

Qlaira[®]: a 'natural' change of direction

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Background

There is no doubt that the combined oral contraceptive pill (COC) has revolutionised and changed women's lives for the better. With the discovery of progestogens in the 1940s/1950s, and the realisation that the accidental addition of synthetic estrogen [mestranol – the inactive precursor of ethinylestradiol (EE)] improved bleeding patterns, the contraceptive pill was born. Ever since, work has been ongoing to reduce its dose, its health risks and its side effects. In the last 50 years, doses of synthetic estrogen have fallen from 150 µg mestranol to just 15 µg EE (Mircette[®] containing desogestrel and Minesse[®] containing gestodene – neither pill is currently available in the UK). These 'ultra low-dose pills' maintain efficacy when modern progestogens are used,¹ but the cost is cycle control: only 72% of women report 'normal cycles'.² In addition, these pills still produce small changes in lipid metabolism, coagulation factors and glucose regulation.¹ Could a 'new pill' formulation using 17β-estradiol or one of its esters offer a 'safer option'?

Advent of 'estradiol pills'

A small number of studies were published in the late 1980s and 1990s investigating pills containing 17β-estradiol using 'standard' progestogens of their day.³ These formulations could provide good contraceptive efficacy but the resultant cycle control was unacceptable to users.⁴ One contraceptive pill containing 'estradiol' is currently on the market in Finland [Femilar[®] – 10 tablets of 1 mg estradiol valerate (E2V) with 1 mg cyproterone acetate (CPA) and 11 tablets of 2 mg E2V with 2 mg CPA] but it is only licensed to prevent pregnancy in women aged over 40 years or in those over 35 years where EE 'does not fit'.⁵ In the 1990s there was a general feeling amongst experts in the field that we were unlikely to see an 'estradiol' pill in our lifetime. So what has changed?

First, the continuous strive to discover new progestogens has resulted in hormones that are more 'target organ'-specific, produce fewer nuisance side effects and inhibit ovulation effectively. Dienogest (DNG) inhibits ovulation at doses of 2 mg mainly by peripheral action on the ovarian granulosa cells rather than suppressing gonadotrophins centrally.^{6,7} It is thought to demonstrate specific activity on the endometrium as it is ten times more potent than levonorgestrel (LNG) as judged by the Clauberg-McPhail assay (a test using estrogen-primed rabbits to measure secretory changes in the endometrium).⁶ DNG also displays anti-androgenic activity.⁸ DNG (2 mg) has been available for more than 10 years worldwide in combination with 30 µg EE as Valette[®], which is the leading COC in Germany (though it is not currently

available in the UK). When compared to other COCs, Valette gives excellent cycle control⁹ and similar benefits on mild to moderate acne to 35 µg EE/2 mg CPA.¹⁰

Second, different regimens have been explored to try and improve cycle control. Trials involving estrogen priming of the endometrium using 2–3 days of E2V have helped to achieve this aim.^{11,12} Finally, reducing the hormone-free interval has been shown to decrease mood changes, headaches, menstrual loss and pelvic pain.¹³ Therefore developing an 'estradiol' pill with this in mind may result in additional non-contraceptive benefits.

What is Qlaira[®]?

Qlaira[®] has recently been launched in the UK. The cost per cycle to the National Health Service (NHS) is £8.39, however Qlaira's success will depend on successful formulary acceptance and appropriate prescribing.

Qlaira has four phases covering 26 days with two placebo tablets making up the 28-day preparation (Figure 1). The first two tablets in the cycle contain 3 mg E2V to prime the endometrium. The next five tablets include 2 mg E2V and 2 mg DNG followed by 17 tablets with 2 mg E2V and 3 mg DNG. Finally there are two tablets with 1 mg E2V only and two placebo tablets.

