





COMBINED ORAL CONTRACEPTIVES

Summary

-  **Cardiovascular side-effects of oral contraceptives, though topical, are rare in practice.**
-  **The greatest risk to health comes from smoking while taking the pill rather than from the type of pill used.**
-  **Women with a personal history of venous thromboembolism or with possible familial thrombophilia should not use any combined oral contraceptive preparation.**
-  **The risk of breast cancer is slightly increased for up to ten years following use of combined oral contraceptives.**

INTRODUCTION

Oral contraceptives are the most popular method of birth control. They are effective, well-tolerated, convenient to use and readily available. Recent "pill scares" have led many users to re-evaluate the risk-benefit ratio.¹

HIGH DOSE OESTROGEN VS. LOW DOSE OESTROGEN PREPARATIONS

The dose of oestrogen varies from 20µg to 50µg in combined oral contraceptives (COCs). Most women nowadays use preparations containing 20 - 35µg of ethinyloestradiol (EE). The relative risk of thrombotic disease has decreased as the EE dose in oral contraceptives has been reduced. Some studies suggest an improved safety with regard to thromboembolic risks in users of oral contraceptives containing 20µg of EE.² Women with a predisposition to thrombosis should refrain completely from using COCs. Many of these women may be recognised by personal or family history of venous thrombosis. If this is positive, a thrombophilia screen should be done. If the screen is negative, a personal or family history would still remain a relative contraindication.

High-dose preparations containing 50µg of EE are used in selected cases, for example, in the presence of breakthrough bleeding on lower dose preparations or with co-administration of enzyme-inducing drugs such as anticonvulsants.

Oestrogen-related side-effects include nausea, dizziness, fluid retention with consequent cyclical weight gain and bloating, breast enlargement and tenderness.

FIRST VS. SECOND VS. THIRD GENERATION PROGESTOGENS

Norethisterone is representative of first generation progestogens which were first used in COCs. It is still used in combined and progestogen-only pills today. This was followed by the introduction of levonorgestrel, a second generation progestogen. The third generation progestogens developed include desogestrel, gestodene and norgestimate.³ Norgestimate is partially metabolised to levonorgestrel and to its metabolites. There is no theoretical reason for a difference in risk between formulations containing levonorgestrel and norgestimate.

Progestogen-related side-effects include vaginal dryness, acne, hirsutism, depression, sustained weight gain, increase in low density lipoprotein and decrease in high density lipoprotein. Third generation progestogens are associated with a lower incidence of androgenic metabolic side-effects such as hirsutism and acne and do not induce adverse changes in lipid metabolism.⁴

MONOPHASIC VS. BIPHASIC VS. TRIPHASIC ORAL CONTRACEPTIVES

Monophasic pills provide a fixed hormone dosage throughout the cycle. Biphasic pills have a fixed oestrogen concentration and a variable amount of progestogen in the cycle. Triphasic preparations have three distinct phases in which the dose of progestogen, and sometimes the oestrogen, is varied.⁵ They are

designed to mimic more closely normal endogenous cyclical hormonal activity. A low progestogen content in the early part of the cycle with triphasics allows greater oestrogen-stimulated endometrial development. The level of progestogen and oestrogen is further increased in mid-cycle to maintain a more normal uterine lining with less mid-cycle breakthrough bleeding or spotting. In addition a higher level of progestogen in the last half of the cycle allows for more regular withdrawal bleeds.

Second generation triphasic preparations contain a lower total amount of progestogen per cycle. Consequently they have less effects on metabolic parameters which are important to the risk factors for oral contraceptive use. They may offer some advantages for women with acne because they are more balanced towards oestrogen.

Triphasics are more complex to take. Some women develop dysmenorrhoea for the first time when taking a triphasic formulation because there is more endometrial proliferation than with monophasic formulations.⁶ They are not necessarily the best choice for all women. The relative benefits may be small and some are expensive.

CONTRAINDICATIONS

It is not possible in this context to give an exhaustive list of contraindications to the COC. Absolute contraindications include past or present vascular disease, oestrogen-dependent neoplasia, hepatic disease, focal migraine and undiagnosed vaginal bleeding. Readers are referred to the contraindications, precautions and warnings applying to all oral contraceptives standardised by the Irish Medicines Board and published in the Summaries of Product Characteristics (Data Sheet).

ORAL CONTRACEPTIVES AND ADVERSE CARDIOVASCULAR EFFECTS

The efficacy and safety of oral contraceptive use by healthy women have been debated since the first studies showing the excess risk of vascular disorders among women taking first generation oral contraceptives were published. These findings precipitated a "pill scare", the first of a number of smaller and larger ones, all related to real or perceived health risks of oral contraceptives.

