The safety and efficacy of low-dose oral contraceptives

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Abstract

Oral contraceptives (OCs) are classified according to the dosage of ethinyloestradiol (EE) and type of progestogen, and whether the dosages of EE and progestogen stay the same during the cycle, or change in a phasic manner. Ultimately, there is no statistically significant difference in efficacy between high-dose and low-dose OCs. There is also no difference in efficacy between monophasic and multiphasic products, which, other than having a lower hormone content, have no benefit over monophasic products.

Several medications, such as rifampicin, some of the anticonvulsants and certain human immunodeficiency virus (HIV) medications, may reduce the efficacy of OCs. Higher-dose OC preparations are recommended in patients taking these concomitant drugs.

The effectiveness of OCs with typical use is largely dependent on compliance, which is influenced by bleeding patterns and side-effects. In this regard, the composition of an OC may play a significant role. The dosage of EE and type of progestogen may relate to specific non-contraceptive benefits, such as improvement in dysfunctional uterine bleeding, dysmenorrhoea, premenstrual tension, endometriosis, iron deficiency anaemia, hyperandrogenism and acne. The third-generation progestogens and anti-androgens are generally regarded as more "skin friendly".

The cardiovascular safety of OCs has long been controversial, and although complications such as myocardial infarction and stroke have been reduced over the years with lower EE dosages, the risk of venous thromboembolism (VTE) has not decreased consistently. In fact, some of the low-dose products containing third-generation progestogens and anti-androgens may be associated with a higher risk of VTE.

Breast cancer is another controversial issue that is associated with OC use. Epidemiological studies do not report an increased risk, whereas other meta-analyses do. The risk may be amplified by genetic susceptibility, although data on the subject are not consistent.

An increased risk of hepatic adenoma and cervical cancer has also been noted with OC use, but the latter seems to be dependent on persistent human papillomavirus infection. On the other hand, ovarian and endometrial cancers are reduced by the use of OCs, although genetic susceptibility may also modify the risk.

As indicated by several studies on risk factors relating to the safety of contraceptives, the choice of contraceptive is more complicated in patients with certain medical conditions. This is because the physiological changes and side-effects that are associated with the method may increase the risk of morbidity or mortality in these women. Before starting on a contraceptive, the woman should undergo a risk-benefit assessment to ensure the safety of the method. This is also true for OCs, and in this regard, the latest World Health Organization (WHO) safety categories may be consulted.

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Introduction

Contraception plays a major role in the management of women's reproductive health. Its most significant impact is to prevent pregnancies that are too early, too late, too many, or too close.[1]

In broad terms, contraception can be defined as any method that prevents pregnancy by either hindering the sperm from reaching a mature ovum, or by inhibiting a fertilised egg from implanting itself in the endometrium.[2] More precisely, contraception refers to the inhibition of ovulation or the prevention of fertilisation of an egg cell, whereas contragestion is the inhibition of implantation due to an unfavourable uterine environment. These two terms are often confused, but ultimately each mechanism plays a role in birth control and family planning.[3]

Different forms of contraception can be used, which includes barrier, hormonal and natural methods.[4-6] Farrer described these methods very elegantly, as well as their advantages and disadvantages.[6] The methods most regularly identified by both women and men are injectables, the male condom, the female condom and the oral contraceptive (OC), or "the pill".[1,7]

In all instances in which a contraceptive preparation is provided, the relevant information must be given to the user in order for an understanding of the reversibility or irreversibility of the particular method to be obtained, as well possible medical risks associated with its use.[2,3,8]

Since OCs were first introduced in the 1960s, the dosage of ethinyloestradiol (EE) has been reduced over the years in an attempt to lessen cardiovascular side-effects, such as myocardial infarction (MI), venous thromboembolic disease (VTE), stroke and other adverse effects, yet still retaining contraceptive efficacy.[8-13]

This article will focus on the efficacy and safety of low-dose oral contraceptives, and may give more clarity regarding the appropriate use and benefits of these drugs.

