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Hormonal anticonception anno 2013: a clinician's view

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Abstract

Hormonal contraception has recently drawn the attention of both national and international Health Organizations mainly because of new data on the risk of venous and arterial thrombosis. This has, fortunately, not led to a 'pill scare' as happened in 1996 when controversy arose with respect to the thrombotic risk of third versus second generation pills. This time, evidence on the thrombotic risk of pills with the newer progestogens is gathering, leading to a re-evaluation of guidelines. In this paper, we summarize this evidence and try to present a clinician's view of the indications and contraindications of hormonal contraception and situate them in the perspective of the numerous non-contraceptive health benefits of hormonal contraception.

Key words: **Contraception, hormonal, safety, side-effects, current opinion, clinical.**

Introduction

Hormonal contraception has come a long way from the first pills with high doses of oestrogen combined with the so called first generation progestogens to the modern formulations with a lower dose of oestrogens and a variety of progestogens (Dhont, 2010). This evolution was driven by the search for a more safe and reliable hormonal contraception and the competition between pharmaceutical companies to bring out the 'best' pill. Other types of hormonal contraception have been introduced and have extended the choice of women for the most appropriate formula. Progestogen-only contraception can be delivered by pills, intramuscular or subcutaneous injections and by a long-acting subcutaneous implant. An intra-uterine device loaded with levonorgestrel was launched 20 years ago and procures a local form of progestogen-only contraception. In case of unprotected intercourse hormonal emergency contraception to prevent ovulation can be offered or a copper IUD can be inserted to prevent implantation.

Very recently the Belgian Ministry of Health organized a consensus conference on hormonal contraception on May 16th 2013 and exactly on the same day an expert meeting was organized by the WHO in Geneva because some controversy had arisen mainly concerning the combined hormonal contraception and the risk of thrombosis. Although the final report of these two meetings is not yet available, it seems appropriate to summarize the main findings of these meetings and to infer some clinically relevant conclusions.

There is a wide variety of combined hormonal contraceptive (COCs) formulas with respect to the dose and type of oestrogens, the dose and type of progestogens, the sequence of hormonal combinations and the route of administration (oral, transdermal and vaginal). Due to this multitude of formulas, large-scale prospective studies to determine which formula scores the best with respect to safety, efficacy and tolerability are almost impossible to realize and hence are not available. Most studies that compare different formulas are sponsored by pharmaceutical companies and are of low to moderate quality. Data on efficacy, serious adverse effects and potential beneficial effects of COCs are derived from case control and cohort studies. Notwithstanding this lack of solid evidence, clinical experience, knowledge of pharmacological properties of contraceptive hormones and epidemiologic studies have led to the formulation of contraceptive guidelines by different national and international organizations (Peremans et al., 2012). The purpose of this paper is not to repeat the excellent guidelines that both lay

people and medical personnel can have access to but to discuss some controversial issues and give a clinician's view.

Combined hormonal contraception

The contraceptive pill has undergone many changes since the so-called Pincus pill was launched in 1961 (Dhont, 2010). The first pills contained, 5 mg norethynodrel and 75 μg mestranol (Enovid®) or 4 mg norethisterone and 50 μg ethinylestradiol (Anovlar®). Key developments were reduction of ethinylestradiol doses (15, 20, 30 μg) and synthesis of new progestogens in order to increase its safety and comfort. In 2001 a parenteral form of COC either via a transdermal patch (Evra®) or a vaginal ring (Nuvaring®) was introduced. Parenteral administration of sex steroids, mainly oestrogen, has a long tradition in hormone replacement therapy. The alleged advantage of this route is the avoidance of the first-pass effect on the liver. Lately, two COCs with natural oestrogen instead of ethinylestradiol have been marketed.

1. Contraceptive efficacy

All COCs have an excellent efficacy when used correctly. In daily practice, however, the efficacy is ten times lower than that obtained in clinical studies. As a rule the efficacy is related to the compliance of the woman, the dose of progestogens and oestrogen and the interval between two pill cycles. The most efficacious formula is when women take the pill continuously. There is a great gap between the theoretical efficacy (method effectiveness) of the pill which approaches one hundred percent and the clinical efficacy (typical use effectiveness) which depends on patients' compliance. The typical use effectiveness during the first year ranges from 2 to 8% depending on the population being studied while the perfect use pregnancy rate is 0.3% (Hatcher et al., 2007). Several factors account for the patient-related pill failures: skipping one or more pills, starting pill intake too late in the cycle, unfamiliarity with the precautions in case of unintended cessation of pill intake, or conscious non-compliance with instructions may all be responsible. Rarely, the contraceptive efficacy is impaired by intestinal malabsorption due to vomiting or diarrhoea or interactions with drugs that decrease the contraceptive oestrogen and/or progestogen levels.

