Chapter

Family Planning

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Abstract

The contraception (the term is the fusion between "contra", against, and conception): includes all methods that prevent conception. According to the physiology of human reproduction, the contraceptive methods can prevent the fecundation by hindering the female and male gametes meeting. In these mechanisms we include: The abstinence by sexual intercourse around the ovulatory phase of the cycle; The use of barriers that block contact between male gametes and female genitalia; The use of methods impeding the ascent of spermatozoa through the female genital tracts (intrauterine devices). The prevention of the oocyte from being available (hormonal contraceptives or oral contraceptives, OC). In this category there is the availability of short acting reversible contraception (SARC) (pill, vaginal ring, patch), and the long acting reversible contraception (LARC) (progestin implants). The ideal contraceptive method has to respond to four fundamental principles: efficacy, safety, reversibility, tolerability. The authors will discuss all the above contraceptive methods with the evaluation of indications and contraindications to each method.

Keywords: hormonal contraceptives , short acting reversible contraception (SARC), long acting reversible contraception (LARC), intrauterine devices , male and female condom

1. Introduction

The family planning identifies the mechanisms through which a couple organizes the time for the conception and in many cases, especially for economic reasons, it is necessary to avoid the pregnancy for a short or long time. The contraception (the term is the fusion between "contra", against, and conception): includes all methods that prevent conception. The history of humanity is marked by the search for contraceptive methods that have found an important milestone in the development of strategies that hinder the meeting of male and female gametes (condom, hood, diaphragm). However, the preferred contraceptive method has become the one that prevent the availability of the female gamete, because in this way the couple has the

advantage to plan conception at the most suitable time, without giving up sexuality. According to the physiology of human reproduction, the contraceptive methods can prevent the fecundation by hindering the female and male gametes meeting. In these mechanisms we include:

- The abstinence by sexual intercourse around the ovulatory phase of the cycle;
- The use of barriers that block contact between male gametes and female genitalia;
- The use of methods impeding the ascent of spermatozoa through the female genital tracts (intrauterine devices or IUD);
- The prevention of the oocyte from being available (hormonal contraceptives or oral contraceptives, OC). In this category there is the availability of short acting reversible contraception (SARC) (pill, vaginal ring, patch), and the long acting reversible contraception (LARC) (progestin implants).

The ideal contraceptive method has to respond to four fundamental principles: efficacy, safety, reversibility, tolerability.

2. The abstinence by sexual intercourse around the ovulatory phase of the cycle

For this method it is necessary to identify the time period of the ovulation through the following mechanisms: a. the calendar method that identifies ovulation basing on the interval between one menstruation and the next, considering the post-ovulatory phase lasting 14 days; b. the evaluation of cervical mucus, abundant and racy in the ovulatory period and with increased thickness in the postovulatory period; c. the assessment of the basal temperature, which increases during the luteal phase (after the ovulation) in relationship to the increase of progesterone secretion and has a reduction near the ovulatory phase; d. the identification of the ovulatory LH peak through monoclonal antibodies capable of binding LH molecules in the urine. All these methods do not interfere on the safety and on reversibility, but they are characterized by both a bad tolerability and efficacy [1]. With a perfect (but very difficult) use of these methods, the contraceptive efficacy is included in a range between 0.4–5% of unwanted pregnancies within a year of use [2].

3. The use of barriers that block contact between male gametes and female genitalia

3.1 The male condom

The male condom is a popular and known method of contraception. However, not everyone knows the differences in their composition. Latex condom protects against unwanted pregnancy and sexually transmitted diseases (STDs), including HIV and Herpes virus, when used correctly [3]. Other materials used in the male

condom are polyisoprene, polyurethane and the material derived from the intestine of lamb. Faced with a low risk of slipping and breaking, due to its high elasticity, the polyisoprene-based condom is burdened by poor sensitivity between the partners [4]. The one based on polyurethane is the thinnest and while ensuring high sensitivity because it is thinner than the same latex condom, it is burdened by the risk of slipping and breaking [5]. The condom obtained from the intestine of lamb does not protect against STDs [6]. The contraceptive efficacy of this method, calculated as percent of unwanted pregnancies within a year of use is 18% for typical use and 2% for perfect use [2].

3.2 The female condom

The female condom is less used and known than the male one. It consists of a thin latex sheath that adapts to the vagina. In practice, the closed part with a ring is inserted into the vagina, while the open part, with another ring, remains outside the vagina. It can be inserted 8 hours before the intercourse. It protects against STDs, but its insertion is difficult and, moreover, it can be disadvantageous in sexual intercourse for both partners [7]. The contraceptive efficacy of this method, calculated as percent of unwanted pregnancies within a year of use is 21% for typical use and 5% for perfect use [2].

