What role for ▼Qlaira in contraception?

Around 25% of women in the UK aged 16–49 years use oral contraception.[1] Annually, around 5 million combined oral contraceptive (COC) items are prescribed in primary care in England alone, at a cost of over £40 million. The effectiveness of such contraception depends on correct and consistent use of the pills and is influenced by unwanted effects that can lead to discontinuation (e.g. bleeding irregularities), and by adherence to specified procedures for when a pill is missed.[1,2] ▼Qlaira (Bayer plc) is the first licensed COC in the UK to include the oestrogen estradiol valerate (E2V, which is metabolised to oestradiol, a natural human hormone) and the progestogen dienogest (DNG).[3] It has been marketed as "the first and only COC to deliver … the same oestrogen as produced by a woman's body".[4] In theory, it might be less likely than other COCs to cause unwanted effects.[3] However, it has a complex dosage regimen, and has its own missed-pill guidance which differs substantially from that for other pills.[3] Here we review the effectiveness and place of Qlaira.

BNF 7.3.1

About COCs

COCs contain an oestrogen and a progestogen, and work primarily by inhibiting ovulation through acting on the hypothalamo-pituitary-ovarian axis to reduce secretion of luteinising hormone and follicle stimulating hormone; they also have effects on cervical mucus and the endometrium.[5] COCs are available in either 21-day packs with a 7-day break between each pack, or as 'Every Day' packs of 21 tablets with active ingredients, followed by seven pills with no active ingredient, taken without a break between packs. During the 7 pill-free or inactive-pill days, the endometrium is shed, resulting in a withdrawal bleed in most women.[5] In addition, unscheduled bleeding or spotting can occur with COC use, and these symptoms, especially if they are irregular, prolonged or frequent, may lead to discontinuation of the pill.[6] Such bleeding is more common with a 20µg ethinyl estradiol (EE) COC than with COCs containing more than 20µg EE.[7]

Some COCs contain a fixed amount of an oestrogen and a progestogen in each active tablet and are termed 'monophasic' (e.g. Microgynon). Others have varying amounts of the two hormones according to the stage of the cycle and are termed 'phasic' (e.g. biphasic such as BiNovum, or triphasic such as Triadene).[8] Previously in the UK, the oestrogen component of available COCs has been EE with various progestogens such as norethisterone or levonorgestrel (so-called second-generation COCs), or desogestrel or gestodene (third-generation COCs).

COCs are generally used by healthy women for preventive purposes; they therefore need to have a well-defined contraceptive efficacy and a very low risk of harm to offer a favourable risk/benefit balance in such individuals.[9]

Contraceptive efficacy can be measured using the Pearl Index (the number of unintended pregnancies per 100 woman-years of exposure), which can be expressed in two ways:

- 'user and method failure' (also called the unadjusted Pearl Index). This represents the failure rate with 'typical' use and includes all pregnancies and all cycles of contraceptive use, except those in which additional methods have been used. The rate is around 12% for condoms; 3% for IUDs and 3% for pills;[10]
- 'method failure' (also called 'true pill failure' or the adjusted Pearl Index). This represents the failure rate with 'perfect' (i.e. correct and consistent) use and excludes pregnancies that can be reliably attributed to non-adherence to the contraceptive regimen.[5,10] The rate is around 2% for condoms; 0.8–2.0% for IUDs and 0.1–0.5% for pills (0.1% for COCs and 0.5% for progestogen-only pills).[10]

What is Qlaira?

Qlaira is the first licensed COC in the UK to include as its oestrogen component E2V, an ester of the endogenously produced human 17ß-oestradiol. It also contains the synthetic progestogen dienogest (DNG), a component of a COC that is more potent than levonorgestrel and has been available for more than 10 years in other countries.[3,11,12] The summary of product characteristics (SPC) for Qlaira gives instructions on when it should be started (relative to the woman's menstrual cycle, or when she stopped using a previous contraceptive method, or had a miscarriage or delivery).[11] The SPC states that in some women, pregnancy needs to be ruled out before commencing Qlaira, and also that some women need an additional method of contraception for the first 9 days of use.[11]

Qlaira is a quadriphasic COC (designed to give a reducing dose of oestrogen over days 1–26 and an increasing dose of progestogen over days 3–24, followed by two inactive tablets), presented as 'wallets' of 28 tablets (see Box 1 for dose schedule and missed-pill instructions).[3,11] Withdrawal bleeding may start around the time of taking the last tablets of a wallet, or after the first tablets of a new wallet.[11]

The SPC states that if the woman is less than 12 hours late in taking any Qlaira tablet, contraceptive protection is not

Box 1: Dose schedule for ▼Qlaira and instructions for missed pills[11]

Days	Tablet colour/ content	Actions to take if one tablet missed for more than 12 hours
1–2 3–7 8–17	Dark yellow (3mg E2V) Medium red (2mg E2V+2mg DNG) Light yellow (2mg E2V+3mg DNG)	Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day). Continue with tablet-taking in the normal way. Use back-up contraception for the next 9 days.
18–24	Light yellow (2mg E2V+3mg DNG)	Discard current wallet, and start immediately with the first pill of a new wallet. Continue with tablet-taking in the normal way. Use back-up contraception for the next 9 days.
25–26	Dark red (1mg E2V)	Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day). No back-up contraception necessary.
27–28	White (inactive)	Discard missed tablet and continue tablet-taking in the normal way. No back-up contraception necessary.