2. Side effects

Side effects can be the result of the effect of the oestrogen (e.g. nausea, bloating) or the progestogen component (breakthrough bleeding, mood swings) or the combined effect of both on the global oestrogenicity of the pill (see risk of thrombosis). Different progestogens can have a variety of pharmacological properties including pure progestogen, oestrogen or anti-oestrogen, androgen or anti-androgen, glucocorticoid and anti-mineralocorticoid effects. Progestogens have been classified as first (norethisterone acetat, lynestrenol), second (levonorgestrel) and third generation progestogens (gestodene and desogestrel). Other progestogens such as drospirenone, dienogest, chlormadinone, nomegestrol acetate) are sometimes but wrongly classified as fourth generation progestogens. Each of these progestogens has its proper pharmacological profile and cannot be, therefore, classified as a single category with some common properties.

a. Breakthrough bleeding

Breakthrough bleeding is most frequent during the first months. Although innocuous, it can lead to incorrect use of the pill and unwanted pregnancy. Information that breakthrough bleeding can occur and should not be a reason for premature cessation of the pill is one of the points that should be stressed at the initial consultation. If the problem persists, it can be advised to switch to a more oestrogenic formula. Although the evidence is limited, triphasic pills and third generation pills score better in this respect (Peremans et al., 2012; Brand et al., 2011; Halpern et al., 2011).

b. Loss of libido

The effect of the pill on libido is variable. As many women report a decrease of libido as there are women who report an increase. On average there are slight variations in a woman's libido with a peak at the time of ovulation, due to the increased production of testosterone. From a pharmacological point of view, in case of loss of libido, COCs with anti-androgenic properties should be avoided.

c. Weight gain

For most women, weight gain is a continuous source of preoccupation and frustration. Pill users tend to blame the pill but most prospective studies show that if weight gain occurs in pill users it is marginal. A recent Cochrane review concluded that there is insufficient evidence for differences in the various COCs in this respect (Gallo et al., 2011).

d. Mood swings

From a theoretical point of view, progestogens can affect the mood and if this is a problem, switching

to a more oestrogenic formula can be advised but there is no evidence for this practice.

e. Interval headache

Some women complain of headaches in the pill-free period. This mostly occurs after several years of use of COCs. Although studies to support it are lacking, it seems logical to switch from cyclic to continuous use of the pill or to an alternative mode of contraception such as a progestogen-only method or an intra-uterine device.

3. Some specific formulas of COCs

a. Biphasic and triphasic hormonal contraceptives

When biphasic and triphasic forms of hormonal contraception were launched, it was argued that they better mimic the cyclic hormonal changes of a natural cycle. This of course is pure nonsense because ovulation and the concomitant hormonal and endometrial changes are as well suppressed as with monophasic COCs. The only difference is that the total dose of progestogens per cycle is lower and that therefore phasic pills can be considered to be more oestrogenic.

b. COCs with a natural oestrogen instead of ethinyloestradiol

Several attempts were made to replace ethinylestradiol with the natural oestrogen oestradiol, but these attempts were abandoned because of problems with cycle control and contraceptive efficacy. These problems were overcome recently by the establishment of a four-phasic combination of oestradiol valerate, which is cleaved to oestradiol and dienogest as the progestogen in an extended cycle of 26/28 days. A second OC containing 17β-oestradiol and nomegestrol acetate, administered according to a 24/4 regimen, was launched a year later. Compared to ethinyloestradiol, natural oestrogens have less affinity for the liver cells. In comparative studies, pills with the natural oestrogen have less effect on Sex Hormone Globulin levels (SHBG) (Raps et al., 2012) which is a surrogate indicator of the oestrogenicity of the pill and on a number of coagulation factors (Gaussem et al., 2011). Whether the inclusion of a natural oestrogen instead of the synthetic ethinylestradiol will result in a lesser risk of thrombotic events remains to be evaluated in large cohort studies (Peremans et al., 2012; Brand et al., 2011).