3.3 The vaginal diaphragm

The diaphragm is a kind of cup-shaped lid, made of latex or silicone. Its placement in the vagina is facilitated by a flexible structure at the edges of the diaphragm. It should be positioned to cover the cervix entirely. Its size should be evaluated by a gynecologist based on the size of each individual woman's cervix [8]. It is used in combination with a spermicide, so it offers a greater contraceptive treatment than the male condom alone. After intercourse, it must remain in place for at least 6 hours, but no longer than 24 hours [8]. The positioning period correlates with the risk of urinary infections and urinary stagnation. After careful hygiene, it can be used for more intercourses as opposed to male and female condoms [8]. The contraceptive efficacy of this method, calculated as percent of unwanted pregnancies within a year of use is 12% for typical use and 6% for perfect use [2].

3.4 The cervical cap

The cervical cap is dome-shaped and is made of silicone. It adapts to the cervix, held in place by the vaginal walls [9]. Thanks to a cord it is possible to easily remove it. Like the diaphragm, it must be used with spermicides. Also inserted 42 hours before sexual intercourse, it should not be removed before six hours after sexual intercourse, but no later than 24 hours [9]. Compared to the diaphragm it has a lower risk of urinary infections, but it is contraindicated in women with neoplastic or preneoplastic pathologies of the uterine cervix. It is not suitable for subjects with anatomical anomalies of the uterine cervix [9]. The contraceptive efficacy of this method, calculated as percent of unwanted pregnancies within a year of use is 24% for typical use and 20% for perfect use, in pluriparous women, whereas it is better in nulliparous women (12% for typical use, 9% for perfect use) [2].

3.5 The spermicides

The spermicides are substances based on nonoxynol-9. The mechanism through which they exert the contraception is the destruction of spermatozoa. They are available in different forms: gel, cream, vaginal film, sponges. They have to be applied at least 15 hours before the sexual intercourse. Irritation on both the vagina and the penis are often reported [10].The efficacy in reducing the risk of STDs has recently been discussed with not encouraging results [11]. The contraceptive efficacy of this method, calculated as percent of unwanted pregnancies within a year of use is 28% for typical use and 18% for perfect use [2].

4. The use of methods impeding the ascent of spermatozoa through the female genital tracts

Intrauterine devices (IUDs) are defined LARC in relationship to the long-lasting contraceptive effect (years), thus they have the advantage of the absence of daily intake of OC. The contraindications to their use are very few. Although poorly used in Europe (10% of women using contraception), IUDs have widespread use in Asia (40% of women). Compared to copper IUDs (Cu-IUDs), which act by exerting a spermicidal effect [12, 13], levonorgestrel-intrauterine system (LNG-IUS) prevents sperm passing through the uterine cervix because it thickens the cervical mucus [12]. Unlike the Cu-IUD, LNG-IUS does not increase the number of endometrial leukocytes, and exerts a suppressive effect on the endometrium, decreasing its thickness in relation to local LNG release [13]. This mechanism of LNG-IUS has been reported to be favorable to reducing menstrual flow and dysmenorrhea [14, 15], whereas in Cu-IUD users increased menstrual flow and dysmenorrhea have been reported [16]. The first LNG-IUS is a 32x32 mm T-shaped device, containing a reserve of 52 mg of LNG (release of approximately 18 mcg/day), approved for a duration of action of 5 years [17]. Due to its size, it is intended for use in women who have already given birth, with a cervical canal compliant with introduction. The need to have a similar contraceptive to offer to the adolescents and the nulliparous women has led to the development of a smaller IUS (30x28 mm) and with LNG content of only 13.5 mg, which induces a very reduced passage of the hormone in the bloodstream (approximately 160 pg./mL in the first 7 days after placement, reduced to up to 60 pg./mL after 3 years), with fewer systemic side effects than the previous one. The applicator (diameter of 3.8 mm compared to 4.75 mm of the previous one) also favors use in adolescents and nulliparous [18–20]. The contraceptive duration is 3 years. Recently, an IUS of the same size has been proposed, but with a higher content of LNG (19.5 mg), so as to allow the contraceptive effect for 5 years [21]. There are very few contraindications to LNG-IUDs [22]. Among these: the presence of antiphospholipid antibodies; the history of breast cancer [22]. In these cases, it is possible to opt for a Cu-IUD [22], or an irreversible contraception, such as female or male sterilization. The contraceptive efficacy of Cu-IUD, calculated as percent of unwanted pregnancies within a year of use is 0.8% for typical use and 0.2% for perfect use [2]. The contraceptive efficacy of LNG-IUS, calculated as percent of unwanted pregnancies within a year of use is 0.2% for typical use and 0.2% for perfect use [2].