The female reproductive cycle

The relevant glands and organs involved in the reproductive cycle are the hypothalamus, pituitary (adenohypophysis), ovaries, fallopian tubes, uterus and vagina. The cycle is regulated by hormones.[3,4]

Gonadotropin-releasing hormone (GnRH) is produced in the hypothalamus, and is transported to the adenohypophysis. In response to GnRH, cells in the adenohypophysis then produce follicle-stimulating hormone (FSH) and luteinising hormone (LH). Both cause a cascade of effects.[3]

The reproductive cycle in the ovaries is divided into a follicular phase (before release of the ovum), ovulatory phase (ovum release) and luteal phase (after ovum release),[3,4,14] as summarised in Table I.

Pharmacology and classification of low-dose oral contraceptives

OCs have several mechanisms of action, but the main one is negative feedback to the hypothalamus. This inhibits GnRH release, and subsequent inhibition of the gonadotropin peak secretion during the mid-cycle. This action prevents ovulation.[4,5,15]

Ovulation is also prevented by the selective inhibition of the pituitary function, possibly due to a decrease in responsiveness to GnRH.[15,16] Oestrogen inhibits the secretion of FSH by the anterior pituitary, so that no dominant follicle gets selected.[2,15,17] Progestogens, which include progesterone and synthetic progestins, suppress LH secretion from the anterior pituitary, and thereby suppress ovulation, but not consistently.[2,8,16-18]

Progestogen alone has the following contraceptive effects:[15,16-18]

• It makes the endometrium less suitable for implantation.
• It makes the cervical mucus less permeable for penetration by the sperm.
• It impairs normal tubal motility and peristalsis.

OCs are classified as combination preparations which contain oestrogen and progestogen, as well as preparations that only contain progestogen (the "mini-pill").[2,15,16] The combined OCs contain either ethinyloestradiol (EE) or mestranol in different dosages. However, progestogens contained in OCs vary.[2,8,17] Progestogens have different progestational, oestrogenic, antioestrogenic and androgenic activity.[2,12,17]

These preparations are further divided in monophasic (dosages of oestrogen and progestogen are fixed) and biphasic and triphasic forms (dosages of oestrogen and progestogen change once or twice during the cycle).[6,8,16]

The disadvantages of the bi- and triphasic preparations compared to monophasic preparations are that they cause water retention, and do not have much effect in dysmenorrhoea and premenstrual syndrome. Directions for use are more complicated, and the cycle length cannot be adjusted as with the multiphasic preparations.[8] These products have a lower steroid content, but they have no additional clinical advantage over monophasic products.[15]

OCs are also classified according to the amount of contained EE.

Table I: Summary of the reproductive cycle[3,4,14]

	Day 1	Menstrual bleeding begins.
The follicular phase		Levels of [a]GnRH and [b]FSH start to increase gradually, and a new cycle starts.
		This phase is characterised by the development of follicles in the ovaries.
		Smooth muscle contractions in the uterus increase.
	Day 2	[c]LH starts to increase.
	Day 5/6	Oestrogen levels increase.
		The new endometrium starts proliferation.
		Production of the cervical mucus starts.
	Day 12	As the FSH levels decline, only one, or occasionally two, of the follicles is selected for maturation.
		In addition to oestrogen (oestrogen reaches peak levels), the primary follicle also produces progesterone and prostaglandin.
The ovulatory phase	Day 13	The ovulatory phase starts with the surge of LH, which causes complete maturation of the dominant follicle.
		Oestrogen decreases.
		FSH increases again, and peaks somewhat.
	Day 14	Ovulation.
The luteal phase		In this phase, the follicle that released the oocyte becomes the corpus luteum, and secretes progesterone and oestradiol.
		LH and FSH decrease.
		The cervical mucus becomes thin and easily permeable.
		Body temperature rises because of increasing progesterone.
	Day 21	Oestrogen declines again.
		Progesterone promotes the thickening of the endometrium, causing it to fill with fluids and nutrients in order to support implantation, should fertilisation occur.
		Smooth muscle contraction decreases.
		Cervical mucus becomes impermeable.
		If the oocyte is not fertilised, the corpus luteum deteriorates for the next seven days.
	Day 28	The deterioration of the corpus luteum causes a decrease in progesterone, which causes degeneration of the endometrium, and ultimately menstruation.

a = Gonadotropin-releasing hormone; b = Follicle-stimulating hormone ; c = Luteinising hormone