c. Parenteral forms of COCs

COCs can also be administered transdermally by a patch or vaginally by a ring. The hypothetic advantage of the parenteral administration of COCs is that the first- pass effect on the liver is bypassed but apparently this does not result in a decreased risk of thrombotic events (Rott, 2013). Because the contraceptive efficacy is comparable to that of oral COCs the choice for this type of contraception depends on the woman's preference. A number of women don't like the patch for aesthetic reasons or because the patch can come loose when the skin gets moist. As for the ring, a minority of women objects to the necessity of vaginal manipulation.

d. Extended or continuous use of the pill

The imitation of a 28-day menstrual cycle achieved by giving the pill for 21 days followed by a pill-free interval of 7 days was based on the popular belief that menstruation every 28 days is a sign of a normal reproductive female function. Regulation of the menstrual cycle by the pill is of course purely symptomatic and it suppresses the physiological function and meaning of menstruation. Only in the last ten years has this been acknowledged leading to the promotion of extended regimens. Bi- and three-cycling (i.e. taking the combined monophasic OC uninterruptedly during 42 or 63 days, respectively, before allowing withdrawal bleeding to take place) were initially advised to women with perimenstrual distress but currently, some women are taking their pill in a continuous fashion for up to one year on a stretch. The extended or continuous use of the pill can have a number of advantages (no interval headaches, less total blood loss and greater contraceptive efficacy) but for some women, the absence of monthly blood loss is difficult to accept (Halpern et al., 2011).

4. Serious adverse effects of COCs

a. Deep venous thrombosis

Oestrogens promote the synthesis of several hepatic proteins and have a well-established prothrombotic effect. There is no doubt that COCs augment the risk of thromboembolism two to fourfold but fatal thromboembolism among young women is extremely rare (1% of the cases) and this increased risk should be balanced against the 5- to 10-fold increased risk associated with normal pregnancy. In 1995 en 1996 a number of reports showed that the risk of thrombosis was two times higher with COCs containing the third generation progestogens (desogestrel and gestodene) compared to those with the second generation pills containing levonorgestrel (Middeldorp, 2005; Jespersen et al., 2005; Jick et al., 2006; Blickstein, 2006). More recently, it was showed the increased risk also applied to pills

containing drospirenone and cyproterone acetate (Dinger et al., 2007; Martinez et al., 2012). Although epidemiological studies indicate that the thrombogenic effect of oestrogens is modulated by the type of the associated progestogen, the debate whether a first user effect or a preferential prescribing is also involved is still going on (Van Hylckama Vlieg A et al., 2009; Lidegaard et al., 2009; Lidegaard et al, 2011, 2012; Reid et al., 2010). Be that as it may, fatal thromboembolism among young women is extremely rare and this increased risk should be balanced against the 5- to 10-fold increased risk associated with normal pregnancy. Taking also into account the numerous non-contraceptive benefits, the balance of overall wellbeing is clearly in favour of the pill. Nevertheless, common sense dictates that second generation pills should be the first choice for women who start COC. It is possible that pills with natural oestrogen are a valuable alternative.

b. Arterial thrombosis

COCs slightly increase the risk for arterial thrombosis (thrombotic stroke and myocardial infarction) but in contrast to deep venous thrombosis no effect of the type of progestogen was observed (Lidegaard et al., 2012). The risk was slightly higher for women taking pills with 30 or 40 μg of ethinylestradiol compared to those taking pills with 20 μg. Smoking, hypertension and age are independent risk factors and should be taken into account when estimating the individual risk of arterial thrombosis when taking COC (see contraindications for COC).

c. Cancer

The effect of COCs on the risk of breast cancer is controversial. In a large cohort study, Hannaford et al. (2007, 2010) did not find a relation between COC and breast cancer whereas in some meta-analyses of observational studies, a marginal increase of cancer risk was observed (Kahlenborn et al., 2006). Long-time use of COCs is associated with an small but significant increase of the risk of cervical cancer (ICESCC, 2007).

5. Non contraceptive benefits of COCs

Although the primary purpose of oral contraceptives is to prevent unwanted conception, it is no wonder that the profound effect on the hormonal regulation of the menstrual cycle could entail some major effects on the female genital tract and the endocrine system. The mechanisms of the non-contraceptive benefits of COCs can be directly related to the anti-ovulatory effect (eg prevention of ovarian cancer), the antiproliferative effect of progestogens on the endometrium (eg prevention of heavy menstrual bleeding, dysmenorrhea and endometrial carcinoma) or be related to the endocrine systemic effects (eg the prevention of acne). Adding the non-contraceptive benefits to those of preventing unwanted pregnancies and their potential complications, COCs are associated with a significant reduction in the mortality rate (Hannaford et al., 2007, 2010).

