thinning due to progressive hair loss. Androgenic alopecia is often accompanied by seborrhea and dandruff. Hair loss in PCOS usually involves thinning at the vertex with maintenance of the frontal hairline (Deplewski and Rosenfield, 2000).

Treatment concentrates on reducing androgen production, reducing circulating free androgens and limiting androgen activity in pilosebaceous units. Since the treatment of hirsutism prevents or slows the formation of new growth of terminal hair and does not affect existing hair follicles, treatment must last at least 6 months before the first clinical results become evident.

Inhibition of ovarian steroid production and reduction of circulating free steroids may be obtained by administration of estrogens and progestins in the form of oral contraceptives. These also reduce adrenal androgen production (De Leo *et al.*, 2007). Moreover, combinations of estrogens and progestins inhibit 5α-reductase activity in androgen peripheral target structures.

If COCs do not work, it is possible to associate anti-androgens with contraceptives to reinforce their effect (Fig. 2). Anti-androgens are compounds that interfere with androgens, compete with them for receptors or reduce peripheral 5α-reductase activity. They include cyproterone acetate (CPA), a powerful progestin that may be administered with EE as a contraceptive pill: EE 35 μg + CPA 2 mg 21/7 regime or 12.5, 25 or 50 mg CPA + 20–30 μg EE with a reverse sequential regime.

Another powerful anti-androgen is flutamide that acts by blocking androgen receptors (De Leo *et al.*, 2000). This drug significantly reduces hyperandrogenemia, hirsutism and acne, with negligible effects on the menstrual cycle and ovulation. However, it is not considered completely safe because of its teratogenic and hepatotoxic effects. It is therefore necessary to invite patients to sign informed consent before taking flutamide, or to practice contraception during administration of the drug.

Finasteride acts as an anti-androgen, inhibiting 5α-reductase intracellular enzyme activity. It is particularly useful for treating moderate hirsutism and androgenic alopecia, less suitable for acne and seborrhea. Because it is teratogenic, a contraceptive method should be practiced during administration.

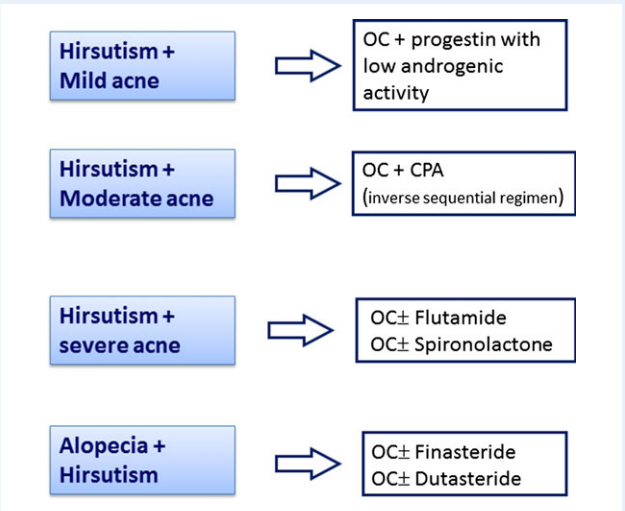

Figure 2 Treatment of hirsutism with oral contraceptives (OCs) and widely used anti-androgens.

Finally, spironolactone, known as a diuretic drug, acts through its aldosterone antagonist activity. Besides competing for androgen receptors, it inhibits ovarian and adrenal biosynthesis as well as 5α-reductase activity. The therapeutic regime envisages one or two doses of 50–200 mg/day for 3–12 months, alone or associated with a COC to avoid induction of metrorrhagia or polymenorrhea as side effects.

PCOS

Administration of COCs in women with PCOS has proven useful because it reduces acne and hirsutism, restores cyclic regularity and improves bone density. The key mechanism of action of oral contraceptives is inhibition of folliculogenesis by suppression of pituitary secretion of gonadotrophins (Yildiz, 2008).

