

Review Article

“Conceiving” the pill

The 45th birthday of the oral contraceptive pill in Europe

Jean Calleja-Agius, Mark Brincat

Abstract

In 1961, the first combined oral contraceptive pill was introduced in Europe. This pill contained ethinylestradiol (0.05mg) and norethisterone (4mg). Nowadays, monophasic pill preparations contain a low dose (20–35 µg) of ethinylestradiol in combination with a progestogen. Progestogens include norethisterone and levonorgestrel (second generation); desogestrel and gestodene (third generation); and the newest progestogen, drospirenone (fourth generation). Risks of the combined oral contraceptive pill include venous thromboembolism and stroke. Benefits, such as protection from ovarian and endometrial cancer, apart from contraception, outweigh the risks if contraindications are observed, and low dose formulations used.

Keywords

Contraception; ovulation inhibition;
historical aspects

Jean Calleja-Agius* MRCOG, MRCPI
Department of Obstetrics and Gynaecology
St Luke's Hospital, G'Mangia, Malta
Email: jean@waldonet.net.mt

Mark Brincat FRCOG, PhD
Department of Obstetrics and Gynaecology
St Luke's Hospital, G'Mangia, Malta

* *corresponding author*

In 1931, Ludwig Haberlandt, Professor of Physiology in Innsbruck, Austria wrote: 'of all the methods available, hormonal sterilisation, based on a biological principle, if it can be applied unobjectively in the human, is the ideal method for practical medicine and its future task of birth control.' His experiments involved transplanting ovaries from pregnant rabbits under the skin of fertile adult does, and he found that they become infertile.

The three most well-known persons who are considered the pioneers in the development of the oral contraceptive pill are Margaret Sanger, Katherine Dexter McCormick and Gregory Goodwin Pincus. They had met in 1951 to initiate the project that resulted in marketing the first oral contraceptive. Margaret Sanger was a nurse specialising in obstetric care, who introduced the term 'birth control' in 1914 in America through a monthly magazine entitled 'The Woman Rebel', which she edited. In 1950, Katherine Dexter McCormick, a philanthropist, sent a letter to Sanger indicating her interest in supporting 'further contraceptive research.' Both women had long been aware of the pressing social and population problems caused by the lack of adequate birth control. The political and social climate was such that it was strictly unlawful to advise, prescribe or instruct on the use of contraceptives. Sanger referred McCormick to Dr Gregory Goodwin Pincus, a biological scientist expert in endocrinology and mammalian reproduction at the Worcester Foundation for Experimental Biology. In 1951, Pincus accepted to start working on the development of a physiological contraceptive for safe mass use, and his research was funded by McCormick.

The first experiments started on 21st April 1951, and in 1960 the first oral contraceptive pill was patented as Enovid-10, containing 0.15mg of mestranol as oestrogen component and 10 mg norethindrol. Clinical trials were carried out in Puerto Rico and Haiti. Pharmaceutical companies became eager to enter the fast-growing oral contraceptive market. In 1961, Schering AG of Berlin, introduced the Pill in Europe. This was called Anovlar, which contained the progestogen, norethisterone (4mg), but the oestrogen component was changed from mestranol to ethinylestradiol (0.05mg). Ortho Pharmaceutical Co. received the approval of the US Food and Drug Administration (FDA) to market its Pill Ortho-Novum, which contained the progestogen norethindrone. Pill use rose from half a million women in the USA in 1961 to about 4 million in 1965, and is now used worldwide. The Pill continues to be the most studied medication to ever come to the market, with new data emerging on its health benefits and risks.¹

Table 1: Pharmacological profiles of various progestins

	<i>Progestogenic</i>	<i>Glucocorticoid</i>	<i>Androgenic</i>	<i>Antiandrogenic</i>	<i>Antimineralocorticoid</i>
Progesterone	+	-	-	(+)	+
Drospirenone	+	-	-	+	+
Levonorgestrel	+	-	(+)	-	-
Gestodene	+	-	(+)	-	(+)
Norgestimate	+	-	(+)	-	-
Desogestrel	+	-	(+)	-	-
Dienogest	+	-	-	+	-
Cyproterone acetate	+	(+)	-	+	-