5. The prevention of the oocyte from being available (hormonal contraceptives or oral contraceptives, OC). It includes also vaginal ring, and patches as SARC and progestin implant as LARC

5.1 Introduction

In modern society, in which the self-determination of the individual and free will have acquired central importance, the possibility of an effective contraception has been a great achievement for women. In fact, making effective contraception means being able to freely choose when to plan the pregnancy and the creation of a family and, consequently, allow the woman to dedicate her time to what she deems most appropriate for her life and her own growth. It is not a coincidence that, starting from the 1970s, when OC began to spread especially in the United States, the prevalence of women with degrees in various disciplines had a peak of growth [23]. Studies of economics applied to medicine illustrate how the adoption of birth control improves economic growth in developing countries, because with fewer dependent children and the ability to plan pregnancy, women can participate more actively to the workforce and increase the productivity of the country [24]. Moreover, the family planning, implemented thanks to effective contraception, can also lead to other demonstrated social benefits, such as an improvement in maternal BMI (body mass index) (linked to a greater temporal distance between one pregnancy and the next), a reduction of the infant mortality, a higher level of child education and schooling, as well as a better overall health status of offspring [24].

It has been estimated that in developing countries the use of OC has led to a reduction in maternal mortality by up to 40%, thanks to the prevention of unwanted pregnancies that would result in clandestine or unsafe abortions, and avoiding pregnancy in high-risk or multiparous women, penalized by higher mortality [25].

Finally, adolescents are among the categories most at risk of unwanted pregnancy and among those most at risk of adverse outcomes if the pregnancy is continued, such as premature birth, low fetal birth weight, greater morbidity and neonatal mortality [26]. Nonetheless, adolescent pregnancy, as well as the use of voluntary abortion, can have significant psychological consequences in young women, with a greater risk of mood disorders in subsequent years [27].

In fact, the advent of OC can be considered a great achievement not only for the affirmation of woman's autonomy, but also for the approval of the whole society.

5.2 History of contraception and evolution of contraceptives

In the history, the first evidence of an attempt at contraception dates back to ancient Egypt, where some papyri describe the use of natural products, such as honey or acacia leaves, to be inserted into the vagina close to intercourse. Ancient Greco-Roman sources speak of herbal products that could cause sterility or induce abortion. Several descriptions of rudimentary condoms appear in history, among which the lambskin condom proposed by Casanova in the eighteenth century as a method of preventing pregnancy and sexually transmitted diseases is certainly characteristic [28]. However, only in the twentieth century was there a turning point in contraception, both for the spread of the need for birth control in the population and for the discovery of effective contraceptive methods.

Faced with a strong social need, Margaret Sanger, an American nurse and writer, pioneer of reproductive and women's rights, opened the first clinic for family planning in Brooklyn in 1916. Shortly after, in 1921, the British scientist Marie Stopes founded one in the UK [28]. But advances in medical science made their contribution to contraception only in the mid-twentieth century, when the first molecules with progestin activity were synthesized, thanks to the work of scientists such as G. Pincus, M.C. Chang and J. Rock, who led to the discovery that these molecules were capable of inhibiting ovulation. Thus, the FDA approved Enovid in 1957, a combination of synthetic estrogen-progestins (mestranol 150 mcg and noretinodrel 9.5 mg), first as a therapy for the control of menstrual disorders, and then, in 1960, as a contraceptive method [29]. In Italy, only in 1971 the contraceptive "pill" was accepted by a sentence of the Constitutional Court as a method of birth control.

Since the invention of the first contraceptive pill, in just over 60 years, advances in pharmacology have now led to numerous OC solutions, with different formulations, methods of administration, short and long-term duration of action, as well as different active molecules, which adapt to the multiple needs and preferences of the female audience. As said previously, the ideal characteristics of a contraceptive method are: its effectiveness, that is the ability to achieve the goal of preventing pregnancy; its reversibility, or the remission of the effect after the suspension of the method; the safety for health and tolerability, because a product that improves a woman's quality of life cannot cause damage to health or cause side effects or discomfort in the intake, which would affect its use. Considering this premise, in the evolution of OC, on the one hand there have been progress in the name of safety, while guaranteeing contraceptive efficacy, characterized by a reduction in the dosage of the estrogenic component (the synthetic estrogen ethinyl estradiol, EE) and from the discovery of new progestogen molecules that have a better metabolic and pharmacodynamic profile on steroid hormone receptors. On the other hand, the same has been done to improve the acceptance by the woman of the contraceptive method, and therefore the tolerability itself, with the creation of different regimens of administration in addition to the oral one (transdermal, transvaginal, subcutaneous, intrauterine), short or long acting [28].

The main health risk in Ref. to OC is that of thromboembolic events, especially venous thromboembolic events (VTE) and secondarily arterial thromboembolic events (ATE), since estrogens have a general effect of hyper-coagulability. In fact, they increase the synthesis in the liver and the biological activity of pro-coagulant proteins such as fibrinogen, prothrombin and other coagulation factors, while reducing the synthesis and activity of anticoagulant factors such as the S protein [30]. The OC, therefore, has always been associated with an increased risk of VTE, which varies according to the dose of estrogen and the associated progestogen. It is very conditioned by additional individual risk factors such as age, weight, the habit smoking and other condition, such as migraine with aura [31]. The reduction of the EE dosage in OC, from more than 50 mcg used in the old OC combinations to the currently used doses of 15–30 mcg, has allowed to reduce the thromboembolic risk by about half, but without completely eliminating it [32]. The associated progestin compound is capable of modulating the overall biological estrogenic effect of the OC and the effect on the blood coagulation, in relationship to its ability to act also on other steroid receptors, such as androgen receptors [33, 34].

