Oral Contraception: Five important issues.

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Introduction

The dosage of the hormones used in the combined oral contraceptive pill have, over the past 40 years, continually decreased in order to provide formulations with minimum side effects while still retaining efficacy.[1-4] Women are concerned that long-term use of combined oral contraceptives (COCs) increases health risks (including an increased risk of cancer or cardiovascular disease).

In this article we would like to highlight some of the above issues and some of the commonly asked questions. This would enable us to provide the necessary advice and guidance to our patients. Oral contraception is an area in the health sector where new products are constantly developed and this means that, to give patients the best available advice, general practitioners, pharmacists and gynaecologists need to stay abreast with the latest literature and developments.
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Low Dose Contraception

Industry has pursued the development of lower dose pill formulations. This is because it is believed that the adverse effects, and specifically the risk of venous thrombo-embolism (VTE) are reduced with the reduction in the oestrogen dose.[1-3] These new low-dose products have less oestrogen in a week's pills than was the daily dose in the first pills from the sixties. Similarly, the daily dose of progestogen from those early brands now covers a complete cycle.

The concern, among users and prescribers, is that with the lowering of the dose there would be a decrease in the efficacy of the pill. COCs are almost 100% reliable, when taken correctly and consistently, with a failure rate of 0.1 pregnancies per 100 women years.[1,2,5] Allowing for 'user-failure', the failure rate can be up to 6 pregnancies per 100 women years, or more. The preparations containing only 20 µg ethinyloestradiol have been shown to be effective contraceptive agents, with pregnancy rates ranging between 0.7 to 2.1 pregnancies per 100 woman years of treatment.[1,2,4] Therefore, the fear that a lower dose is less effective seems unfounded.

These low-dose COCs have comparable cycle control and reduced symptoms of bloating and breast tenderness.[2,4] With regards to risk and specifically VTE risk, the question of whether further reduction of the oestrogen dose below 35 µg confers additional benefits, remains controversial and we will elaborate on this issue later.[2,6,7]

Reversibility

The use of COCs does not impair long-term fertility.[8] The Oxford Family Planning Association (Oxford-FPA) contraceptive study demonstrated that there is an initial delay of two to three months in the time taken to give birth to a child.[8] In this study fertility of both nulligravid and parous women who stopped taking COCs, was initially impaired when compared to women who stopped using other methods of contraception.[8] However, the effect of COCs on fertility becomes negligible by 42 months after cessation of contraception in nulligravidae and by 30 months in multiparae.[8] Impairment was independent of the length of use of COCs.[8]

Women discontinuing COCs with higher doses of oestrogen (>50 µg) had greater conception delays than those on lower doses who, in turn, had longer delays than other method users.[9] In the Nurses' Health Study II, 88% of users of COCs reported an eventual pregnancy within four years, which suggests that absolute fertility is not impaired. The median length of time to pregnancy was 2.2 years.[10]

Fluid Retention and Weight Gain

Fluid retention and weight gain are minor side effects of the COCs. Few placebo-controlled, randomised studies have been done to establish the incidence and severity of these symptoms in users of different oral contraceptive formulations.[11,12] However, among women and many clinicians there is a perception that oral contraceptives cause fluid retention and weight gain and that this may differ in different products.[4,11] This perception may lead to women quitting hormonal contraception prematurely or even deter them from starting contraception.[4,11]A recent systematic review of the literature showed no effect of COCs on weight gain.[11]

A recent study evaluated the effect of the new combination of 30 µg of ethinyloestradiol and 3 mg drosperinone. This study indicated that the antimineralocorticoid effect of the drosperinone has a beneficial

effect on fluid retention and the associated symptoms. Body weight remained stable or decreased slightly during the study.[12] These findings would have to be confirmed in the future by more extensive studies.