5.1. Preventive effects of COCs

a. Ovarian cancer

Based on epidemiological data, Fathalla (1971) formulated the hypothesis that 'incessant' ovulation is a risk factor in ovarian neoplasia. Several epidemiological studies have indeed shown that the relative risk of ovarian cancer augments significantly with increasing number of lifetime ovulations. (Hildreth et al., 1981; La Vecchia et al., 1983; Risch et al., 1983; Wu et al., 1988; Purdie et al., 2003). Although the precise mechanism of the relation between the number of ovulations and the development of ovarian cancer is not known, the protective effect of the use of COCs is mainly by reducing the number of ovulations.

b. Endometrial cancer

Most endometrial cancers (70% to 80%) are induced by chronic oestrogen stimulation. The progestogen compound of COCs protects from oestrogen-induced hyperplasia and changes in proliferative status A recent review of all studies on the relation between endometrial cancer and hormonal contraception was recently published by Mueck et al. (2010). More than 15 case-control studies and at least four large cohort studies demonstrated a decrease in the risk of endometrial cancer of about 50% for ever users of COCs. In most of these studies, this protective influence persisted for more than 10-15- or even 20 years after cessation of COC intake. In the Royal College of General Practitioner's oral contraception study, however, the protective impact of COCs was restricted to 5 years or less after cessation of pill use (Hannaford et al., 2007). An increasing protective influence with longer duration of COC use has been found in most studies. The beneficial impact was independent of the composition of the COC, i.e. dosage and type of progestogen, combined with ethinylestradiol 30-50 mg/day. COCs with higher progestogen potency seem to be somewhat more effective.

c. Colorectal cancer

Several case-control and cohort studies have focused on the relation between colon cancer and the

use of COCs and a number of meta-analyses have been performed; however, the conclusion is not unanimous. In the Nurses' Health Study women who used oral contraceptives for 96 months or longer had a 40% lower risk of developing colorectal cancer (RR = 0.60; 95% confidence interval (CI) = 0.40-0.89; P for trend = 0.02) compared with women who never used oral contraceptives (Martinez et al., 1997). In a meta-analysis, the combined RR of colorectal cancer for COC ever use from 8 case-control studies and from 4 cohort studies was 0.82 (Fernandez et al., 2001). The favourable effect of COC use on the risk of colon cancer was confirmed in a recent meta-analysis by Bosetti et al. (2009). The summary relative risk of colorectal cancer for ever versus never COC use was 0.82 (95% CI, 0.69-0.97) from 11 case-control studies, 0.81 (95% CI, 0.75-0.89) from seven cohort studies, and 0.81 (95% CI, 0.72-0.92) from all studies combined (Bosetti et al., 2009). The results were similar for colon and rectal cancer. No difference was evident according to duration of COC use both for colon and rectal cancer.

d. Functional ovarian cysts

It has been acknowledged for a long time that COCs greatly reduce the incidence of functional ovarian cysts (Ory, 1982). From this observation it was inferred that COCs could be used to treat functional ovarian cysts but randomized controlled trials as summarized in a recent review have shown that COCs do not hasten the resolution of functional ovarian cysts (Grimes et al., 2009). There are two types of functional ovarian cysts: follicular and luteal cysts. Follicular cysts arise from follicles that fail to rupture at the time of ovulation and which can continue to grow up to a diameter of 5 cm. After ovulation, the corpus luteum can be transformed into a mostly hemorrhagic corpus luteum cyst. In both cases, acute complications due to torsion or rupture can occur. Because COCs suppress ovulation, it is evident that the occurrence of luteal cysts will be completely prevented. The degree of prevention of follicular cysts will depend on the type of COCs. High-dose pills will be more effective than low-dose pills. Because follicles start growing in the pill-free interval, the continuous use of COCs will also be more effective in preventing follicular cysts than the usual 21/28 regimen.

e. Endometriosis

Although the precise etiopathology of endometriosis is unknown, reflux of endometrial cells at the time of menstruation is generally considered to be the initiating event. Extra-uterine implantation and growth of endometrial cells is further promoted by the cyclic production of oestrogens. COCs could prevent the initiation or extension of endometriosis by two mechanisms. The volume of menstrual flow is reduced and progestogens either directly or by their anti-oestrogenic effect prevent implantation and growth of endometrial cells. A number of case-control and cohort studies have shown indeed that the risk of endometriosis is reduced in pill users (Vercellini et al., 2011). It cannot be excluded, however, that the suppression of symptoms, including potential subfertility, postpones a diagnostic evaluation, including laparoscopy and that therefore studies on the favorable effect of COCs on the risk of endometriosis are somewhat biased. Whether COCs are instrumental in the primary prevention of endometriosis remains to be answered.