- no effect (+) mild effect + strong effect

In Malta, the hormonal oral contraceptives were introduced in the mid-1960s, but were being advertised as menstrual cycle regulators. In spite of their availability on the local market in the 70s, only 2% of the female population interviewed were using hormonal contraception. Twenty years later, by 1993, the usage rate had increased to 15.8%.²

Pharmacology

The term 'combined oral contraception' (COC) is used to describe monophasic preparations containing a low dose (20–35 µg) of ethinylestradiol in combination with a progestogen. Progestogens include norethisterone and levonorgestrel (second generation); desogestrel and gestodene (third generation); and the newest progestogen, drospirenone (fourth generation). The progestogenic component of a COC usually determines the overall metabolic and clinical effects, and consequently, distinguishes between different brands and influences choice (Table 1). Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen.

The oral contraceptive pills available in Malta include Mercilon®, Meliane® Cilest®, Gynera® and Minesse®. Mercilon® (Organon) contains 150 µg desogestrel and 20 µg ethinylestradiol. Cilest® (Janssen-Cilag) contains 250 µg of norgestimate and 35 µg ethinylestradiol. Gynera® (Schering) contains 75 µg gestodene and 30 µg ethinylestradiol. Minesse® (Wyeth-Ayerst) is different from the other combined oral contraceptive pills because it is a 24 day regimen, with each pill containing 60 µg gestodene and only 15 µg of ethinylestradiol.

Contraceptive technology has rapidly progressed as further insights into basic mechanisms of physiology and pharmacology have been gained. The introduction of drospirenone as a progestin in COCs was one recent development. Unlike other progestins, drospirenone is a derivative of spiroactone and has anti-mineralocorticoid activity. The antimineralocorticoid activity of drospirenone reduces the oestrogen-induced water retention, via the renin-angiotensin-aldosterone-system. In addition, drospirenone exhibits anti-androgenic activity by blocking androgen receptors. Yasmin® (Schering) is a monophasic COC formulated as tablets containing 30µg ethinylestradiol and 3mg drospirenone, taken once daily for 21 days followed by a 7-day

hormone-free interval. A new low-dose formulation based on drospirenone has been developed and is marketed under the brand name Yasminelle®. Yasminelle® is formulated with a lower oestrogen dose than Yasmin® (20µg vs 30µg ethinylestradiol), but with the same drospirenone dose (3mg). In Yasminelle®, ethinylestradiol is contained in a betadex (beta-cyclodextrin) clathrate—one molecule of ethinylestradiol within two molecules of betadex. This formulation was done in order to improve stability at low hormone concentrations and prolong shelf-life. The calculated dissociation half-life of this complex molecule is 26 minutes. Therefore the pharmacokinetics and relative bioavailability of ethinylestradiol are unaffected. A multicentre trial showed that Yasminelle® is an effective contraceptive with a Pearl Index of 0.23 (upper limit of 97.5% CI 0.84), with improved emotional and physical well-being, stable body weight, reduction of acne and good overall tolerance.³ The main disadvantage over the higher dose ethinylestradiol formulations is that of an increased rate of intracycle bleeding (20.8% in the first cycle and up to 11.3% in subsequent cycles). A study comparing Yasminelle® with ethinylestradiol 20 µg/desogestrel 150µg (Mercilon®) showed a comparable cycle control, safety, and efficacy profile.⁴

Risks of the Combined Oral Contraceptive Pill

Venous thromboembolism

By 1970, the risk of venous thromboembolism (VTE) was known to be associated with the dose of oestrogen, which was consequently reduced. A WHO study in 1995 concluded that COC users had a relative risk of 3.2-4.1 of venous thromboembolism compared with non-users.⁵ Therefore relative risk of venous thromboembolism is increased with combined oral contraceptive use. Nevertheless, the rarity of venous thromboembolism in women of reproductive age means that the absolute risk remains small.⁶

The risk appeared within 4 months of starting the COC and disappeared within 3 months of stopping, and decreases with duration of use, however remaining higher than in non-users. The risk was higher with COCs containing third-generation progestogens than with those containing second-generation

Table 2: Risk table for combined oral contraceptive (COC) users and risk of venous thromboembolism