New *ultra low-dose* preparations contain only 15-20 μg EE.[5,6,8,9] Some of the new OCs consist of 24 active and four inactive tablets, compared to traditional OCs that contain 21 active tablets and seven inactive tablets.[5,6,8] A higher occurrence of breakthrough bleeding was found with ultra low-dose preparations in some studies. However, data are limited and results are inconsistent.[5,9,17]

The low-dose products contain < 50 μg EE, typically ≤ 35 μg.[8,9,13,15,17] Follicular development is still possible with EE dosages of ≤ 35 μg,[5,15] but these products provide the same contraceptive efficacy as high-dose preparations. However, they may have a lower risk of VTE, stroke and MI.[2,8,9,12,13,15] This will be discussed in the section on safety.

High-dose preparations contain 50 μg or more EE.[8,17] Because of cardiovascular side-effects, these preparations should only be used for specific indications, such as:[8]
- Cases where dysfunctional uterine bleeding and endometriosis are not adequately controlled by low-dose preparations.

- Patients who use hepatic enzyme-inducing agents, such as anticonvulsants and nevirapine.
- Clients who get persistent breakthrough bleeding after low-dose preparations have been used for 3-6 months, and other causes of bleeding have been excluded.

Table II gives an overview of the available OCs, their progestogen content and classification.

Contraceptive efficacy

Failure rates can be calculated by two methods: the Pearl index, or a life table:[3]
- The *Pearl index* is defined as the number of unintended pregnancies per 100 woman-years of use.[3,5,9,20]
- *Life index* contraceptive efficacy is defined as the number of women who become pregnant using a specific contraceptive in the first year of use. For example, if 100 women are using an OC, and 12 women become pregnant during the first year, the first-year failure rate is calculated to be 12%.[3]

Table II: Progestogens in oral contraceptives[8,15,17,19]

Progestogens	Progestogen generation or class	Product examples	Classification
Cyproterone acetate	Anti-androgen	Diane-35®, Adco-Fem 35®, Claro 35®, Cyprene-35 ED®, Diva-35®, Ginette®, Minerva®	Low-dose monophasic combined
Desogestrel	Third-generation	Marvelon 150/30®, Mercilon®	
Drospirenone	Anti-androgen and anti-mineralocorticoid	Ruby®, Yasmin®, Yaz®	
Gestodene	Third-generation	Femodene ED®, Melodene®, Minesse®, Minulette®, Mirelle®	
Levonorgestrel	Second-generation	Nordette®, Loette®	
Norgestimate	Third-generation	Cilest®	
Levonorgestrel	Second-generation	Nordiol®	High-dose monophasic combined
Norethisterone	First-generation	ªNorinyl-1/28®	
Norgestrel	Second-generation	Ovral®	
Gestodene	Third-generation	Tri-Minulet®, Triodene ED®	Low-dose triphasic
Levonogestrel	Second-generation	Logynon ED®, Triphasil®	
Norethisterone	First-generation	Trinovum®	
Norgestimate	Third-generation	Tricilest®	
Levonorgestrel	Second-generation	Biphasil®	High-dose biphasic

a = Norinyl-1/28® contains mestranol, whereas all the other products contain ethinyloestradiol. Mestranol is metabolised to EE in the liver.[2]

A "perfect-use" failure rate is defined as a situation in which all the rules regarding compliance and usage are followed strictly.

With typical use, the failure rate is influenced by the following factors:[5,6,8]
- User-guidance mistakes by dispensers.
- Mistakes regarding usage.
- Deliberate non-compliance.
- Restricted access to medication.
- Drug interactions.
- Vomiting and diarrhoea.