The three serious cardiovascular side-effects to consider in relation to COCs are myocardial infarction (MI), stroke and venous thromboembolism (VTE). Since the October 1995 "pill scare", controversies have raged over whether there are differences in the risk profiles of second and third generation oral contraceptives. This particular "pill scare" was triggered by a warning issued by the British Committee on Safety of Medicines (CSM) about third generation oral contraceptives with respect to VTE. The warning was based on the then unpublished results of epidemiological studies, suggesting that COCs containing desogestrel and gestodene were associated with an increased risk of VTE, compared to users of second generation preparations.⁷⁻¹¹

More recent reports afford a better interpretation of the results of the studies.^{1,12,13} The main points of the evidence to date are that the weak odds ratios contrasting desogestrel and gestodene containing third generation versus second generation oral contraceptives for venous thromboembolism, ranging from 1.5 to 2.3 in the 1995-1996 studies, could be explained by bias rather than by a causal relationship and are probably of no public health significance.^{12,14} Absolute rates of VTE for these third generation oral contraceptive users reported in 1995-1996 are lower than those for users of second generation oral contraceptives in 1988-1991.¹ There is no difference in risk for VTE between first starters on second generation oral contraceptives versus first starters on desogestrel/gestodene containing oral contraceptives. Users of third generation oral contraceptives appear to be at lower risk of acute MI than users of second generation oral contraceptives in one study.^{1,11,15} Trends in other studies require confirmation. Occurrence rates of stroke are low, they are declining and no differences between second and third generation oral contraceptives are apparent.^{16,17}

Controversy will continue until publication of further studies which may add new aspects to this particular field.

ORAL CONTRACEPTIVES AND CANCER

The research to date on the links between oral contraceptives and breast cancer are copious and contradictory. The main findings of a recent meta-analysis of worldwide epidemiological data suggests women who are currently using COCs or have used them in the past ten years are at a slightly increased risk of being diagnosed with breast cancer.^{19,20} There is no evidence of an increase in the risk of breast cancer being diagnosed ten or more years after cessation of use and the cancers diagnosed are less advanced clinically than the cancers diagnosed in those who have never used COCs. The relation observed between breast cancer risk and hormone exposure is unusual and may be due to an earlier diagnosis of breast cancer in those who have ever used COCs, the biological effects of hormonal contraceptives or a combination of reasons. Any woman who has had breast cancer should not be offered the COC. Progestogen-only methods should be used only in consultation with her breast specialist. Ideally she should be encouraged to use a non-hormonal method such as an intra-uterine device or barrier contraception, if sterilisation is not appropriate.

Studies have indicated that carcinomas of the ovary and endometrium are reduced, perhaps by 50 per cent amongst current users. A protective effect can be detected in ex-users for up to 15 years.²⁰

Studies have shown an increased risk of cervical cancer but it is still unclear if the combined pill has a causative role because of potential confounding factors - such as smoking and sexual activity. Cigarette smoking is a far stronger and recognised co-factor with respect to cervical cancer.²⁰

MIGRAINE

Whether oral contraceptives can be prescribed safely in the patient with migraine depends upon many factors including patient age, type of migraine and the presence or absence of other stroke risk factors.^{21,22} The underlying worry is that the coagulation changes caused by oestrogen may change an ischaemic state from being transient to permanent (stroke).

Absolute contraindications to oestrogen in the COC whether pre-existing or occurring for the first time in a pill taker include

- focal migraine in which the symptoms can be explained by transient cerebral ischaemia.
- crescendo migraine, where the migraine is present all day with increasing severity even without focal symptoms.
- current use of ergotamine as therapy (may increase the risk of localised ischaemia).
- first ever focal migraine attack occurring with concomitant COC use.

Progestogen-only contraception may not stop the migraine but may eliminate the added concern that the contraceptive might amplify the small risk of thrombotic stroke.

WHICH PILL?

The individual characteristics of the woman seeking contraception and the preparations available must be considered and discussed in each case. Assuming the pill is not contraindicated, any woman <35 years and free of all risk factors (venous and arterial), might reasonably choose a second generation oral contraceptive. She could switch to a third generation oral contraceptive if she experiences side-effects. Young women smokers who use the pill are 10 times more likely to suffer an MI than users who do not smoke.¹⁸ If the pill is to be prescribed under these circumstances a third generation pill would seem appropriate.

For older women a third generation oral contraceptive may be a reasonable choice because of the apparently better metabolic profile of these pills. The presence of combined risk factors would contraindicate the use of any COC e.g. smokers over 35.

HORMONAL EMERGENCY CONTRACEPTION

The most common of these methods, the Yuzpe method, involves taking two doses of combined oestrogen-progestogen pills, with each dose containing 100µg of EE and 500µg of levonorgestrel - one dose is taken up to 72hrs after unprotected intercourse and the other taken 12 hours later.^{23,24} The Yuzpe regimen is equally effective at preventing pregnancy when treatment is started on the first, second or third day after unprotected intercourse.²⁵ There is no evidence of the efficacy of this method if initiated later than 72 hours after unprotected intercourse. The Yuzpe regimen appears most likely to work by rendering the endometrium inhospitable for implantation. If used within the first 10 days of the menstrual cycle it may delay ovulation and if given after ovulation, may affect the formation of a corpus luteum.²⁶ There is currently no authorised preparation in Ireland although a specific preparation is licensed in the U.K. Awareness of emergency contraception may be of particular relevance to users of barrier methods of contraception.

COSTS

☰ Almost 590,000 prescriptions for contraceptives were prescribed in 1996 costing the GMS almost £900,000.

☐ Over 550,000 prescriptions for combined oral contraceptives were prescribed in 1996 costing the GMS almost £840,000.

(*Bar chart to be inserted here.)

References

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