Qlaira: novel multiphasic oral contraceptive taken continuously

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KEY POINTS

- **Qlaira is a multiphasic oral contraceptive containing estradiol valerate and dienogest plus two inert tablets**
- **the metabolic effects of Qlaira differ from those of a monophasic COC containing ethinylestradiol and levonorgestrel but the differences are small and their clinical significance is unclear**
- **the tablets are taken continuously; 3x28=£25.18**
- **its Pearl Index is 0.79 including user and method failures, and 0.42 for method failures alone**
- **limited data suggest that, compared with a monophasic COC, Qlaira is associated with a similar frequency but shorter duration of intracycle bleeding and fewer women experience withdrawal bleeding**
- **adverse effects appear to be typical of a COC**
- **Qlaira is a novel COC with the potential of having less metabolic impact compared to currently prescribed ethinylestradiol-containing COCs, and would be particularly suitable for women over 35**

Qlaira is a new multiphasic COC that is taken continuously and comprises four combinations of estradiol valerate and the progestogen dienogest, plus two inert tablets. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy, and adverse effects and Dr Mansour discusses its place in contraception.

The combined oral contraceptive (COC) of choice offers good cycle control and the lowest risk of adverse effects at the lowest doses of oestrogen and progestogen.[1] A monophasic preparation is preferred for initial use.[2] Phased preparations are generally reserved for women who do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.[1] Other criteria influencing choice include age, risk factors for cardiovascular disease and experience of adverse effects with previous use.[1]

The technology

Qlaira is a multiphasic oral contraceptive comprising four combinations of estradiol valerate and the progestogen dienogest, plus two inert tablets (see Figure 1). The oestrogen dose decreases from 3mg on days 1-2 to 2mg on days 3-24 and 1mg on days 25 and 26. The dienogest dose increases from 0mg on days 1-2 to 2mg on days 3-7 and 3mg on days 8-24, then decreases to 0mg for days 25 and 26. The inert tablets are taken on the last two days, *ie* days 27 and 28.

Qlaira is taken continuously. Withdrawal bleeding usually starts during the intake of the inert tablets at the end of the cycle but may start after the first doses of the next cycle are taken. Prescribing precautions and contraindications are the same as for other COCs.

The hormones in Qlaira are not components of other COCs. Dienogest is, like norethisterone, a nortestosterone derivative but it lacks androgenic activity and has about one-third the antiandrogenic activity of cyproterone acetate.[3] Estradiol valerate is an ester of 17beta-estradiol,[3] a natural oestrogen more widely used in hormone replacement therapy.

The metabolic effects of Qlaira differ from those of a monophasic COC containing ethinyloestradiol and levonorgestrel, but the differences are small and their therapeutic significance is unclear.[4]

Clinical trials

Efficacy studies of Qlaira have not yet been published in full.

One European noncomparative trial, available as an abstract,[5]

involved 1377 women who used Qlaira for 20 cycles. The primary end-point was the number of unintended pregnancies; 303 women discontinued treatment prematurely, most commonly (46 per cent) due to adverse effects.

Thirteen pregnancies occurred during a total of 23 368 treatment cycles, of which six were attributed to method failure. The Pearl Index (number of pregnancies per 100 woman-years of use) was 0.73; after excluding failures due to user error, this decreased to 0.34. This is slightly lower than the figures from all clinical trials (0.79 and 0.42 respectively).[3]

The proportion of women experiencing withdrawal bleeding ranged from 77 to 82 per cent; the median duration of bleeding was four days and median intensity was light. Bleeding during the cycle occurred more often during the first 10 weeks, decreasing in mean duration (from 5.9 to 4.8 days) and intensity over time.

Eighty per cent of women said they were satisfied or very satisfied with Qlaira; emotional and physical well-being was maintained in 71 and 58 per cent respectively and improved in 19 and 28 per cent.

A randomised double-blind trial compared Qlaira and a monophasic COC containing ethinylestradiol 20µg per day plus levonorgestrel 100µg per day over seven cycles in 798 women.[6] The primary end-points were bleeding and cycle control.