Pharmacokinetics and pharmacodynamics

After ingestion E2V is rapidly absorbed through the gut wall where it is hydrolysed to 17β-estradiol (1 mg E2V being equivalent to 0.76 mg 17β-estradiol). Stable serum levels are achieved within the physiological range of the follicular phase of the menstrual cycle (about 180 pmol/l).¹⁴ Qlaira's regimen appears complex but it does allow for stable levels of 17β-estradiol throughout the cycle with no obvious 'estrogen withdrawal' during the placebo phase, suggesting that there is still endogenous production of estrogen.¹⁴ This may prevent 'hormone withdrawal' symptoms and menstrual complaints. Further research is underway investigating this area. Steady-state levels of DNG are achieved 2–3 days after dosing at each dose level and fall during the 6 days of no DNG administration.¹⁴

Efficacy data

A large, multicentre, open-label European study recruited 1377 women aged between 18 and 50 years and followed them for 20 cycles.¹⁵ The corrected Pearl index for all those entering the study was 0.34, with Qlaira being equally effective in the over- and under-35s (corrected Pearl index of 0.4).¹⁵ A further study comparing Qlaira with a 21/7 20 µg EE/100 µg LNG pill (Miranova[®] – not available in the UK) resulted in just one method failure (in the Miranova group).¹⁶ These Pearl indices are similar to those reported for conventional EE-containing pills.¹⁵

Cycle control

In a large, multicentre, double-blind, double-dummy, randomised controlled study to compare bleeding pattern, cycle control and safety of Qlaira versus Miranova over seven cycles Qlaira users had significantly fewer bleeding/spotting days with shorter and lighter withdrawal bleeds.¹⁶

Bleeding patterns were not affected by the age of the woman. Approximately 20% of women taking Qlaira did

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Table 2 Qlaira®s missed pill guidance as stated in the Summary of Product Characteristics²⁰

Day	Colour and content of tablet	If this pill is forgotten for more than 12 hours:
1–2	Dark yellow tablets (3.0 mg E2V)	Take missed pill immediately and the next tablet taken at usual time (even if this means taking two tablets on the same day) Continue with tablet taking in the normal way
3–7	Medium red tablets (2.0 mg E2V + 2.0 mg DNG)	Abstain or use an additional contraceptive method for the next 9 days
8–17	Light yellow tablets (2.0 mg E2V + 3.0 mg DNG)	
18–24	Light yellow tablets (2.0 mg E2V + 3.0 mg DNG)	Discard current wallet Start taking the Day 1 pill from a new packet immediately and continue taking these pills at the correct time Abstain or use an additional contraceptive method for the next 9 days
25–26	Dark red tablets (1.0 mg E2V)	Take the missed tablet immediately and the next tablet at the usual time (even if it means taking two tablets on the same day) Additional contraception is not necessary
27–28	White tablets (placebos)	Discard the forgotten tablet and continue tablet taking in the normal way Additional contraception is not necessary

If more than 12 hours has elapsed the last missed pill should be taken immediately and the next pill taken when due. It may mean taking two pills at the same time. An additional contraceptive method should be used as detailed in the table above. Not more than two tablets are to be taken on a given day.

If a woman has forgotten to start a new wallet or if she has missed one or more tablets during Days 3–9 of the wallet she may already be pregnant (provided she has had intercourse in the 7 days before the oversight). The more tablets (of those with the two combined active ingredients on Days 3–24) that are missed and the closer they are to the placebo tablet phase, the higher the risk of pregnancy.

If the woman missed tablets and subsequently has no withdrawal bleed at the end of the wallet/beginning of the new wallet, the possibility of a pregnancy should be considered.

DNG, dienogest; E2V, estradiol valerate.

Metabolic changes

Several studies have looked at the metabolic changes with Qlaira when compared to other COCs. A single-centre, open-label, randomised controlled trial investigated the impact of Qlaira versus Logynon® (triphasic EE/LNG COC) on plasma lipids and haemostatic variables over seven cycles.¹⁷ Overall use of Qlaira resulted in more favourable lipid profiles than Logynon with high-density lipoprotein (HDL)-cholesterol increased from baseline to Cycle 7 by 7.9% in the Qlaira group and decreased by 2.3% in the Logynon cohort ($p = 0.055$). Both preparations had similar effects on other lipid parameters.¹⁷

This study¹⁷ also explored haemostatic changes, with Qlaira having a lower impact on such measures when compared to Logynon. Levels of prothrombin fragment 1 + 2 and D-dimer remained relatively unchanged in the Qlaira group but markedly increased in Logynon users (although they remained within the normal range and generally stable).¹⁷