Surgical sterilisation, Depo-Provera® and intrauterine devices have first-year failure rates of less than 1% for perfect use. These methods are the most effective because they are not dependent on regular user action. OCs also have a theoretical first-year failure of less than 1%, but because of non-compliance or incorrect use, typical use first-year failure rates increase dramatically.[15]

The actual failure rates for combination and progestogen-only pills are at least 5-8%, mostly due to missed pills or not resuming therapy after the pill-free interval.[15,17,18] Some authors report the actual failure rate of progestogen-only products to be slightly higher than that of combined OCs.[3,6,18] The "mini-pill" must be taken at the same time every day to maximise the contraceptive effect.[6,8,17,18]

Preparations with 20 µg EE were compared to 35 µg EE products in a number of studies, and no differences in efficacy were recorded.[9,15] Overall, in these studies, the Pearl index for women taking products with 20 µg EE ranged from 0.2-1.0.[9]

As stated previously, not resuming therapy after the pill-free interval is one of the reasons for higher failure rates with typical use.[15] This pill-free interval may cause increased, and even rebound, ovarian activity, which may lead to contraceptive failure. Legro et al conducted a study (n = 62) to compare the effects of continuous and cyclic oral contraception. In the cyclic OC group, there were 11 suspected ovulatory cycles out of 60 cycles vs. only one ovulatory cycle in the continuous OC group over a study period of 168 days. These differences approached statistical significance (p-value = 0.054), but there were no pregnancies in either group.[21] In another study (n = 641), with a continuous OC regimen compared to a cyclic OC product, one woman became pregnant on continuous OC compared to three pregnancies in the cyclic comparator group, but the significance of this difference is not clear.[22]

A study (n = 1 417) was also done to compare the contraceptive efficacy, cycle control, compliance and safety of a weekly transdermal contraceptive patch and a daily OC. The overall and method failure Pearl indexes were 1.24 and 0.99 respectively for the patch, compared to 2.18 and 1.25 for the OC. Although the patch was numerically superior, the differences were not of any statistical significance. There was an 88.2% perfect compliance in the patch group, as opposed to only 77.7% in the OC group. One conclusion from this study was that the lower compliance rate with OCs could have resulted in the numerically higher actual failure rates compared to the patch.[20]

Drug interactions

Several medications may alter the active ingredient levels of OCs, which may subsequently alter efficacy.

Enzyme-inducing agents, such as anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate), accelerate the metabolism of the contraceptive hormones. However, sodium valproate, lamotrigine, gabapentin and levetiracetam do not seem to reduce the efficacy of OCs.[8,15,23]

Reports of OC failure due to broad-spectrum antibiotics are somewhat conflicting and anecdotal, but rifampicin reduces the levels of OC hormones quite dramatically.[4,8,15,23]

Nevirapine and HIV protease inhibitors also cause drug interactions with oral contraceptives.[8,15,23]

In a study conducted to determine the effects of St John's wort on desogestrel-containing OC therapy, no statistically significant differences were found in follicle maturation and serum oestradiol or progesterone levels between the three cycles (control cycle = OC alone, Cycle A = OC and St John's wort twice a day, Cycle B = OC and St John's wort three times per day). However, the area under curve (AUC, 0.24 h) of 3-ketodesogestrel decreased significantly in cycles A and B compared to the control cycle, and the incidence of intracyclic bleeding increased from 35% to 78% and 88% during cycles A and B, respectively.

Although there was no evidence of ovulation during concomitant use of the OC and St John's wort, it was concluded that bleeding irregularities may cause a decrease in compliance, and together with the decrease in serum concentrations of 3-ketodesogestrel, the risk of unintended pregnancies may increase.[15,24]

Non-contraceptive benefits of OCs

Oral contraceptives also have indications other than contraception, including the management of:

Menorrhagia and dysfunctional uterine bleeding

Progestogens prevent endometrial proliferation, and oestrogen provides stability to the endometrium.[9,17] OCs that contain 19-nor progestogens and lower dosages of oestrogen tend to cause more glandular atrophy and, usually, less bleeding.[16]

Dysmenorrhoea

Patients who experience this condition should take preparations with a higher progestogen component.[17] Suppression of ovulation may be followed by painless periods.[4,16,23]

Endometriosis

In this case, the patient should use a product that has a higher progestogen and a low oestrogen component.[17] Continuous OC use should also be considered in these patients, as long-term administration of progestogen or combination therapy prevents the periodic breakdown of endometrial tissue.[15,16,17]

Premenstrual tension or premenstrual dysphoric disorder (PMDD)