The mean frequencies of episodes of bleeding or spotting were not significantly different during the first (Qlaira 3.7 *vs* monophasic COC 4.1) and last three months (3.0 *vs* 3.1) but Qlaira was associated with significantly fewer days on which bleeding/spotting occurred (17.3 *vs* 21.5 and 13.4 *vs* 15.9 days; see Table 1).

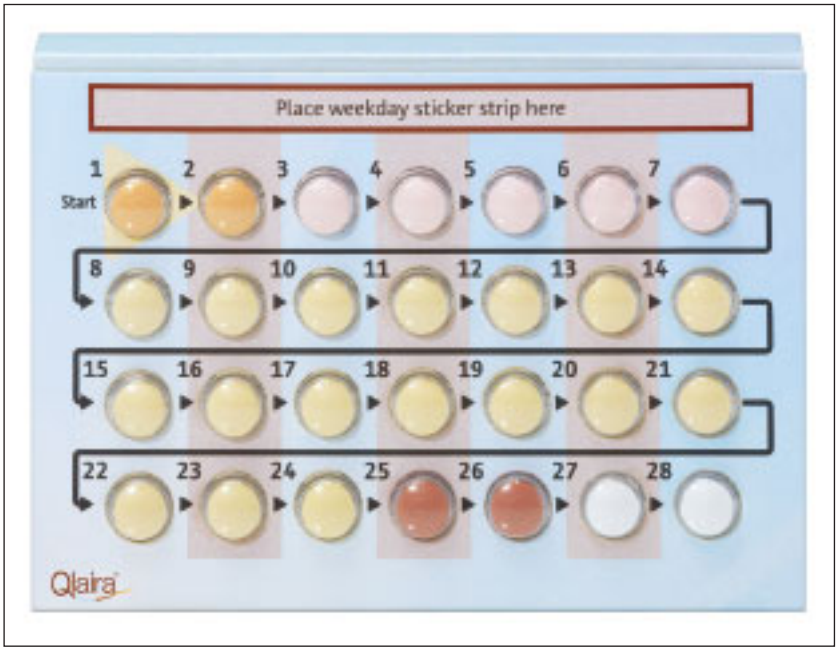

Figure 1. Each wallet (28 tablets) contains sequentially: two dark-yellow tablets each containing 3mg estradiol valerate; five medium-red tablets each containing 2mg estradiol valerate and 2mg dienogest; 17 light-yellow tablets each containing 2mg estradiol valerate and 3mg dienogest; two dark-red tablets each containing 1mg estradiol valerate; and two white tablets containing no active substances

Withdrawal bleeding was less frequent (78-83 *vs* 90-94 per cent) and of shorter duration (4.1-4.7 *vs* 5.0-5.2 days) with Qlaira. Eighty per cent of women expressed satisfaction with both preparations.

Adverse effects

The adverse effects associated with Qlaira appear to be typical of a COC. Common events include headache, abdominal pain, weight gain, acne, breast discomfort and dysmenorrhoea.[3]

Adverse effects were a secondary end-point in the trial comparing Qlaira with a monophasic COC and reported numbers were low: breast pain was more common with Qlaira (3.3 *vs* 1.1 per cent) and acne less common (1.3 *vs* 2.3 per cent).[6]

	Qlaira (n=399)	EE/LNG (n=399)
Days with bleeding/spotting (n ± SD)		
90-day reference period 1	17.3 ± 10.4	21.5 ± 8.6
90-day reference period 2	13.4 ± 9.3	15.9 ± 7.1
Episodes of bleeding/spotting (n ± SD)		
90-day reference period 1	3.7 ± 1.4	4.1 ± 0.9
90-day reference period 2	3.0 ± 1.3	3.1 ± 0.9
90-day reference period 1 started on day 1 and ended on day 90 of treatment 90-day reference period 2 started on day 91 and ended on day 180 of treatment		

Table 1. Occurrence of bleeding/spotting days and episodes during treatment with Qlaira and ethinylestradiol/levonorgestrel (EE/LNG)[6]