f. Iron-deficiency anemia

It is well known that COCs reduce menstrual blood loss by about 50% both in quantity and duration (Nilsson et al., 1967; Larsson et al., 1992). This applies not only to normally menstruating women but also to women suffering from heavy menstrual blood loss. About 10% of menstruating women suffer from heavy menstrual bleeding defined as a menstrual blood loss of >80 ml. It is particularly in those women that COCs are able to prevent iron-deficiency anemia. In normally menstruating women, no difference was observed in the biomarkers of iron deficiency between users and non-users of COCs (Casabellata et al., 2007).

5.2. Non-contraceptive therapeutic indications of COCs

a. Heavy menstrual bleeding

COCs are associated with a decreased menstrual flow by limiting endometrial proliferation. Although COCs are widely used as a first-line treatment for heavy menstrual bleeding it is remarkable that until very recently there was a lack of published randomized trial data to definitely prove the efficacy of COCs. One small nonrandomized crossover trial 19 (n = 45) showed that COCs were effective in modulating blood loss, on average, providing a 40% to 50% decrease, along with a decrease in the occurrence of dysmenorrhea (Fraser et al., 1991). Due to this lack of solid proof of efficacy, Farquhar and Brown (2009) concluded in a recent Cochrane review paper that there were not enough trial data to recommend COCs for abnormal uterine bleeding. It should be remembered in this respect that lack of evidence does not necessarily mean that COCs cannot be effective in reducing blood loss in women

with heavy menstrual bleeding. Clinical experience for several decades attests to the place of COCs in the treatment of heavy menstrual bleeding. Solid proof of the efficacy of COCs was recently provided by two randomized trials with an oral contraceptive containing estradiol valerate and dienogest (Jensen et al., 2011; Fraser et al., 2011). The reduction of blood loss in the study group varied from 60% to 70% compared to the placebo group. Less frequent menses or amenorrhea can be achieved with extended oestrogen-progestogen COC regimens but there are no studies to prove that this mode of administration is superior to the cyclic use of COCs for treating heavy menstrual bleeding.

b. Dysmenorrhea

Dysmenorrhoea or painful menstruation is associated with ovulatory cycles. Headaches, nausea and vomiting can be accompanying symptoms. With the withdrawal of progesterone and oestradiol at the end of the ovulatory cycle a cascade of endometrial events starts, including the production and release of prostaglandins which are thought to be the main factor in painful uterine contractions. As COCs suppress ovulation and reduce the proliferation of endometrium and hence the production of prostaglandins, they could be effective in reducing the symptoms of dysmenorrhea. A recent Cochrane review concluded that preparations of COCs with doses less than 35 mcg were effective and should be the preparation of choice (Wong et al., 2009). Two recent randomized trials showed that COCs are effective for the treatment of primary dysmenorrhea (Harada et al., 2011) as well as for secondary dysmenorrhea due to endometriosis (Harada et al., 2008). Even better results can be obtained by COCs used in a continuous fashion. Headaches, genital irritation, tiredness, bloating and menstrual pain were significantly less in the extended cycles (Edelman et al., 2005).

c. Premenstrual syndrome

Premenstrual syndrome (PMS) is a psychological and somatic disorder of unknown etiology. The symptoms of PMS regularly occur during the luteal phase of the menstrual cycle and resolve by the end of menstruation. The severe and predominantly psychological form of PMS is called 'premenstrual dysphoric disorder'. PMS results from ovulation and appears to be caused by progesterone produced following ovulation in women who have enhanced progesterone sensitivity. COCs prevents ovulation and should be effective for the treatment of PMS. However, evidence from the limited studies available does not support the efficacy of oral contraceptive agents containing progestogens derived from 19-nortestosterone (Freeman et al., 2001). The introduction of an oral contraceptive pill containing low-dose ethinylestradiol and a new progestogen, drosperinone has offered clinical efficacy for PMS (Dickerson et al., 2002). Drospirenone is a spironolactone derivative with antimineralocorticoid and anti-androgenic activity. Drospirenone's anti-androgenic activity makes it also effective in the reduction of acne and seborrhoea. The antimineralocorticoid activity helps to reduce some of the bothersome symptoms (such as swelling) associated with the premenstrual phase of the menstrual cycle. Thus, this pill has the potential to improve women's quality of life but the increased risk of thrombosis compared to second generation pills should also be taken into account. Continuous oral contraception provides greater suppression of the ovary and endometrium and avoids the cyclic interruption of the hormonal exposure which may trigger some symptoms associated with PMS. It has been shown that this mode of oral contraception is associated with improved patient symptomatology (Edelman et al., 2005; Legro et al., 2008).