Monophasic 24/4 regimens and continuous OCs reduce hormonal fluctuations.[8,15,19,22] Although it is very difficult to determine the effect of OCs on behaviour and mood, they are being used successfully in the treatment of these syndromes. This is most likely due to the oestrogen component.[9,15,16] Yaz® (0.02 mg EE and 3 mg drospirenone) has been registered for the treatment of the emotional and physical symptoms of PMDD.[13,15,19]

Hyperandrogenism and hirsutism

OCs are successfully used in women with hyperandrogenism (mostly due to polycystic ovary syndrome) because of their overall anti-androgenic effect.[15,17] Both oestrogen and progestogen inhibit gonadotropin secretion, which decreases ovarian androgen secretion. OCs also decrease the serum-free androgen concentrations by increasing the plasma levels of sex hormone-binding globulin (SHBG) and inhibiting adrenal androgen secretion.[15-17,25] In addition, progestogens inhibit 5-α reductase, resulting in decreased dihydrotesterone (DHT).[17,25] Preparations that contain levonorgestrel must be avoided in women with hyperandrogenism, because it may aggravate the problem.[15] To the contrary, the third-generation progestogens may be more effective than older generation progestogens in reducing hirsutism and acne in women with hyperandrogenism, although this has not been clinically proven.[15,17]

Acne

OCs may improve acne by blocking the androgen receptor or causing a decrease in bioavailable testosterone, which in turn leads to lower sebum production.[9,16,25] The "skin-friendly" progestogens (third-generation) with low androgenic action and the anti-androgens may be particularly useful.[8,15,17,25] There is some speculation that drospirenone formulations are the most effective contraceptive products in the treatment of acne and hirsutism.[25] However, in a comparative trial with Diane-35® (n = 125), the median reduction in total facial acne lesions was 62% with Yasmin® and 59% with Diane-35® after 9 cycles. The difference was not statistically significant.[26] Therefore, superiority is not proven and more head-to-head trials are needed.[15,25]

OCs may also have the additional benefit of protecting women against:

- **Iron-deficiency anaemia:** The reduction in blood loss caused by progestogens may be useful in iron deficiency anaemia.[15,16,23] An increase in serum iron and total iron-binding capacity has been noted in clients who use OCs.[16]
- **Ovarian cysts and cancer:** The risk of ovarian cysts is reduced by products that contain high oestrogen dosages.[15,17] Ovarian cancer may be prevented for 10-30 years after the OC has been discontinued. It is suggested that OCs protect against ovarian cancer because of their ovulation-suppressing effects, thereby reducing the chance that DNA-damaged cells within the ovaries will multiply. Less stimulation of the ovaries by gonadotropin and progestogen-induced apoptosis are also possible mechanisms of protection.[15,27,28] Low-dose OCs seem to be as effective as high-dose OCs in preventing ovarian cancer.[12] Depending on how long OCs were used, they can give a 30-60% reduction in the risk of ovarian cancer.[27] Although OCs may decrease the risk of ovarian cancer in some women, they may also increase the risk of breast cancer in certain cases, even to the point that they should not be used.[27,28] This risk will be discussed in the section on safety.
- **Endometrial cancer:** The reduction in the risk of endometrial cancer is most likely due to suppression of endometrial proliferation by progestogen.[9,12,15,17,23]

OCs also decrease the risk and incidence of benign breast disease, ectopic pregnancy and pelvic inflammatory disease.[4,9,15,17,23] Combined hormonal contraceptives have little effect on bone health, but may preserve bone mass in the perimenopause.[23] OCs may prevent postmenopausal hip fractures in women who used them in their 30s.[9,15,17]

Safety

Cardiovascular disease

The reduction of EE dose in OCs from 50 µg to 30 µg has decreased cardiovascular-related death in OC users by 60%. It was thought that reducing EE to 20 µg would further decrease these incidents. However, data are still inconclusive, and this fact is demonstrated in the following paragraphs.[9]

Hypertension

OCs can cause a mild increase in blood pressure within the normal range. However, there have been some reported cases of overt hypertension. In the Nurses' Health Study, only 41.5 hypertensive cases per 10 000 person-years could be attributed to OC use. This risk decreased after cessation of therapy.[12] Hypertensive OC users are at increased risk of MI and stroke.[12,23]