References

1. Joint Formulary Committee. *British national formulary 57*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain. March 2009.
2. Faculty of Family Planning and Reproductive Health Care. *Clinical guidance. First prescription of combined oral contraception*. July 2006 (updated January 2007). www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJan06.pdf.
3. Bayer. *Qlaira*. Summary of Product Characteristics. May 2009.
4. Parke S, *et al. Metabolic effects of an oral contraceptive based on natural estradiol (estradiol valerate/dienogest)*. Proceedings of the 11th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Paris. 27-30 Nov 2008. 138A. (Abstract No. 578072).
5. Parke S, *et al. Efficacy/safety of an oral contraceptive based on natural estradiol (estradiol valerate/dienogest)*. Proceedings of the 11th World Congress on Controversies in Obstetrics, Gynecology & Infertility, Paris. 27-30 Nov 2008. 138A. (Abstract No. 578073).
6. Parke S, *et al. Eur J Contracept Reprod Health Care* 2008;13:94-5.

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Place in therapy

There is no question that the Pill has revolutionised women's lives. However, since its introduction in the 1960s the COC has been constantly refined to reduce the hormone dose in the hope of minimising health risks and side-effects.

No one Pill suits all women, with some complaining of oestrogen side-effects such as breast tenderness, nausea, fluid retention and leg cramps, and others hormone withdrawal effects in the pill-free interval that include bloating, mood change, headaches and abdominal cramps. The introduction of Pills delivering estradiol is novel and may be advantageous for these women.

The significance of natural oestrogen

Qlaira is a novel COC with the potential of having less metabolic impact when compared to currently prescribed ethinylestradiol-containing COCs. This information alone may attract some users, but Qlaira would be particularly suitable for women over 35. Women often want 'the lowest-dose pill' or are worried about taking 'too many hormones' – Qlaira may suit their needs.

It is also suitable for those who complain of oestrogen side-effects or hormone withdrawal symptoms, and Qlaira may offer hope for those with regular heavy menstrual bleeding. Further studies are underway in both these areas.

It must be remembered that Qlaira has the same indications and contraindications as other COCs with its long-term safety yet to be determined. A postmarketing surveillance study is planned but we will have to wait four to five years before interim data on Qlaira's safety are available.

Dienogest benefits?

Dienogest has been available for more than 10 years worldwide in combination with ethinylestradiol 30µg as Valette (but not available in the UK); it is also the leading COC in Germany. This COC gives excellent cycle control often with no withdrawal bleeds and similar benefits on mild-to-moderate acne as ethinylestradiol/cyproterone acetate 35µg/2mg (co-cyprindiol).

These effects are partly related to the presence of the progestogen dienogest, which is thought to demonstrate specific activity on the endometrium and displays antiandrogenic activity. By combining estradiol valerate and dienogest in this novel four-phased regimen, good cycle control has been achieved.

Hormone doses

The doses of estradiol valerate and dienogest in Qlaira are similar to those found in hormone replace-

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ment therapy. Trials involving oestrogen priming of the endometrium using two to three days of estradiol valerate have helped to achieve good cycle control.

Reducing the hormone-free interval with Qlaira, which has just two placebo pills, may help decrease hormone withdrawal and menstrual symptoms experienced by some who take a standard 21/7 regimen.

Is Qlaira effective?

A large multicentre open-labelled European study recruited 1377 women aged between 18 and 50 years and followed them for 20 cycles. 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). There are several other studies that have confirmed these findings.

This clearly demonstrates that Qlaira is as effective as traditional COCs containing ethinylestradiol.

Advantages in terms of bleeding/spotting

Qlaira gives a similar bleeding pattern as a 20µg levonorgestrel Pill with 12-14 per cent of women having intracyclic bleeding/spotting. However, about 20 per cent of women taking Qlaira have no withdrawal bleed, which may be advantageous for many.

There are no published data recording Qlaira's effect on dysmenorrhoea or pelvic pain, but from looking at these bleeding data I would expect an improvement.

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