One of the most important recent population studies, which assessed the thromboembolic risk associated with the use of OCs over 10 years of observation, reported an absolute risk of VTE in women not using OC of 3 cases out

of 10.000/year; the risk increases to 6.3 cases per 10.000/year in women using OC. It decreases after the first year of use; but with the same EE dose and length of use, the compounds that have the lowest risk profile are those containing LNG as progestin, compared to the other OC with progestin such as desogestrel (DSG), gestodene (GSD), drospirenone (DRSP) and cyproterone acetate (CPA), which demonstrated a higher relative risk than the EE/LNG combination [32]. For this reason, to date, the OC with EE + LNG is the one considered as the referent in clinical studies that evaluate the thromboembolic risk associated with OC. In any case, it must be considered that the risk of VTE events associated with pregnancy is higher, equal to 17 cases out of 10.000 pregnancies [35].

The progestin component is the one that has undergone major changes in the evolution of OC (**Table 1**). Thanks to the action on the progesterone receptors at a central level, the progestin compound guarantees the inhibition of ovulation and the contraceptive effect. On the other hand, the ability of the progestin to bind and activate other receptors for steroid hormones, such as those for androgens, glucocorticoids and mineralocorticoids, affects the metabolic safety profile and the appearance of unpleasant side effects [34].

The first progestogen molecules used in OC were testosterone derivatives, which maintained the androgenic activity and could cause manifestations such as acne, seborrhea and hirsutism and, mainly, negative effects on glucidic and insulin metabolisms. Advances in pharmacology have subsequently created compounds with greater selectivity and potency on progesterone receptors and more similar to progesterone itself. Thus, modern progestin compounds used in OC, such as DRSP or dienogest (DNG), are characterized by this selectivity, plus the absence of activation of glucocorticoid and androgen receptors, but rather a mild antiandrogenic activity, which may be clinically useful for managing some symptoms complained of by women [34, 36].

Progestinic compounds	**AE**	**EST**	**AND**	**AA**	**GLU**	**AM**
Progesterone	+	—	—	+/−	+	+
Chlormadinone acetate	+	—	—	+	+	—
Ciproterone acetate	+	—	—	+++	+	—
Dienogest	+	—	—	++	—	—
Drospirenone	+	—	—	+	—	+
Desogestrel/Etonorgestrel	+	—	+	—	+/−	—
Gestodene	+	—	+	—	+/−	+
Levonorgestrel	+	—	+	—	—	—
Medrossiprogesterone acetate	+	—	+/−	—	+	—
Nomegestrolo acetate	+	—	—	+	—	—
Noretisterone	+	+	+	—	—	—
Norelgestromin	+	—	+	—	—	—

AE: antiestrogenic, EST: estrogenic, AND: androgenic, AA: antiandrogenic, GLU: glucocorticoid, AM: antimineralcorticoid.

Table 1.
Biological activities of progestinic compounds.

5.2.1 Contraception with "natural estrogen"

EE has remained a pillar in the OC for about 50 years, although the doses used have been progressively reduced. The use for contraception of an estrogen molecule analogous to 17β estradiol (E2) synthesized by the human body has always been limited by the lower power of E2 compared to EE on estrogen receptors and, consequently, by the inability to stabilize the endometrium and subsequent bleeding [37]. Only after the discovery of progestin compounds with a high power on progesterone receptors and a high antiproliferative activity on the endometrium, it was possible to create an OC with E2, which would allow good control of uterine bleeding. The potential metabolic advantages of using E2 in place of EE are many: the lower activation of estrogen receptors in the liver results in a lower stimulation of the synthesis of multiple proteins, including those involved in the mechanisms of coagulation, the sex hormone binding globulin (SHBG), angiotensinogen, or some lipoproteins [38].

The lower influence on the renin-angiotensin-aldosterone system (RAAS) determines a lower influence of E2 on blood pressure, the slight increase of which is a possible side effect of EE-based OCs, due to a mild sodium-retentive effect. The clinical evidence, in this regard, does not report a modification of the blood pressure values measured during treatment with OC based on E2 [39, 40]. Furthermore, in the evaluation of cardiovascular risk associated with OC, many studies have evaluated the dosage of coagulation markers (fibrinogen, D-dimer, protein S), of lipoproteins and triglycerides, of glucose metabolism, and their modifications during OC treatment. Despite being a laboratory-only evaluation, E2-based OCs induce only minimal or no modification of these parameters, with effects that in some cases have been shown to be significantly better than OCs with EE/LNG [33, 41, 42]. In light of these data, in theory, OCs containing E2 should have a better cardio-vascular and metabolic safety profile. However, the evidence comes mainly from studies evaluating lower cardio-metabolic outcomes (blood pressure, laboratory values) and not the effects of real clinical interest such as VTE or ATE. The young age of E2 OCs, compared to more than 60 years of experience with EE, requires time to evaluate the real impact of this promising new contraception with large-scale surveillance studies.