Myocardial infarction

Previously, it was suggested that OCs might increase the risk of MI. However, because of the low incidence of MI in young healthy women of reproductive age, doubling the risk would still render an extremely low attributable risk.[12] The contrary is true for older women who smoke, or those with other CV risk factors. In these women, the risk of MI outweighs the risk of unwanted pregnancy.[9,12,16,23,29] However, it does seem that women who had used OCs are not at a higher risk for coronary heart disease later in life.[9,12,16,17]

The newer, third-generation OCs, i.e. containing desogestrel, norgestimate and gestodene, have better effects on the lipid profile than second-generation progestogens. However, this does not directly translate to lower MI risk. While some studies suggest no difference between the MI risk related to second- and third-generation progestogens, others suggest that third-generation progestogens may have a lower risk. Data are still inconclusive.[9,12,29,30]

Stroke

A higher ischaemic stroke risk has been reported in most studies, but not in all.[12,17,31] In two meta-analyses, it was concluded that the results of studies cast doubt on the true association between oral low-dose OCs and stroke risk.[32,33] In the one meta-analysis, 16 valid studies showed a positive association between current OC use and stroke risk, and in 11 studies a significant risk was found.[33] Other studies were also reviewed, and in all of them, the absolute risk of stroke was very low in young women (11.3 per 100 000 patients per year).[31,32] Stroke risk seems to be no different for second- and third-generation progestogens, but preparations containing less than 50 µg EE are associated with a lower risk than high-dose products.[12,17] Generally studies reveal a higher odds ratio in smokers, women with hypertension, diabetes, increased body mass index, age > 35 years, and relatively heavy users of alcohol.[16,17,23,31,32]

Migraine with aura is associated with a greater stroke risk than migraine without aura. Women with a history of migraines and who are taking OCs have a higher risk of cerebral thromboembolism, and this risk outweighs the risk of unwanted pregnancies in women older than 35 years.[23,32]

Venous thromboembolic disease

The risk of VTE is increased in both high- and low-dose contraceptive products, but according to most studies, the VTE risk is higher for high-dose contraceptives, compared to low-dose products.[13,16,34] The risk also varies with the different types of progestogens. Desogestrel, gestodene and cyproterone acetate appear to have a higher risk of thromboembolism, compared to second-

generation progestogens (levonorgestrel). Norgestimate does not seem to be associated with an increased risk vs. levonorgestrel.[12,13,34] The risk of VTE in users of OCs containing drospirenone is not yet clear.[34]

Other factors influencing VTE risk are:
- The risk of VTE is twice as high in obese OC users than in non-obese users.[12,23]
- The risk of VTE may be increased in older women and in smokers.[12,34]
- VTE risk is higher in first-time users in the first six months to a year of starting the OC. The VTE risk disappears after one to three months of discontinuation of OCs.[16,34]

Effects on the liver

Changes in bile acid components may cause an increase in symptomatic gall bladder disease and jaundice associated with the use of OCs.[16] An increased risk of hepatic adenomas has also been noted, but the risk of hepatocellular carcinoma is unchanged.[12,16,23]

Carbohydrate metabolism

High-dose OCs may give abnormal glucose tolerance test results, compared to low-dose OCs that render normal results. However, low-dose OCs may cause insulin resistance.[12] In addition, the more potent progestogens, such as norgestrel, may cause progressive decreases in carbohydrate metabolism over years of use.[16] Progestogen-only OCs must be used with caution in women with a history of gestational diabetes mellitus, as the latter may lead to type 2 diabetes.[12]

Cervical cancer

Women who used OCs may have a higher risk of developing cervical cancer, especially if infected with human papillomavirus (HPV). In a systematic review of 24 epidemiological studies that included 16 573 women, a positive correlation was found between women using combined OCs and the length of time the therapy was used. The risk of in situ, as well as invasive carcinoma, was increased with OC use of more than five years.[12,23]

Breast cancer

There is conflicting evidence with respect to the risk of breast cancer and OC use.[12,23,27] Epidemiological studies have generally not shown any relationship between OC use and the occurrence of breast cancer later in life. To the contrary, a small, but significant increase in the overall relative risk of breast cancer was observed in some meta-analyses. However, because OC users are young, this represented a very small increase in the absolute risk.[12]

