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 control[9] 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.

Qlaria 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

J Fam Plann Reprod Health Care 2009; **35**(3): 139–142

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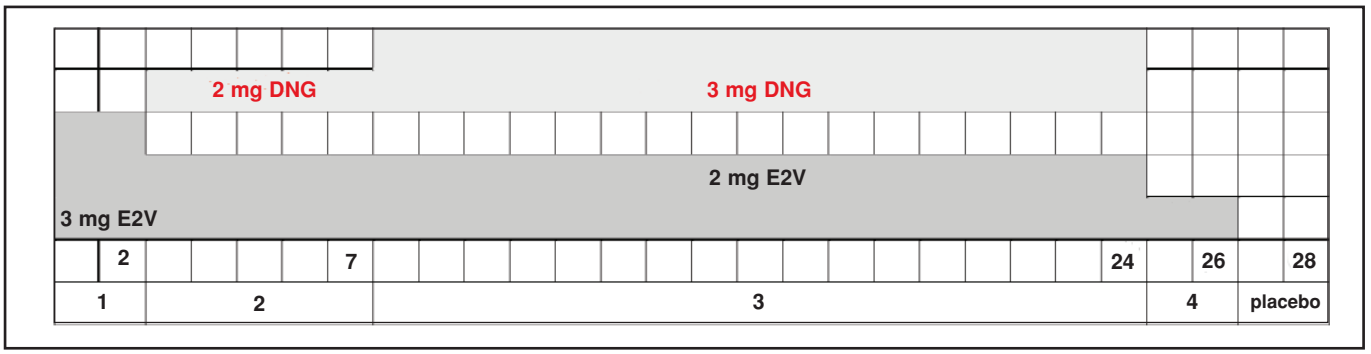

Figure 1 Dose regimen for Qlaira® (one cycle). DNG, dienogest; E2V, estradiol valerate.

not experience a withdrawal bleed every cycle compared to 8% in the Miranova group. Both preparations had a similar intracyclic bleeding pattern (14% with Qlaira and 12% with Miranova).[16]

These findings are very similar to the open-label European study[15] where withdrawal bleeding occurred in 76.8–81.6% of women over 20 cycles. The median length of withdrawal bleeding was 4 days and said to be 'light'.[15] There are no published data recording Qlaira's effect on dysmenorrhoea or pelvic pain.

User satisfaction

In the open-label 20-cycle European study (n = 1377) 79.5% of women were either satisfied or very satisfied with Qlaira and just over two-thirds of the full analysis set would consider taking Qlaira in the future. Just 7.4% were dissatisfied or very dissatisfied. Of the 21.4% (295 women) who dropped out of the study, 142 women complained of adverse events including breast pain, headaches, acne and weight gain but only 37 women discontinued use because of menstrual bleeding problems.[15]

Table 1 Guidance on starting Qlaira® based on the Summary of Product Characteristics[20]

Circumstances	Start when?	Extra precautions for next 9 days?
Quick start	At any time if it is reasonably certain that she is not pregnant	Yes
Menstruating	Day 1 start	No
	After Day 1	Yes
Amenorrhoeic	Any time if it is reasonably certain that she is not pregnant	Yes
Post-abortion or miscarriage	Immediately	No
	After the first day post-abortion	Yes
Postpartum		
(a) not breastfeeding	Days 21–28 postpartum	No
	From Day 28 onwards	Yes
(b) breastfeeding	If >6 months and amenorrhoeic, treat like other amenorrhoeic women	
	If >6 months and menstruating, treat like other menstruating women	
Switching from other combined hormonal methods	Immediate start	No
Switching from POP, implant, IUS or injection	Immediate start following discontinuation of POP, removal of implant or IUS, when next injection is due	Yes
Switching from a non-hormonal method (other than IUD)	Immediately	Yes
Switching from an IUD (not in SPC for Qlaira)	Start Day 1 of cycle. IUD can be removed at the same time. Qlaira can be started at any other time, if it is reasonably certain she is not pregnant:	No
	– if she has been sexually active	Start Qlaira and then remove IUD at the next period or after 9 days
	– if she has not been sexually active	Start Qlaira and then remove IUD after 9 days or at the next period
	– if she is amenorrhoeic or has irregular bleeds	Start Qlaira. If unprotected sex has occurred in preceding 7 days advise IUD removal 9 days after pill start

IUD, intrauterine device; IUS, intrauterine system; POP, progestogen-only pill; SPC, Summary of Product Characteristics.

Table 2 Qlaira®'s missed pill guidance as stated in the Summary of Product Characteristics[20]

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 study[17] 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 groups[17] 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 packets[20] 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

Funding None identified.

Competing interests The author has received research grants, honoraria and expenses for attendance at advisory boards and sponsored symposia from Bayer Schering Pharma and Organon Laboratories (part of the Schering-Plough Corporation).