The only "real life" population study, carried out on routine clinical practice, which investigated the safety profile from the cardiovascular point of view of OCs containing E2 valerate (EV) (specifically the first commercialized combination of EV/DNG), is the INAS-SCORE study (The International Active Surveillance study "Safety of Contraceptives: Role of Estrogens"), published in 2016 [43]. As a prospective, non-interventional cohort study, conducted in the USA and in 7 different European countries, the INAS-SCORE study recruited more than 50.000 women with a new OC prescription, following them for a follow-up period of 2 to 5 and a half years, for a total of more than 100.000 women per year observation. The main objective of the study was to evaluate the incidence of venous and arterial thromboembolic events occurring in women with a new EV/DNG prescription compared to "other" OCs and, in particular, to the EE/LNG subgroup. From the first analysis of the study results, there is a risk of VTE of 7.2 new cases per 10.000 women/year (95% CI: 3.3–13.7) with EV/DNG, 9.1 per 10.000 women/year (95% CI: 6.9–11.8) with other OCs, 9.9 of 10.000 women/year (95% CI: 4.8–18.3) with EE/LNG and 3.5 of 10.000 women/year (95% CI: 1.6–6.7) in the population of women not using OCs. Similarly, the incidence of ATE was also lower in the group of EV/DNG users. The relative risk of VTE with the EE/LNG OC was not higher than that of the other OCs or the EE/LNG combination, while the analysis of European data (where

the use of EV/DNG was more widespread) revealed a significantly lower risk of VTE of EV/DNG compared to the class including all other OCs. The INAS-SCORE study, despite being a single first evidence, therefore demonstrated with high statistical strength that contraception with EV/DNG is associated with a cardiovascular risk similar, if not even lower, to the EE/LNG combination and the other COCs [43]. The extension phase of INAS-SCORE study focused on VTE and ATE with an implementation of follow-up procedures. More than 50.000 OC users were followed for 2 to 7 years. In the Europe database the results show that the EV/DNG exerts a lower risk of VTE and ATE vs. all OCs with a similar or lower risk vs. EE/LNG [44].

There are two contraceptive formulations containing E2 currently on the market: the combination of E2V and DNG (E2/DNG) (Qlaira®, Bayer S.p.A.), multiphasic OC with dynamic dosage with 26 active tablets plus 2 placebo, approved in Italy since 2009 [45] (Klaira®, Bayer S.p.A.), and the association of micronized E2 with nomegestrol acetate (NOMAC) (Zoely®, Theramex), in a monophasic regimen with a dosage of 1.5 mg and 2.5 mg respectively and with a 24 + 4 administration schedule (24 active tablets plus 4 placebo), available on the market since 2011 [46].

E2V represents the esterified form of E2 which allows for a greater bioavailability of estrogen when administered orally; 1 mg of E2V is equivalent to 0.76 mg of E2. After being absorbed, E2V is split in the liver into E2 and valeric acid [47]. The DNG associated in OC with E2V is a derivative of 19-nortestosterone with a peculiar chemical structure as it is the only progestin compound to associate properties of both 19-nortestosterone derivatives and progesterone derivatives, which leads to an high action on progesterone receptors and antiandrogenic activity, equal to 40% compared to that of CPA (the progestin compound with greater antiandrogenic activity [48]). The anti-estrogenic action of DNG at the uterine level is protective for the endometrium by stabilizing bleeding, and contributes to the contraceptive efficacy due to the effect on cervical mucus [37, 49]. Contraceptive treatment with E2V/DNG was associated with an improvement in the lipid profile, with a decrease in LDL cholesterol levels and an increase in HDL cholesterol, and with a lesser influence on carbohydrate metabolism parameters and clotting markers, compared to the combination EE/LNG [34, 41, 50].

The second contraceptive with natural estrogen associates E2 with NOMAC, a derivative of 19nor-progesterone with powerful progestin activity more marked than that of natural progesterone, anti-estrogenic activity and mild antiandrogenic activity. Having no androgenic, glucocorticoid or mineralocorticoid activity, NOMAC has proved to be a safe progestin from a cardiovascular and metabolic point of view [51]. Studies reported so far show that E2/NOMAC does not modify the lipidic and glucose metabolism, does not induce significant changes in blood pressure and C-reactive protein and has an almost negligible influence on the blood coagulation system [42, 52]. During treatment, no changes in bone metabolism and bone mineral density were observed [53].