Because of the uncertainty of the risk of breast cancer in women with a family history of breast cancer, a historical cohort study was conducted to determine whether the use of OCs in these women related to a higher risk of breast cancer. The relative risk of breast cancer in the entire study population was 1.4, and did not differ according to the duration of OC use. In sisters and daughters of persons who were previously diagnosed with breast cancer, the risk increased significantly in those who had ever used OCs, compared to those who never had (relative risk = 3.3). The increased risk was not seen in granddaughters, nieces or relatives by marriage,[35] and seemed to be more prominent in subjects who had used older formulations containing higher dosages of oestrogen and progestogen.[12,27,35]

In another study involving users and former users of OCs, the risk in women aged 35-44 years who had a family history of breast cancer were higher, but not significantly, compared to users in the same age group without a family history. In this study, the relative risk did not increase consistently with higher dosages of oestrogen, or with longer periods of use.[36]

Incidental use during pregnancy

Accidental OC use during early pregnancy is not connected to an elevated risk of congenital anomalies. However, there may be an increase in the incidence of congenital urinary tract abnormalities.[12,23]

Absolute contraindications

The following absolute contraindications and warnings related to combined OCs must be noted:[2,5,8,15,23]
- A history of arterial or venous thrombosis, or thrombogenic mutation (Factor V Leiden, prothrombin mutation, protein S, protein C and antithrombin deficiencies).
- Coronary or ischaemic heart disease, or structural heart disease with complications and severe hypertension.
- Smoking or cardiovascular disease, including migraine with aura, or focal symptoms of transient ischaemia, in women over the age of 35 years.
- Migraine with aura in women of any age, and even a simple migraine in women who are 35 years and older.
- History of oestrogen-dependent tumour.
- Oestrogen-containing products should be stopped four weeks before major surgery because of the risk of thromboembolic events, and alternative contraceptive methods should be used.
- Active liver disease.
- Hypertriglyceridaemia, diabetes for > 20 years, or diabetes with nephropathy, neuropathy or retinopathy.
- Undiagnosed abnormal uterine bleeding.
- Pregnancy and lactation (< six weeks postpartum).

The World Health Organization (WHO) has developed categories for scenarios where combination OCs should not be used, or should be used with extreme caution, as well as situations in which the advantages generally outweigh the disadvantages, and where no restrictions on use should apply.[2,5,23]

Conclusion

Over the last few decades, there have been noteworthy advances in the development of new contraceptive products, including a change from high-dose to low-dose to ultra low-dose combined OCs that contain different progestogens.

While the different combined OCs are equally effective in preventing pregnancy, in choosing a product, the advantages and disadvantages of each formulation should be assessed. Choice is strongly influenced by the individual's medical history and preferences.[3]

By counselling clients on the benefits, side-effects and risks of OC use, and how to take the tablets correctly and compliantly, which in turn, prevents unwanted pregnancies, low-dose OCs can impact significantly on women's lives