Venous Thrombo-embolism (VTE)

The first reports of VTE associated with the use of COCs appeared in the 1960s.[6] Since then, this risk has been studied extensively and led to much controversy and debate. Recent studies indicate that the risk of VTE is lower for modern day low-dose pills.[1,8]

In a large study of 2 739 400 oral contraceptive prescriptions received by 234 218 women, the VTE risk appeared to be proportional to oestrogen dose.[7] On the basis of pharmacy data collected in Michigan between 1960 and 1986, this study showed that the adjusted relative risk of venous thromboembolism in users of formulations containing 50 g of oestrogen was 1.5 (95% confidence interval (CI) 1.0-2.1, p = 0.04) and the relative risk in users of formulations containing more than 50 g of oestrogen was 1.7 (95% CI 0.9-3.0, p = 0.06), when compared to the VTE risk of users of formulations containing less than 50 g of oestrogen.[7] However, the WHO in 1998 stated that among users of combined oral contraceptive preparations containing less than 50 µg of ethinyloestradiol, the risk of VTE is not related to the dose of oestrogen.[3]

Cohort studies in the United States in the early 1980's and in the United Kingdom in the 1990's found an increased relative risk of VTE of 2.7 to 2.8 for users of current COCs compared with non-users.[9, 10] Case-control studies conducted in Europe reported a relative risk of 2.1-4.4.[6,15]

The most recent, well publicised debate was about the apparent increase in risk with the use of COCs containing gestodene and desogestrel (GSD/ DSG), the so called '3rd generation' progestogens. In 1995 the committee on Safety of Medicines (CSM) in the UK alerted doctors to the findings of three studies which apparently demonstrated a twofold increased risk of VTE for COCs containing GSD/ DSG compared to COCs containing the 'second-generation' progestogens levonorgestrel or norethisterone (LNG/ NET). This led to debate and further studies to assess this perceived differential in risk for VTE. Several, but not all recent studies have confirmed these findings.[6,15-19] To put this into perspective, the spontaneous incidence of VTE in healthy non-pregnant women (non-user) is approximately 5 cases per 100 000 women per year. The incidence in users of LNG/ NET pills is approximately 15 cases per 100 000 women per year and the incidence in users of GSD/ DSG pills is approximately 25 cases per 100 000 women per year of use.[20] This must be seen against the background risk of 60 cases per 100 000 pregnant women per year. The risk of VTE also increases with age and other factors such as obesity. In 1999, the CSM in the UK issued a revised statement supporting all types of COC to be an appropriate choice as first line contraception, provided that women have no medical contra-indications and are fully aware of the small difference in risk of VTE.

The contra-indications referred to above are listed in Table 1.

These contra-indications are with specific reference to VTE and do not cover other well known contra-indications such as diabetes and smoking. The aim should be to choose the appropriate contraception for each patient, which might not be oral contraception.

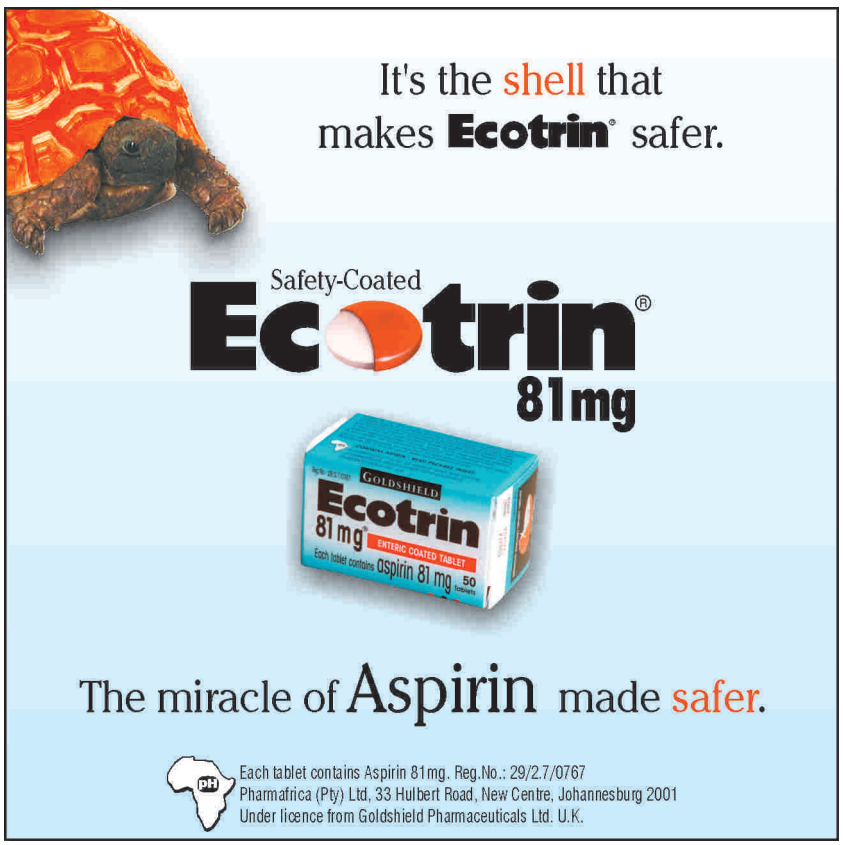
Table I: Absolute and relative contra-indications adapted from Guillebaud (*Contraception Your Questions Answered Choices,3rd edition: 1999:183)*