5.2.2 Prospects for the future of OC with natural estrogen

Although the introduction of natural estrogen in OC has created a great alternative to traditional compounds with EE, it is not surprising that pharmacological research is still active in seeking and combining new molecules, always in the name of a better profile of safety and acceptability of the drug. One of the molecules that is most arousing curiosity for a possible future use both in OC and in hormone replacement therapy for menopause is estetrol (E4). Estetrol is also a "natural" hormone, since it is

synthesized by the fetal liver during pregnancy. Although known for a long time and considered a weak estrogen, E4 has aroused low interest until the discovery of a poor pharmacokinetic and pharmacodynamic interaction in the liver [54]. In vitro and in vivo studies have shown that E4 does not induce hepatic synthesis of SHBG and does not affect the activity of cytochrome P450, which inhibits ovulation in a dose-dependent manner and which acts as estrogen in the vagina, uterus and bone [55]. These premises have supported phase II studies with the use of E4 as an OC in combination with DRSP or LNG, which have shown efficacy in inhibiting ovulation, with a low metabolic impact on the synthesis of liver proteins [56–58]; phase III studies show the efficacy and safety of the OC containing 15 mg of E4+3 mg of DRSP [59].

5.3 Different way of estroprogestin OC

To reduce the discomfort of taking the pill daily, different routes of administration have been available. These include the transdermal route of administration with the patch containing EE and the progestin norelgestromin. The patch, applied to the abdomen, arm or shoulder, ensures the disposal of contraceptive doses for one week. Therefore, it must be replaced weekly. Another route of administration is the vaginal one. The vaginal ring releases daily a very low dose of EE and the progestin etonorgestrel (ETN). Both of these routes of administration have the advantage of ensuring constant doses of hormones and are not conditioned by intestinal absorption. This is very beneficial for women with food intolerances. Furthermore, with these routes of administration an excellent cycle control was found, as well as an excellent metabolic profile on the lipid and glucose side [60, 61].

5.4 Hormonal contraception with progestogen only compound

In many cases where the use of estrogen (including E2) is contraindicated, progestogen compound alone can be used [22]. The oral formulation contains 75mcg of DSG. This pill must be taken every day and the most annoying side effect is the irregular bleeding. The progestin, especially ETN, can also be used as a LARC. The ETN implant releases enough hormone for its contraceptive effect for at least three years. Even with the implantation of ETN the most notable side effect is irregular bleeding [62]. The absence of other serious side effects and its wide spectrum of application make the contraceptive with progestin only in both SARC and LARC formulations an excellent choice for effective, safe and reversible contraception.

Recently, a SARC with the only progestin compound, contained DRSP at the daily dose of 4 mg in a formulation of 24 active pills plus 4 placebo pills, was proposed with the aim to reduce the irregular bleeding in comparison with the only DSG. This contraceptive method demonstrated an excellent efficacy [63, 64] associated with a good tolerability in relationship to a minor irregular bleeding in comparison with DSG only pill [65].

5.5 Non-contraceptive benefits of hormonal contraception

Although the therapeutic goal of OC is the prevention of conception and pregnancy, it can confer multiple additional health and quality of life benefits to women, which are often little known to the female public. Under this point of view, contraception can be used with a "therapeutic" goal. The extra-contraceptive benefits can derive directly from the contraceptive mechanism of action (the inhibition of the

ovulation), or they can depend on a direct action of the hormonal components. Most of the additional benefits are obtained on the symptoms that often occur during menstrual cyclicality, such as dysmenorrhea, menstrual headache, premenstrual symptoms, peri-ovulatory pain and ovarian cyst formation, heavy menstrual bleeding and symptoms of hyperandrogenism. Other no less important benefits include the prevention of ectopic pregnancies, pelvic inflammatory disease, oncological risk (reduction of ovarian, endometrial and colorectal cancer), and the improvement of endometriosis symptoms [66, 67]. The set of benefits that can be obtained from long-lasting contraception in women without contraindications thus creates an absolutely favorable benefit/risk ratio (**Figure 1**).

The direct anti-ovulatory and endometrial effect of OC is capable of effectively treating dysmenorrhea and heavy menstrual bleeding. Dysmenorrhea, especially primary dysmenorrhea, is believed to be linked to an increased production or individual susceptibility to the effect of prostaglandins: the premenstrual hormonal fall, in particular of progesterone, favors an increase in the synthesis of prostaglandins at the endometrial level [68], therefore, abolition of ovulation with OC, counteracts the etiopathogenetic mechanisms of dysmenorrhea. Furthermore, OCs lead to a lower stimulation of endometrial proliferation, with consequent reduction of menstrual fluid and the levels of prostaglandins produced during menstruation, therefore of the uterine contractions necessary to allow menstrual flow [69]. Thanks to these actions, it is well established that different types and different formulations of contraceptives are effective remedies for dysmenorrhea [69]. Even the newest OC with a low dose of EE or containing E2 have shown good results in the control of dysmenorrhea [39, 70, 71], DNG is effective in relieving dysmenorrhea as it has an additional inhibitory action at the level of cyclooxygenase-2 m-RNA, demonstrated by in vitro studies, which allows to reduce the synthesis of prostaglandins [72]. With regard to heavy menstrual cycles, one of the most frequent causes of anemia in women, since they often result from an imbalance in the synthesis of progesterone, when taking an