d. Endometriosis

Medical therapy is an important alternative or complement to surgery for symptomatic endometriosis. Because endometriosis is an oestrogen-dependent disease, medical treatments are based on their systemic or local anti-oestrogenic effects. Both progestogens and COCs are as effective as more sophisticated and more expensive drugs such as GnRH analogues or aromatase inhibitors (Vercellini et al., 2011). COCs also reduce the rate of post-operative endometriosis recurrence and should be considered an essential part of long-term therapeutic strategies in order to limit further damage to future fertility.

e. Acne

Acne is a common skin disorder that occurs in both sexes and particularly affects teenagers when androgens start stimulating the sebaceous glands to increase production of sebum. Although the etiopathology of acne is complex, reduction of androgen production or antagonizing their effect on the sebaceous glands is one of the pillars of a successful treatment. COCs reduce the steroid production by the ovaries, the oestrogen component increases the production of sex hormone-binding globulin (SHBG) whereas the progestogen component can interact to varying degrees with the androgen receptors. Newer synthetic progestogens, like the third-generation gonanes, desogestrel and norgestimate, have less activity at the androgen receptor and more specificity for the progestogen receptor, thus the

androgenic effects are minimized. Cyproterone acetate is a synthetic derivative of 17-hydroxyprogesterone, approved in Europe for the treatment of acne, hirsutism and alopecia. It may be used as a sole agent or in combination with ethinylestadiol. In the latter case it is prescribed as an oral contraceptive particularly for the treatment of acne (Diane®). Drosperinone is a relatively new fourth-generation progestogen that partially blocks endogenous androgens from binding the androgen receptor. A recent Cochrane review provided a comprehensive assessment of the efficacy of COCs for the treatment of acne in women (Arowojolu et al., 2009). It was found that all types of COCs were effective for the treatment of acne and that in this respect only subtle differences exist between COCs with different types of progestogens. This proves that the effect of COCs on the androgen level is the most important factor.

f. Perimenopausal symptoms

The years of fluctuating ovarian function leading up to the final cessation of menstruation are termed the perimenopause. This commonly lasts around 2-3 years, usually in a woman's late forties or early fifties. During the perimenopause, menstrual bleeding typically becomes irregular, and menopausal symptoms may be experienced. Although fertility is low, most perimenopausal women are anxious to avoid any risk of pregnancy. Vasomotor symptoms are experienced by up to 80% of women during the menopausal transition. Hot flushes, nightsweats and palpitations may significantly affect daily life and interfere with sleep reducing quality of life for perimenopausal women. Oestrogen-containing hormonal regimens offer effective treatment for vasomotor symptoms and remain the treatment of choice if symptoms are severe. For perimenopausal women with irregular, anovulatory cycles, COCs regulate the menstrual bleeding pattern, reducing both bleeding and pain. In healthy older women, these very significant menstrual benefits may well outweigh any small risks associated with COC use. These need to be evaluated in the context of each woman's individual risk profile and weighed against the potential benefits: effective contraception, predictable bleeding patterns with less heavy and less painful menstrual loss, reduction in vasomotor symptoms, maintenance of bone mineral density and protection against ovarian and endometrial cancer (Kaunitz, 2001).

6. Contraindications for COCs

When considering the use of COCs, some absolute and relative contraindications must be considered. These contraindications mainly are related to the existence of risk factors for thrombotic or ischemic disease. The distinction between absolute and relative contraindications should be made by balancing the benefits of hormonal contraception against its risks and the availability and acceptability of alternative methods of contraception.

Absolute contraindications include:

- Genetic predisposition for thrombosis and/or personal antecedents of thrombosis
- Family history of myocardial infarct or CVA in first degree relative < 45 years
- Atherogenic lipid profile
- Blood pressure above 140/90
- Heavy smoking in women > 35 ys old
- Impaired liver function
- Diabetes mellitus with diabetic complications
- Morbid obesity (body mass index > 39)
- Migraine with aura
- Carcinoma of the breast

Progestogen-only hormonal contraception

As in COCs, progestogen-only derivates have a triple mechanism of action: suppression of ovulation, altering the viscosity of cervical mucus and induction of endometrial changes. If used consistently they are more than 99% effective in preventing pregnancy (UKMEC, 2009).