Absolute contra-indications
- Family history of VTE with confirmation of a clotting factor abnormality such as Factor V Leiden, deficiencies of Protein S, Protein C or Antithrombin III.
- BMI >39
- Being bedridden.
- Varicose veins with a past history of thrombosis.

Relative contra-indications:
- Family history of VTE with normal clotting factors.
- BMI 30-39
- Wheelchair bound.
- Extensive varicose veins.

Breast Cancer and other Neoplasms

An analysis of epidemiological data indicates that the current and recent



use of COCs is associated with a small increased risk of diagnosis of breast cancer, which is unrelated to the dose or duration of COC use. [21] For women up to the age of 35, the risk of breast cancer remains very low irrespective of the use of hormonal contraception, and is about 1 in 500.[21] The Collaborative Group on Hormonal factors in Breast Cancer found in 1996 that there is a relative risk of 1.24 in current users of COCs.[21] With a background risk of 1 in 500 this translates to one extra case of breast cancer for every 2000 users. This difference in risk between users and non-users decreases after cessation of use and disappears after 10 years.[21]

It was also noted that the increased risk of breast cancer diagnosed among COC users has been limited to localised disease that could possibly be due to earlier diagnosis because of increased visits to the clinician.[21] These risks are not associated with the duration of use, dose or type of hormone in the COC.[21]

Prescribers and patients must put these facts into perspective when deciding on contraception. For every 1 000 women at age 45 who had stopped using COCs at age 35 there would be one extra case of breast cancer compared with "never-users" (women who had never used COCs) or those who had stopped more than 10 years before. In real terms this means that there would be 10 cases amongst the "never-users" and 11 in the group who used COCs. A recent study by Marchbanks *et al* showed that among women from 35 to 64 years of age, current or former users of COCs have not been associated with a significantly increased risk of breast carcinoma.[22]

The Cancer and Steroid Hormone Study (CASH) showed that up to an 80% reduction in risk of epithelial ovarian cancer is associated with COC use, and the protection commenced within the first year of use.[23] The risk of ovarian cancer decreases with the increasing duration of COC use. The incidence is 40% (RR=.60) and 51% (RR=0.49) for four and eight years of use respectively (p<0.001).[3]

The CASH study also showed that COC use reduces the risk of endometrial cancer by 50%.[24] The magnitude of protection is directly related to the duration of COC use, and protection continues for many years after stopping COC use.[24] The incidence of endometrial cancer is reduced by 54% (RR=0.46) and 66% (RR=0.34) for four and eight years of use respectively (p<0.001).[3]

The use of COCs has been associated with an increased risk of cervical intra-epithelial neoplasia and cervical cancer.[1,25] The human papillomavirus(HPV) has been implicated as the main causative agent in cervical cancer. COC use most likely acts as a co-factor in the developement of this disease.[1,25] Hormonal contraception for less than five years did not increase the risk of cervical cancer. However, the risk increased with use of hormonal contraception for five to nine years and was greatest for ten years or longer.[1,25]

To summarise the effect of COCs on cancers: there is a small increased risk for breast and cervical cancers and there is a reduced risk for ovarian and endometrial cancer with the use of low dose COCs.[3] Uncertainty remains regarding a reduced risk for colorectal cancer and the increased risk for liver cancer.[3]

In conclusion, COC is a safe and effective form of reversible contraception. The side-effects and risks must be seen in the context of overall disease among women of reproductive age, the total mortality to which young women are exposed in their daily lives and against the risks of an unwanted pregnancy or medically complicated pregnancy. There are also numerous non-contraceptive benefits such as reduced menstrual blood loss, reduced dysmenorrhoea, improved acne, decreased risk of cyst formation and a lower risk of ovarian and endometrial cancer.

See CPD Questionnaire, page 38

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