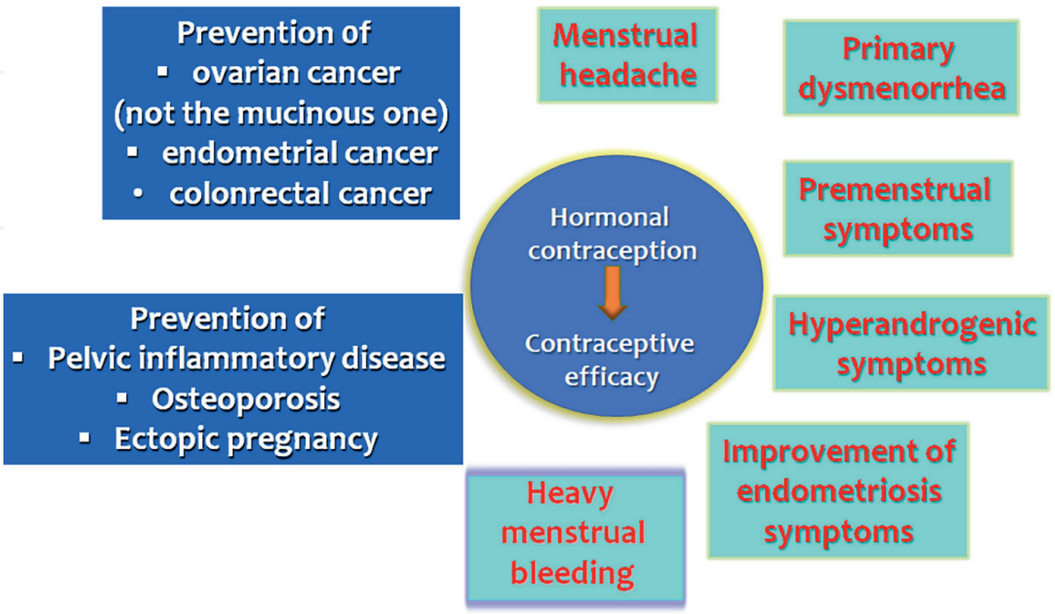

Figure 1.
The contraceptive efficacy of hormonal contraception is associated with many beneficial effects on woman's symptoms dependent on cyclical changes of sexual steroids and on the inhibition of ovulation.

OC an antiproliferative effect on the endometrium is obtained, which have the ability to improve this deleterious menstrual symptom [73]. The new contraceptives with natural estrogen seem even more effective than those with EE in reducing menstrual bleeding, as demonstrated by a comparative study between an OC with E2V/DNG compared with a compound of EE/LNG [74]. In fact, the dynamic multiphase regimen of the E2V/DNG mimics the physiological modifications of the woman's menstrual cycle, with a predominance of estrogen which guarantees endometrial proliferation during the first part of the cycle, and a dominance of DNG in the advanced phase that ensures the maturation and stability of the endometrium; the short 2-day hormone-free interval is sufficient to guarantee the appearance of withdrawal bleeding, which is mostly scarce or sometimes absent [75]. Furthermore, maintaining a stable plasma concentration of hormones has shown an improvement in other symptoms related to the menstrual cycle, such as the menstrual headache [76].

Among the other cyclical disorders that can benefit from an OC is premenstrual syndrome (PMS) or simply the set of unpleasant symptoms such as irritability, decreased mood, headache, tension and swelling, which often anticipate the menstruation. PMS can affect up to 30–40% of women of reproductive age [77], most often with mild symptoms, but in some cases the manifestations may involve considerable discomfort. The etiopathogenesis of PMS is currently unknown, but ovarian steroids, their cyclic fluctuation and their action both on neurotransmitters and neurosteroids in the central nervous system are likely to have a causal action [78]. An interesting epidemiological survey conducted in England on 974 women aged between 20 and 34 years (PMS found in 24% of these) showed a significantly lower prevalence of PMS symptoms in users of OCs, regardless of the type of contraceptive [79]. Both the use of extended intake regimens compared to cyclic ones [80], and some estrogen-progestogen combinations, have shown greater efficacy in the control of this symptomatology: in particular the OC with EE/DRSP, likely in relationship to the antimineralcorticoid and central activity of the DRSP. This OC reduces the premenstrual manifestations compared to the OC with EE/LNG [81] a remarkable result was also observed with the combination E2/NOMAC [82], probably due to a direct central effect of this progestogen. DNG could also have beneficial effects on mood or cognitive functions for an action at the level of the central nervous system. For example, in the context of menopausal hormone replacement therapy it has been reported that treatment with E2 and DNG has achieved an improvement in alertness and cognitive functions better to E2 therapy alone, with a documented activation of some brain areas on electroencephalography [83].