The ideal contraceptive for women with PCOS should limit antral follicle development and reduce the quantity of androgens; oppose the action of androgens on pilosebaceous units at peripheral level; restore the normal balance between estrogens and progestin in the endometrium, ensuring good control of the menstrual cycle.

The most indicated contraceptive is therefore one containing 30 μg EE, which is the most effective in controlling the cycle and reducing ovarian androgen production in all phases of the cycle, including the HFI, by virtue of strong ovarian suppression that reduces the quantity of antral follicles. Pills with 30 μg EE also effectively inhibit adrenal steroidogenesis (De Leo *et al.*, 2007, 2009) and stimulate liver production of SHBG more than those with lower doses of EE. SHBG binds and transports T in the bloodstream. The active fraction of T (and all sex steroids) is however the free fraction (fT), i.e. that not transported by SHBG. Consequently, greater production of SHBG causes a larger bound fraction of T (inactive) and therefore a smaller fT (active), giving the pill a greater anti-androgenic effect (De Leo *et al.*, 2009).

Regarding the type of progestin, the increase in SHBG occurs mainly with third generation oral contraceptives containing 30 μg EE and GSD or DSG, which reduce the fraction of fT by an average of 40–50% (World contraceptive use, 2007). Better efficacy has been observed with the combination of 30 μg EE and DRSP due to inhibition of adrenal androgens (De Leo *et al.*, 2007). Second generation pills containing 30 μg EE and LNG stimulate SHBG production less because the androgenic activity of the progestin opposes the action of the estrogen (De Leo *et al.*, 2009). Exceptions among second generation pills are the triphasic COC with LNG, among third generation are biphasic pills with 30–40 μg EE and 25–125 μg DSG and the monophasic pill with 35 μg EE and 2 μg CPA. These pills have a hormonal balance clearly in favor of estrogens and induce a significant increase in SHBG and a consequent reduction in fT (De Leo *et al.*, 2009). These actions are particularly evident with the biphasic EE/DSG pill and especially with the monophasic EE/CPA formulation, which reduce fT by 55–60% and 65–66%, respectively, via a sharp increase in SHBG (De Leo *et al.*, 2009).

CPA, DNG, DRSP and CMA are progestins with anti-androgenic activity. They act largely by blocking androgen receptors on target organs, but also by reducing cutaneous activity of 5α-reductase, the enzyme responsible for converting T to 5α-dihydrotestosterone. A review of nine RCTs with CPA administered at variable doses between 2 mg (Diane/Dianette®) and 25–100 mg showed that all doses brought about a significant improvement in hirsutism with respect to placebo (Vrbikova and Cibula, 2005).

Other studies have assessed the efficacy of oral contraceptives containing DRSP in treating hirsutism, finding a 50% reduction in clinical manifestations of hyperandrogenism after 6–12 months of therapy, a significant reduction in circulating androgens and a significant increase in SHBG (Yildiz, 2008).

A recent study compared four different pills and evaluated concentrations of SHBG and androgens. The results showed that formulations containing 30 μg EE and DRSP, CMA, DSG or GSD elicited a sharp increase in serum levels of SHBG in all women, especially in those treated with DRSP and CMA. Free androgen, T, total testosterone and androstenedione concentrations decreased by 40–60% in all groups and most sharply in women treated with CMA and DRSP. Androgen plasma levels are correlated with concentration of SHBG, which binds to androgens. The significant increase in SHBG concentrations induced by these formulations was certainly determinant in reducing androgen concentrations (De Leo *et al.*, 2010).

When prescribing COCs for women with PCOS, it is however necessary to recall that they can have a series of negative metabolic effects, they increase triglyceride and total cholesterol levels, aggravate insulin resistance and cause weight gain (Nader and Diamanti-Kandarakis, 2007). These effects vary in strength with the type of pill used and the metabolic and anthropometric characteristics of the woman. Indeed, the different effects of pills on carbohydrate metabolism in women with PCOS may also be determined by the woman's grade of androgenicity, family history of diabetes and anthropometric or environmental differences that may affect the action of insulin and the natural history of PCOS (Nader and Diamanti-Kandarakis, 2007).