	Relative Risk	Absolute Risk per 100,000 woman-years
Not using COC		5 in 100,000
COC containing levonorgestrel or norethisterone	3-fold increase	15 in 100,000
COC containing gestodene or desogestrel	5-fold increase	25 in 100,000
Pregnancy	12-fold increase	60 in 100,000

progestogens. The relative risks were 2.6, 5.3 and 5.7 for COCs containing levonorgestrel, desogestrel and gestodene, respectively, all of which are within the recognised range.⁶

According to the Royal College of Obstetricians and Gynaecologists, a levonorgestrel- or norethisterone-containing combined oral contraceptive should be advised as a pill of first choice. However, after counselling, a woman may choose a desogestrel- or gestodene containing combined pill.⁶

Describing risk in relative terms may sound more alarming than in absolute terms. The risk of VTE in non-users is low (5 per 100,000 woman years). This increases to 15 per 100,000 woman years with COCs containing levonorgestrel or norethisterone and to 25 per 100,000 woman years with COCs containing desogestrel or gestodene.⁶ Thus, venous thromboembolism is uncommon in women of reproductive age and despite a five-fold increase in risk for women using gestodene- or desogestrel-containing COCs, the absolute risk remains small (Table 2).⁶

Myocardial infarction

COCs are contraindicated in smokers over the age of 35, due to increased risk. A recent study in the UK concluded that there was no association between COCs and myocardial infarction.⁷ A European multicentre study has also shown that there is a reduced risk associated with third-generation COCs.⁸

Stroke

COCs with a higher dose of ethinylestradiol increase the risk of stroke. Recent studies concluded that the relative risk of haemorrhagic stroke is 1.0-1.73, and for ischaemic stroke is 2.85. No difference was found between pills containing different progestogens.^{9,10}

Hypertension

COCs have been shown to cause a 'statistically significant but clinically unimportant' rise of 1.0mmHg in diastolic pressure.¹¹

Breast cancer

In 1996, a meta-analysis of 54 studies, ranging from 1976 to 1992, reached two main conclusions. Firstly, during COC use and for 10 years afterwards, the relative risk of developing breast cancer is 1.24 in users and 1.07 5-9 years after stopping. Breast cancers in COC users tended to be less advanced than

in non-users. Secondly, there is no excess risk of breast cancer 10 or more years after stopping COC use. The dose and type of hormone had little effect.¹²

One should note that in the above meta-analysis, many subjects had been taking the pill in the high-dose era. There is evidence that low-dose COCs stimulate the breast less, and therefore further studies are required, as the effects of currently used COCs may be less than those in this analysis.¹²

Cervical cancer

After differences in sexual activity and the use of barrier methods (which have a protective effect) have been accounted for, there appears to be no increase in the risk of cervical squamous carcinoma among women who take COCs.¹³ However, COC usage increases the risk of cervical adenocarcinoma, with a relative risk of 4.4 in women using the pill for more than 12 years.¹⁴

Liver disease

COC use increases the risk of hepatocellular adenoma and carcinoma. There is relative risk of 1.6 of symptomatic gallstones for current COC use, and use for more than 15 years.¹⁵

Table 3: Benefits of the Pill: Risk Reduction in %¹⁷

Ectopic Pregnancy	90%
Cancer	
Ovary	40%
Endometrium	40%
Benign Breast Disease	40%
Ovarian Cysts	
Solid Tumours	20%
Follicular Cysts	49%
Luteal Cysts	78%
Fibroids (after 5 years' COC use)	15%
Pelvic Inflammatory Disease	50%
Menorrhagia	50%
Iron Deficiency Anaemia	50%
Dysmenorrhoea	40%

Bowel disease

Recent use of COCs increased the risk of both ulcerative colitis (relative risk of 2.0) and Crohn's disease (relative risk 2.6). Women who had used COCs for more than 6 years had an increased risk of Crohn's disease (relative risk of 5.1), but the risk of ulcerative colitis was not associated with duration of use and seemed to be restricted to high-oestrogen COCs.¹⁶

Benefits of the pill: risk reduction in %¹⁶

Use of the COC pill has been shown to decrease the risk of a number of pathological conditions in women. The risk reduction for these is shown expressed as a percentage (Table 2).

Conclusion

Over the past 45 years, there have been great developments in the field of oral contraception. Nowadays, the health benefits of the pill greatly outweigh the risks, provided contraindications are observed, and low dose formulations are used.

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