Increases were seen in sex hormone binding globulin (SHBG), corticosteroid-binding globulin and thyroxine-binding globulin for both groups¹⁷ but these were more marked in those taking Logynon. SHBG rose by 63% with Qlaira (but remained within the normal range) and 117% with Logynon, resulting in mean values exceeding the normal range.¹⁷

A further open-label, crossover study compared the haemostatic effects of Qlaira with Microgynon® over three cycles.¹⁸ Although all primary outcome variables remained within normal range, there was a significantly smaller intra-individual rise in D-dimer with Qlaira ($p = 0.01$) and less pronounced effects on other haemostatic parameters than with Microgynon.¹⁸ To date there have been no published data investigating the effects of Qlaira on glucose metabolism or blood pressure.

Long-term safety

Before we reach for our prescription pads and start prescribing Qlaira to those with cardiovascular risk factors, women aged over 35 years with contraindications to taking

EE-containing pills or to those who suffer with diabetic microvascular disease, let us reflect on past 'pill scares'. In the 1990s Mercilon® users (a 20 µg EE/150 µg desogestrel pill) appeared to have a greater risk of venous thromboembolism than women taking Marvelon® (a 30 µg EE/150 µg desogestrel pill).¹⁹ This is nonsense, of course, and simply a result of 'prescriber bias'. Don't 'kill off' Qlaira with similar actions – remember it will have the same indications and contraindications as other COCs. A post-marketing surveillance study is planned but we will have to wait 4–5 years before interim data on Qlaira's safety are available.

SPC guidance on starting Qlaira

The Summary of Product Characteristics (SPC)²⁰ for Qlaira gives guidance on how to start taking this pill (Table 1). The advice may appear complicated and could be simplified to the following:

Qlaira should be commenced on Day 1 of the menstrual cycle, immediately following discontinuation of combined hormonal contraception, an abortion, a miscarriage or before 28 days postpartum. In these situations no additional contraceptive method is required. If Qlaira is commenced directly after discontinuation of a progestogen-only method, additional contraception such as condoms is required for the next 9 days.

Missed pills

Qlaira requires correct and consistent pill taking. My personal view is that the advice for missed pills given in the SPC (Table 2) and on the pill packets²⁰ is complicated and difficult to follow. I would suggest the following simple 'missed pill' advice to potential Qlaira users:

If a pill is forgotten for more than 12 hours the missed pill should be taken immediately and the next pill when it is due (even if this means taking two tablets on the same day). If the missed pill is between Days 18–24 this packet should be discarded and the Day 1 tablet from a

new packet taken immediately. Abstinence or use of an additional contraceptive method is required for the next 9 days.

Who may choose Qlaira?

Qlaira is a novel COC with the potential of having less metabolic impact when compared to current EE-containing COCs. This information alone may attract some users, but particularly for women aged over 35 years or with uncomplicated diabetes Qlaira may be a good choice. Women frequently ask for 'the lowest dose pill'; they may like the idea of having a pill containing estradiol rather than EE. They may be worried about 'too many hormones' but find the bleeding pattern associated with progestogen-only methods unacceptable. Qlaira may suit their needs.

Qlaira may also be very suitable for those who complain of 'estrogen withdrawal symptoms' such as headaches, mood changes or pelvic pain during the hormone-free week of conventional pill taking. Since about 20% of women each month have no withdrawal bleed when using Qlaira, it may offer hope for those with regular heavy menstrual bleeding. Further studies are underway in both these areas.

However, Qlaira has a similar Pearl index to conventional pills and its bleeding pattern in general is similar to a 20 µg EE/100 µg LNG pill. Therefore it is not the pill for women who want a regular monthly bleed or demand excellent cycle control. We have not yet achieved 'the perfect pill', but Qlaira provides us with a genuinely new option for women.

Statements on funding and competing interests

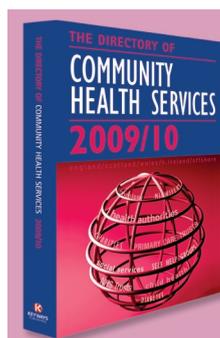
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