The beneficial effects of metformin, an insulin-sensitizing drug, on cardiovascular risk factors and insulin sensitivity have led many authors to propose associating metformin with COCs in insulin-resistant PCOS patients. Compared to the pill alone, this combination has been found to cause a more significant reduction in androgen levels, without inducing significant differences in BMI, waist/hip ratio or glycemia/insulin ratio (Elter *et al.*, 2002). More recent results confirm these findings, stressing that administration of metformin with oral contraceptives causes a sharper reduction in androgens than the pill alone, without aggravating insulin resistance (Elter *et al.*, 2002).

Oral contraceptives and assisted reproductive techniques

Synchronization of the menstrual cycle with protocols for assisted reproductive technology is a key organizational consideration for fertility clinics when planning cycles of ovulation induction. Synchronization can be achieved in several ways, all of which involve inhibition of ovulation via the hypothalamic–pituitary–ovarian axis. Here, we address the use of oral contraceptives to facilitate synchronization. In clinical practice (unpublished data), the term synchronization means that a cohort of women undergoing controlled ovarian stimulation for oocyte retrieval has to menstruate synchronously, by taking COCs for periods different from those normally used for birth control (Garcia-Velasco and Fatemi, 2015). In this way, oocyte retrieval can be performed on a given day.

In choosing a suitable medication to achieve synchronization, specific attention must be paid to the estrogen dose and the type of progestin. It is important to consider the type of menstruation, as optimal preparation of the endometrium is essential to increase the chance of implantation. Formulations should have an optimal balance between the estrogen and progestin components, such as 20–30 μg

EE combined with a progestin, which gives distinct uterine characteristics, so that when endometrial shedding occurs any small alterations in the endometrial mucosa can be eliminated, resulting in complete homogeneity of the uterine cavity (Griesinger *et al.*, 2008).

Natural estradiol may play a role, however, the estrophasic formulation of these compounds may limit their use in this field (Guivarc'h-Levêque *et al.*, 2011). The progestin, DNG, shows promise and its use alone or in combination with EE has been found to produce a perfectly regular uterine cavity prior to ovarian stimulation.

Side effects of oral contraceptives

Reduction of the dose of EE to 20 μg has a small effect on control of the cycle, whereas reduction of the dose to 15 μg has greater repercussions (Gallo *et al.*, 2013). In one control study comparing a formulation containing 20 μg EE and DSG and another with 15 μg EE and DSG spotting was observed in 14% and 11% of cycles, respectively (Poindexter, 2001). Onset of amenorrhea was however higher with the 15 μg formulation than with the higher dose (Fruzzetti *et al.*, 2001; Poindexter, 2001). Reducing EE is therefore associated with a low incidence of side effects. Breast tension, headache and nausea in particular are much less frequent in women taking very low-dose formulations (Fig. 3A,B).

Weight gain may be a major discomfort associated with COC. Some studies report that 20–30% of women put on weight while taking COC (Christin-Maitre, 2013), while others failed to find any significant increase in weight (Gallo *et al.*, 2014). These studies had limitations, such as the use of different COCs and assessment of women in different age groups (Flegal and Troiano, 2000; Gallo *et al.*, 2004).

A recent review in the Cochrane database did not reveal substantial weight differences between the different combinations of contraceptives used. Also, discontinuance of pill use due to weight gain was not significantly different in the various groups (Gallo *et al.*, 2011). Thus, available evidence is insufficient to say whether hormonal contraceptives are associated with weight gain, although it seems unlikely that they have a specific effect on this symptom (The ESHRE Capri Workshop Group, 2006; Nelson *et al.*, 2007; Gallo *et al.*, 2011).