Due to the absence of the cycle controlling effect of the oestrogen part of COCs, the main reported side-effect and the most frequent reason for cessation this contraception, is a change in menstrual bleeding patterns: 2 in 10 women have no bleeding, 4 in 10 women have a regular bleeding pattern and 4 in 10 women have irregular bleeding (Ahrendt et al., 2010). The FSRH guideline on progestogen-only hormonal contraception (2008) and the UK Medical Eligibility Criteria for Contraceptive Use (2009) could not demonstrate a significant rise in minor side effects (weight change, acne, nausea) in comparison to COCs, although also they are sometimes a reason for cessation.

It has been stated that in case of thrombophilia or (familial) history or predisposition of breast cancer, progestogen-only contraception is preferable to COCs. The Danish retrospective cohort study by Lidegaard et al. (2012) examined the risk of thrombotic stroke in users of progestogen-only methods. No significant difference is observed with the minipill containing desogestrel, with the levonorgestrel IUD and with the implant in comparison with no use of hormonal contraception (Lidegaard et al., 2012). These findings were confirmed in a meta-analysis of six observational studies (Chaktoura et

al., 2009). Concerning breast cancer, a growing body of evidence indicates that the former assumption that progestogens do not promote breast cancer development is false (Giersig, 2008). Caution is advised in patients with a familial or personal history of breast cancer (UKMEC, 2009). More data from well-designed studies are needed to identify the real risk potential of progestogen for breast cancer, mainly for the levonorgestrel IUD.

1. Progestogen-only pill (POP)

In clinical trials, efficacy of POPs is equal to that of COCs. An important bias cannot be excluded due to the difference between study and real life compliance of patients. The Eligibility Criteria add that POPs are more than 99% effective in preventing pregnancy "if used consistently" . Patients should be advised to take caution in case of forgetting a levonorgestrel-POP for 3 hours and a desogestrel-POP for 12 hours (UKMEC, 2009).

2. Intramuscular long-acting progestogen contraception (DMPA, depot medroxy progesterone acetate)

Up to 50% of progestogen-only injectable contraceptive users will discontinue by 1 year. The most common reason for discontinuation is changes in bleeding pattern. In comparison to the other progestogen-only methods, DMPA is associated with weight change (augmentation) and with a delay of fertility up to 1 year after discontinuation of the progestogen-only injectable contraception (UKMEC, 2009).

3. Subcutaneous implant of progestogen

The primary mechanism of action of this etonogestrel containing device placed subcutaneously is suppression of ovulation. Hatcher et al. (2007) state the contraceptive implant to be the most effective method of reversible contraception, with a typical-use pregnancy rate of 0.05%, although this statement is not evidence based but rather experience based. The main problem is the change in menstrual bleeding patterns that commonly occurs: amenorrhoea or infrequent, frequent or prolonged bleeding which frequently leads to early cessation. Other reported adverse effects include gastro-intestinal difficulties, headaches, acne, breast pain, vaginitis and weight gain (although the latter is not statistically significant) (ACOG, 2011).

4. Levonorgestrel IUD

The levonorgestrel IUD (Mirena®) causes endometrial suppression preventing implantation and changes the amount and viscosity of cervical mucus which also contributes to its antifertility effect. It releases 20 μg of levonorgestrel daily and may be effective for up to 7 years (Sivin et al., 1991). The systemic adverse effects are minimal, although some women may experience hormone-related effects, such as headaches, acne, nausea, breast tenderness, depression and cyst formation (ACOG, 2011). The failure rate is 0.2 per 100 women (Hatcher et al., 2007). Besides its effective contraception, it diminishes the menstrual flow and relieves menstrual discomfort.

Emergency contraception

Emergency contraception is used to prevent pregnancy after unprotected or inadequately protected sexual intercourse. The use of the Yuzpe regime (combination of 2x100mcg of ethinyloestradiol plus 0.5 mg of levonorgestrel, taken 12 hours apart and within 72 hours after unprotected intercourse) became popular in the late 1970s and early 1980s (Yuzpe et al., 1977), but was associated with substantial nausea and vomiting and is therefore abandoned in current practice (Cheng et al., 2012). Because the only mode of action of hormonal emergency contraception is by preventing ovulation, it can only be effective when taken before ovulation occurs.