5.6 Tolerability of the contraceptive and therapeutic adherence

The tolerability of the OC is one of the most relevant aspects because it is what mainly conditions adherence to treatment and its continuity over time. If the contraceptive method is poorly tolerated, it will be suspended or used discontinuously, and the direct consequence is the loss of contraceptive efficacy and the uselessness of the method itself. On the other hand, tolerability and adherence to treatment are certainly improved if the contraceptive confers benefits on the general quality of life, and if the woman is aware of the safety of the drug she is taking and of the risk/benefit ratio. Despite all the progress that has been witnessed in the creation of increasingly safer contraceptives that are well suited to the various preferences that every woman may have, the analysis of the 2016 ISTAT data highlights that the use of OC so-called short-acting in Italy it is less than 15%. But in addition to the low use of

effective contraceptives found in the population of Italian women, another negative fact to be noted is that a detected number of women who start a OC use stop it within a year of therapy. An interesting interview conducted through online questionnaires on more than 5000 women users of OC, in various European countries, America, Russia and Australia, highlighted in all countries a high rate of interruption of the treatment; the main reason for the interruption-change of the reported contraceptive is the appearance of side effects, which vary from 25 to 60% between countries [84]. In Italy, the survey found a contraceptive treatment interruption rate of 44% [84]. Even considering the most recent OCs with low doses of EE and II-III generation progestin compound, which are expected to show an higher tolerability profile, another Italian survey reported a high discontinuation rate, around 35%, with 25% of women who stop for the onset of adverse effects, in particular, in order of frequency: bleeding irregularities, weight gain, water retention, headache, gastrointestinal symptoms, mood changes, androgenic symptoms, decreased libido, breast tenderness [85].

More generally, population studies that analyze the problem of therapeutic continuity with various contraceptive methods, show a continuation with OCs at 12 months, which varies according to the case series from 55 to 70% approximately [2, 86]. The problem is particularly relevant in adolescents and young women, where an unwanted pregnancy is associated with greater risks for health, for the outcome of the pregnancy itself and for psychological well-being. An interesting survey conducted on a sample of almost 7500 women in Washington state, aimed to compare adherence at 12 months with different methods of contraception divided into SARC (oral OC, vaginal ring, transdermal patch and contraception with progestin only) and LARC (intrauterine contraception, subcutaneous implant of progestin compound), precisely in the various age groups: given that the adolescent age, between 14 and 19 years, showed the most low percentages of continuity at 12 months, this was in any case higher than 80% with the LARC, while with the SARC it was lower, by 44% in the youngest and by 52% from 20 years of age: more than 50% of women who used SARC were not satisfied with the treatment [87]. For this reason, considering both the greater efficacy in the context of everyday life, and the highest adherence, the American guidelines recommend LARC as the first contraceptive choice in adolescents [88]. Certainly, a low profile of adverse events and good bleeding control, improving the tolerability of the contraceptive, can also improve compliance with OCs. Another discomfort that is sometimes complained of while taking OC concerns libido and the sexual sphere. In the light of the pharmacodynamic characteristics of E2 compared to EE and of the two associated progestogens DNG and NOMAC, which are devoid of androgenic and glucocorticoid activity, contraception with natural estrogen pills it would expect metabolic neutrality (and therefore on body weight) and a scarce influence on the mechanisms underlying salt and water retention. If we consider that weight gain, swelling and water retention are among the side effects of OC most reported and most feared by the female public, having a contraceptive available that does not affect these aspects or that affects only in a low percentage of cases, would certainly increase the tolerability of the treatment.

The antiandrogenic profile of an OC can affect libido, mainly if the strong estrogenic activity increases SHBG levels, who plays a key role in the availability of androgens. The poor action of E2 on liver proteins, including SHBG, and the effect of E2 at a central and peripheral level, justify the optimal results with improvement of libido and sexuality obtained both during treatment with E2V/DNG [89] and when switching from a contraceptive with EE to a combination with E2/NOMAC [90].

Finally, the control and regularity of genital bleeding are two very important aspects in influencing the tolerability of the contraceptive. The fact that E2, compared to EE, has a very weak proliferative action at the endometrial level and, consequently, favors an unstable and easily bleeding endometrium, has for years limited the use of this estrogen in contraception. Today, however, the two OCs with E2 have been shown to have a substantially comparable profile to the OCs with EE as regards bleeding irregularities, with a progressive reduction in the appearance of spotting over time [74, 91]. Furthermore, contraception with E2, compared to that with EE, is associated with a reduction in the duration of withdrawal bleeding, with greater frequency with the absence of bleeding [74, 91], and these characteristics could also improve the woman's tolerability.

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