References

1. Department of Health, Medical Research Council, OrcMacro. South Africa demographic and health survey 2003. Pretoria: Department of Health; 2007 [homepage on the Internet]. Available from: http://www.doh.gov.za/docs/misc/sadhs-f.html
2. Wells BG, Dipiro JT, Schwinghammer TL, Hamilton CW, editors. Pharmacotherapy handbook. 5th ed. New York: McGraw-Hill, 2002; p. 274-292.
3. Theron F, Grobler F. Kontrasepsie: teorie en praktyk. 3rd ed. Pretoria: Van Schaik, 2000; p. 1-16.
4. Beers MH, Berkow R, editors. The Merck manual of diagnosis and therapy. 17th ed. USA: Merck Research Laboratories, 1999; p. 1925-1933 and p. 1995-2002.
5. Zieman M. Overview of contraception. UptoDate [homepage on the Internet]. c2009. Available from: http://www.utdol.com
6. Farrer F. Contraception: a review. S Afr Pharm J. 2009;76(6):18-22.
7. Godeau E, Gabhainn SN, Vignes C, et al. Contraceptive use by 15-year-old students at their last sexual intercourse. Arch Pediatr Adolesc Med. 2008;162(1)66-73.
8. Gibbon CJ, editor. South African medicines formulary. 8th ed. Cape Town: Health and Medical Publishing Group, 2008; p. 230-237, 326 and 425.
9. Thorneycroft IH, Cariati SL. Ultra-low-dose oral contraceptives: are they right for your patient? Medscape [homepage on the Internet]. c2009. Available from: http://www.medscape.com/viewarticle/408944_print
10. Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med. 2001;161:1065-1070.
11. Van Vlijmen EFW, Brouwer J-LP, Veeger NJGM, et al. Oral contraceptives and the absolute risk of venous thromboembolism in women with single or multiple thrombophilic defects. Arch Intern Med. 2007;167:282-289.
12. Martin KA, Douglas PS. Risk and side effects associated with estrogen-progestin contraceptives. UptoDate [homepage on the Internet]. c2009. Available from: http://www.utdol.com
13. Masimasi N, Sivanandy MS, Thacker HL. Update on hormonal contraception. Cleve Clin J Med. 2007;74(3):186-198.
14. Aitken RJ, Baker MA, Doncel GF, et al. As the world grows: contraception in the 21st century. J Clin Invest. 2008;118(4):1330-1343.
15. Martin KA, Barbieri RL. Overview of the use of estrogen-progestin contraceptives. UptoDate [homepage on the Internet]. c2009. Available from: http://www.utdol.com
16. Katzung BG, editor. Basic and clinical pharmacology. New York: Lange Medical Books/McGraw-Hill, 2004; p. 672-679.
17. Lalley JJ. Oral contraceptives overview [homepage on the Internet]. c2009. Available from: http://www.med.umich.edu/obgyn/resdir/contraception/OralContLalley.htm
18. Kaunitz AM. Progestin-only pills (minipills) for contraception.UptoDate [homepage on the Internet]. c2009. Available from: available from URL http://www.utdol.com
19. YAZ®: a low-dose oral contraceptive with drospirenone and a 24/4 regimen. S Afr Pharm J. 2009;76(7):38.
20. Audet M-C, Moreau M, Koltun WD, et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive. JAMA. 2001;285(18):2347-2354.
21. Legro RS, Pauli JG, Kunselman AR, et al. Effects of continuous versus cyclical oral contraception: a randomized controlled trail. J Clin Endocrinol Metab. 2008;93(2):420-429.
22. Grobler A. Continuous oral contraceptive use. Medifile. 2007;21(10):51-56.
23. World Health Organization. Medical eligibility criteria for contraceptive use. 4th ed. Geneva: World Health Organization, 2009; p. 1-42 [homepage on the Internet]. Available from: http://whqlibdoc.who.int/publications/2009/9789241563888_eng.pdf
24. Pfrunder A, Schiesser M, Gerber S, et al. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. Br J Clin Pharmacol. 2003;56(6):683-690.
25. Olutunmbi Y, Paley K, English JC. Adolescent female acne: etiology and management. J Pediatr Adolesc Gynecol. 2008;21:171-176.
26. Tan JKL. New developments in hormonal therapy for acne. Skin Therapy Lett. 2007;12(7):1-3.
27. Friedenson B. A current perspective on genetic testing for breast and ovarian cancer: the oral contraceptive decision. Medscape [homepage on the Internet]. c2009. Available from: http://www.medscape.com/viewarticle/408191_print
28. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Eng J Med. 2001;345(4):235-240.
29. Dunn N, Thorogood M, Faragher B, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ. 1999;318:1579-1584.
30. Tanis BC, Van Den Bosch MAAJ, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. N Eng J Med. 2001;345(25):1787-1793.
31. Petitti DB, Sidney S, Bernstein A, et al. Stroke in users of low-dose oral contraceptives. N Eng J Med. 1996;335(1):8-15.
32. Chan W-S, Ray J, Wai EK, Ginsburg S, et al. Risk of stroke in women exposed to low-dose oral contraceptives. Arch Intern Med. 2004;164:741-747.
33. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA. 2000;284(1):72-78.
34. Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy. Arch Intern Med. 2004;164(18):1965-1976.
35. Grabrick DM, Hartmann LC, Cerhan JR, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. JAMA. 2000;284(14):1791-1798.
36. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Eng J Med. 2002;346(26):2025-2032.