References

1 van der Mooren MJ, Klipping C, van Aken B, Helmerhorst E, Spielmann D, Kluft C. A comparative study of the effects of gestodene 60 microg/ethinylestradiol 15 microg and desogestrel 150 microg/ethinylestradiol 20 microg on hemostatic balance, blood lipid levels and carbohydrate metabolism. *Eur J Contracept Reprod Health Care* 1999; **4**(Suppl. 2): 27–35.

2 Gestodene Study Group 322. The safety and contraceptive efficacy of a 24-day low-dose oral contraceptive regimen containing gestodene 60 microg and ethinylestradiol 15 microg. *Eur J Contracept Reprod Health Care* 1999; **4**(Suppl. 2): 9–15.

3 Hirvonen E, Stenman UH, Mälkönen M, Rasi V, Vartiainen E, Ylöstalo P. New natural oestradiol/cyproterone acetate oral contraceptive for pre-menopausal women. *Maturitas* 1988; **10**: 201–213.

4 Kivinen S, Saure A. Efficacy and tolerability of a combined oral contraceptive containing 17 beta-estradiol and desogestrel. *Eur J Contracept Reprod Health Care* 1996; **1**: 183.

5 National Agency for Medicines. Femilar tablets: Summary of Product Characteristics [in Finnish]. 14 May 2007. http://spc.nam.fi/indox/english/html/nam/humspc/5/102855.shtml [Accessed 3 May 2009].

6 Oettel M, Carol W, Elger W, Kaufmann G, Moore C, Romer W, *et al.* A 19-norprogestin without 17β-ethinyl group II: dienogest from a pharmacodynamic point of view. *Drugs Today* 1995; **31**: 517–536.

7 Sasagawa S, Shimizu Y, Nagaoka T, Tokado H, Imada K, Mizuguchi K. Dienogest, a selective progestin, reduces plasma estradiol level through induction of apoptosis of granulosa cells in the ovarian dominant follicle without follicle-stimulating hormone suppression in monkeys. *J Endocrinol Invest* 2008; **31**: 636–641.

8 Rabe T, Kowald A, Ortmann J, Rehberger-Schneider S. Inhibition of skin 5 alpha-reductase by oral contraceptive progestins *in vitro*. *Gynecol Endocrinol* 2000; **14**: 223–230.

9 Wiegratz I, Kutschera E, Lee JH, Moore C, Mellinger U, Winkler UH, *et al.* Effect of four different oral contraceptives on various sex hormones and serum-binding globulins. *Contraception* 2003; **67**: 25–32.

10 Palombo-Kinne E, Schellschmidt I, Schumacher U, Gräser T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. *Contraception* 2009; **79**: 282–289.

11 Hoffmann H, Moore C, Zimmermann H, Elger W, Schwarz S, Gräser T, *et al.* Approaches to the replacement of ethinylestradiol by natural 17beta-estradiol in combined oral contraceptives. *Exp Toxicol Pathol* 1998; **50**: 458–464.

12 Endrikat J, Parke S, Trummer D, Schmidt W, Duijkers I, Klipping C. Ovulation inhibition with four variations of a four-phasic estradiol valerate/dienogest combined oral contraceptive: results of two prospective, randomized, open-label studies. *Contraception* 2008; **78**: 218–225.

13 Coffee AL, Sulak PJ, Kuehl TJ. Long-term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. *Contraception* 2007; **75**: 444–449.

14 Lu M, Uddin A, Foegh M, Zeun S. Pharmacokinetics and pharmacodynamics of a new 4-phasic estradiol valerate and dienogest oral contraceptive. Poster presented at the American College of Obstetricians and Gynecologists 55th Annual Meeting, San Diego, CA, USA, May 2007.

15 Parke S, Nahum GG, Wildt L, Palacious S, Romer T, Bitzer J. Efficacy and tolerability of a new oral contraceptive containing estradiol and dienogest. Poster presented at the American College of Obstetricians and Gynecologists 56th Annual Meeting, New Orleans, LA, USA, May 2008.

16 Ahrendt H-J, Makalova D, Parke S, Mellinger U, Mansour D. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a 7-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinylestradiol/levonorgestrel. *Contraception* 2009; (in press).

17 Parke S, Nahum GG, Mellinger U, Junge W. Metabolic effects of a new 4-phasic combined oral contraceptive containing estradiol valerate and dienogest. Poster presented at the American College of Obstetricians and Gynecologists 56th Annual Meeting, New Orleans, LA, USA, May 2008.

18 Klipping C, Junge W, Mellinger U, Duijkers I, Parke S. Hemostatic effects of a novel four-phasic combined oral contraceptive containing estradiol valerate and dienogest. Poster presented at the European Society of Contraception Biannual Meeting, Prague, Czechoslovakia, April 2008.

19 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestogens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet* 1995; **346**: 1582–1588.

20 Bayer plc. Qlaira: Summary of Product Characteristics. http://emc.medicines.org.uk/document.aspx?documentId=21700 [Accessed 3 May 2009].