The natural estrogen in more recent formulations offers a potential advantage regarding metabolic aspects, besides having fewer general side effects. Different studies of the E2V/DNG formulation generally show that it is well tolerated, out of 1377 women taking it, only 0.9% interrupted the study because of weight gain (Palacios *et al.*, 2010). Nelson's team showed that in a sample of 2266 women taking this pill, only 1.5% complained of weight gain among the side effects (Nelson *et al.*, 2009).

Another well-tolerated formulation contains EE and DRSP. The progestin has a very similar formula to natural progesterone as well as an anti-mineralcorticoid effect, by virtue of which it seems to improve fluid retention in healthy women after only 3 months of treatment (Elger *et al.*, 2003). In women with physical symptoms of water retention, such as breast tension, swelling of the extremities and abdominal heaviness, DRSP proved to reduce total and extracellular water retention (Fruzzetti *et al.*, 2007).

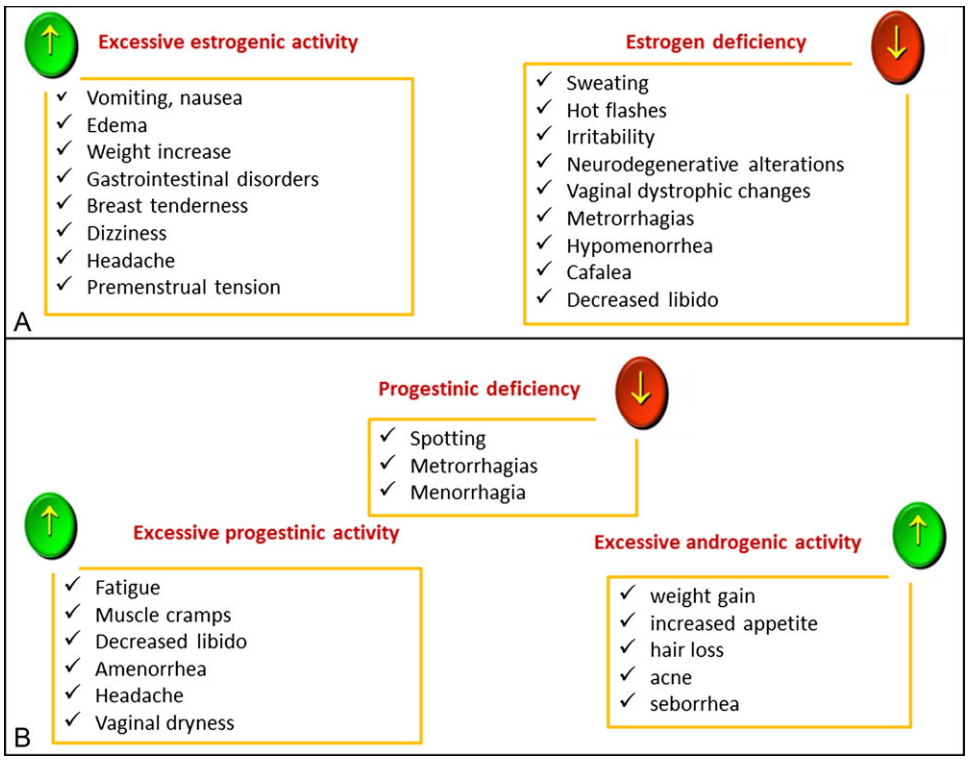

Figure 3 Side effects related to hormone dose of OCs. (A) Side effects related to estrogen dose. (B) Side effects related to progestin profile.

Table II Oral contraceptives and body weight in reproductive life.