1. Levonorgestrel

Levonorgestrel (Yuzpe regime 2 × 0.75 mg 12 hours apart or single dose of 1.5 mg) appears more effective and better tolerated than the classical Yuzpe regimen (Cheng et al., 2012). It can be administered up to 3 days (according to WHO up to 5 days) after unprotected sexual intercourse. Its limitations are the non-optimal efficacy which is decreasing the later the drug is taken and the fact that it is only approved for up to 72 hours after unprotected sexual intercourse. The regimen has no effect on the endometrium, corpus luteum function and implantation, is not abortive and doesn't harm the foetus if accidentally taken in early pregnancy. It has no impact on the rate of ectopic pregnancies. It has become the standard method used up to this day in most countries (Gemzell-Danielsson et al., 2013).

2. Ulipristral acetate

Ulipristal acetate, a selective progesterone-receptor modulator, was first described in 2010 for the use of emergency contraception (Glasier et al., 2010). It inhibits or significantly delays follicular rupture for over five days if given immediately before ovulation by postponing the luteinising hormone peak

concentration (Brache et al., 2010). Two trials (Creinin et al., 2006; Glasier et al., 2010) compared ulipristal acetate with levonorgestrel 1.5 mg single-dose. UPA appeared more effective (RR 0.63) than levonorgestrel within 72 hours after unprotected intercourse, which was significant at a marginal level (P = 0.08). When the 72- to 120-hour data from the Glasier 2010 trial were included in a meta-analysis, ulipristal acetate was associated with a lower risk of pregnancy than levonorgestrel and the difference was significant at the 0.05 level (Cheng et al., 2012). It is as safe as levonorgestrel. No thrombo-embolic events have been reported following ulipristal acetate-administration. No effect on endometrium, corpus luteum function and implantation has been observed (Gemzell-Danielsson et al., 2013).

3. Cu-IUD

Although a very common practice, the effectiveness of inserting an IUD as an emergency contraceptive method has not been adequately investigated (Cheng et al., 2012). There are data from non-randomised studies (Fan et al., 2001; Han et al., 2001; Zhang et al., 1999; Wu et al., 2010) which suggest that insertion of a Cu-IUD for emergency contraception could be effective in preventing unintended pregnancy (failure rate 0.09%). A more recent review concludes that a Cu-IUD prevents pregnancy when placed within 5 days after unprotected sexual intercourse in at least 95% of cases (Lalitkumar et al., 2013). The adverse consequences and side effects of the Cu-IUD are the same whether it is used as an emergency contraception or as an ongoing method of contraception. However, because of the duration of use is shorter when the Cu-IUD is used for emergency contraception, risks such as expulsion and side effects such as heavy menstrual bleeding are really not an issue unless a woman chooses to keep the device for long-term contraception (Glasier et al., 2010).

Conclusion

Oral contraceptives not only are one of the most effective methods of contraception, they also confer a number of health benefits, either by prevention of some diseases or through their use in the treatment of some gynaecological disorders or menstrual cycle-related discomforts. Besides a proven substantial reduction in the risk of ovarian and endometrial cancer, preventive effects on benign breast disease, endometriosis, fibroids, rheumatoid arthritis, colon cancer are less pronounced and in certain cases not unequivocally proven. Since the birth of the pill some 50 years ago, numerous changes in dosage and composition have been introduced with the aim, apart from some commercial motives, to reduce side effects without affecting the contraceptive efficacy. The oestrogen and progestogen dosage has been reduced, new progestogens have been added, alternative modes (24-day cycles, extended use of COCs) and routes of administration (transdermal, vaginal) are now offered, and more recently, ethinylestradiol has been replaced by natural estradiol combined with a selective progestogen compound. Randomised studies on all these new formulations have mainly focused on contraceptive efficacy, cycle control and biochemical variables as a substitute for potential adverse health effects.

In promoting new brands of pills, imitation of the natural cycle was and remains sometimes forwarded as an argument. The restoration of a menstrual cycle, however, is not necessarily in favour of long-term beneficial side effects. Repeated and year-long menstruation is a rather recent phenomenon in human history and in fact is involved in the increase in some diseases like ovarian, endometrial and colon cancer. In the long run, new formulations of oral contraceptives should also be evaluated with respect to their beneficial non-contraceptive side effects.

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