	Adolescence	Fertile age	Perimenopause
 **Normal weight** **BMI: 18.5-24.9 Kg/m²**	EE 15-20 mcg Neutral Progestin	EE 20-30 mcg Neutral Progestin	EE 15-20 mcg or NE Neutral Progestin Or antiandrogenic
 **Overweight** **BMI: >25 Kg/m²**	EE 15-20 mcg or NE Antiandrogenic progestin	EE 15-20 mcg or NE Antiandrogenic progestin	EE 15-20 mcg or NE Antiandrogenic progestin
 **Underweight** **BMI: <18.5 Kg/m²**	EE ≥ 30 mcg Neutral progestin or mild antiandrogenic	EE > 30 mcg Neutral progestin or mild antiandrogenic	EE 15-20 mcg or NE Neutral progestin

In the various phases of female reproductive life, the best combination of oral contraceptive should be chosen on the basis of body weight (EE, ethinylestradiol; NE, natural estradiol). Neutral progestins are deso/etonogestrel, GSD, medroxyprogesterone acetate and norelgestromin. Anti-androgenic progestins are clormadinone, cyprterone acetate, DNG and drospirenone.

Data on the effects of contraceptives containing only progestins, such as medroxyprogesterone acetate, show a weight increase of 3–6 kg in 36 months of treatment, although the increase varied widely from woman to woman (Clark *et al.*, 2005; Berenson and Rahman, 2009). It was also demonstrated that women risked a weight gain of more than 5% in the first 6 months of treatment (two injections) (Le *et al.*, 2009).

Finally, the effect that obesity may have on pharmacokinetics is relatively unknown. It has been demonstrated that in women with a BMI > 30 kg/m^2, the half-life of LNG is significantly longer and correlated with a lower serum peak and slower attainment of steady state than in women of normal weight (BMI < 25 kg/m^2) on the same hormonal therapy with 20 μg EE and 100 μg LNG (SFP Guideline, 2009).

According to the WHO *Medical eligibility criteria for contraceptive use* (5th ed., 2015), contraceptive methods can be used in women with BMI > 30 kg/m^2 with careful monitoring (WHO, 2015). If BMI > 30 kg/m^2 is associated with other risk factors for VTE, the woman is no longer eligible for COC use (WHO, 2015).

Conclusions

Despite much progress in the field of contraception, there are still challenges for research, such as reduction of the number of unwanted pregnancies. According to WHO estimates, only 30–40% of the 182 million pregnancies reported every year in developing countries are intentional and only 40–50% of the 23 million pregnancies occurring in industrialized countries are wanted (WHO, 2007). Many unwanted pregnancies occur in women who do not use contraceptives. Discontinuation of the pill and switching to other methods is common, often due to side effects. It is therefore fundamental to personalize the choice of contraceptive as much as possible and find new approaches that improve compliance and reduce fears about taking hormonal contraceptives (Table 2).

Another challenge of no less importance is improvement of the risk/benefit ratio, by increasing benefits and reducing risks, especially oncological and cardiovascular ones. A COC protects significantly against ovarian and endometrial cancer (Crame, 2012). Some studies have also reported a reduced risk of colorectal cancer among pill users (Stageman *et al.*, 2013). On the contrary, the pill may be associated with increased risk of breast cancer, although the size and nature of this risk are unclear. Another unsolved problem regards the relationship between cervical cancer and oral contraceptive use. Long-term pill use may be a cofactor contributing to increased risk of cervical cancer in women positive for HPV (Moreno *et al.*, 2002). However, the public health implications of oral contraceptive use for cervical cancer are limited. In any case, such implications are greater in middle-income and low-income countries, as well as in central and eastern Europe and Latin America, where cervical cancer screening and control remain inadequate (Asiaf *et al.*, 2014).

Regarding cardiovascular risk, the guidelines of the Centre for Disease Control and Prevention (CDC), USA, recommend that women with specific risks, such as a history of VTE, smoking and age older than 35 years or migraine with aura, should not use COC because the risks may exceed the benefits (Farr *et al.*, 2010). Other methods such as intrauterine devices or pills containing progestin alone should be considered for these women.

Future challenges also regard personalization, matching each woman with the contraceptive that best meets her needs in terms of efficacy and protection of reproductive health. New formulations give specialists a range of choice for prescribing the best tolerated contraceptive in every case, thus reducing cases of discontinuance.

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Conflict of interest

We declare no conflict of interest.

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