reduced: in such cases, the woman should take the tablet as soon as she remembers and should take subsequent tablets at her usual time.[11] However, if she is more than 12 hours late in taking any one tablet, contraceptive protection may be reduced (of note, instructions for missing a light yellow pill differ depending on whether this occurs up to day 17 or from day 18 onwards). If more tablets are missed, there is a higher likelihood of pregnancy; however, no specific advice about this risk is given in the SPC.[11]

In women with severe gastrointestinal disturbances (e.g. vomiting, diarrhoea), absorption of Qlaira may be incomplete and additional contraceptive measures should be taken.[11] If a woman vomits within 3–4 hours after taking an active tablet, she should take the next tablet as soon as possible, as long as this is within 12 hours of the usual time of tablet-taking. If more than 12 hours have elapsed, then the advice on missed tablets should be followed. If the woman does not want to change her normal tablet-taking schedule, she will have to take the corresponding tablet(s) needed from another pack; this could increase the possibility of errors in pill-taking.[11]

Clinical efficacy of Qlaira

Non-comparative studies

Two non-blinded non-comparative dose-finding studies were carried out to establish the regimen for a quadriphasic preparation of E2V/DNG, based on ovulation inhibition.[13]

In 2008, a poster (not published in full) was presented of a multicentre non-blinded non-comparative study involving 1,377 women aged 18–50 years who received the regimen that comprises Qlaira.[14] In the whole sample, the Pearl Index was 0.73% (the primary outcome measure; upper limit of 95% CI 1.24; lower limit not stated) and adjusted Pearl Index 0.34% (upper limit of 95% CI 0.73). The age range (and therefore fertility) of participants differed from that typically set for trials of contraceptive efficacy (e.g. 18–40 years or 18–45 years), making indirect comparisons with other trial results unreliable.[2] In the subset of women aged 18–35 years, the Pearl Index was 0.94% (upper limit of 95% CI 1.65) and adjusted Pearl Index 0.40% (upper limit of 95% CI 0.92). The discontinuation rate due to adverse events was around 10%.

Comparative study

A double-blind randomised controlled trial, involving 798 women aged 18–50 years, compared the drug combination used in Qlaira (E2V/DNG) with a very low dose monophasic COC containing 20µg EE and 100µg levonorgestrel (EE/LNG), each used for seven cycles.[15] In this study (as in that described above) the age range (and therefore fertility) of participants differed from other trials of contraceptive efficacy, making comparisons with other trial results unreliable.[2] In addition, the progestogen dose used in the comparator arm was lower than is currently available in the UK. This again makes it difficult to compare reliably the results of the study with data for standard products, particularly as lower doses of both oestrogen and progestogen are more likely to be associated with breakthrough bleeding.[2] The primary efficacy outcomes were bleeding pattern (number of bleeding/spotting days; number and length of bleeding/spotting episodes) and cycle control (incidence and characteristics of scheduled withdrawal and unscheduled intracyclic bleeding). Bleeding was recorded by the woman on daily diary cards.[15]

Scheduled withdrawal bleeds were shorter in women taking E2V/DNG (4.1–4.7 days per cycle vs. 5.0–5.2 days with the EE/LNG preparation, $p<0.05$).[15] More women on E2V/DNG did not have withdrawal bleeding (mean proportion 19.4% vs. 7.7% per cycle, $p<0.0001$). The intensity and duration of such bleeds may be of importance to women; and the absence of withdrawal bleeding may be seen either as an advantage (e.g. by those who otherwise have regular heavy menstrual bleeding) or as a disadvantage (e.g. if it leads to anxiety about possible unwanted pregnancy).[3,11,12,15]

The rate of intracyclic bleeding was described as "comparable" between the two groups (occurring in around 14% [range 10.5–18.6%] of women on E2V/DNG per cycle vs. 12% [9.9–17.1%] on EE/LNG; no p value stated).[15] Of note, unscheduled bleeding is more common in women using a 20µg EE COC (such as the comparator in this trial) than with COCs containing more than 20µg;[7] the trial results offer no direct evidence on how Qlaira compares with COCs containing higher doses of EE.

Although pregnancy was not a primary outcome, the trial report stated that one unintended pregnancy occurred in the EE/LNG group, and was attributable to "method failure".[15] A total of 338 adverse events were reported during the study (27.1% with E2V/DNG vs. 25.6% with EE/LNG, no p value stated).

Unwanted effects

The SPC states that, in clinical trials, unwanted events possibly caused by Qlaira included the following:

- common (i.e. each occurring in 1–10% of women): headache, abdominal pain, nausea, acne, breast discomfort, amenorrhoea, dysmenorrhoea, intracyclic bleeding, weight increase;
- uncommon (occurring in 0.1–1% of women): fungal infection, increased appetite, depressed mood, decreased libido, dizziness, hypertension, migraine, diarrhoea, nausea, vomiting, alopecia, pruritus, rash, breast enlargement, breast mass, fibrocystic breast disease, cervical dysplasia, dysfunctional uterine bleeding, dyspareunia, menorrhagia, ovarian cyst, pelvic pain, fibroids, oedema;
- rare (occurring in fewer than 0.1% of women): urinary tract infection, fluid retention, vertigo, contact lens intolerance, altered liver function tests (may require discontinuation until tests return to normal), chloasma.[11]

There are no longer-term safety data available for Qlaira, and the relative risks of venous thromboembolism, breast and cervical cancer are unknown.[2]

Contraindications

The SPC states that there are no epidemiological studies on the effects of COCs that contain estradiol or estradiol valerate, and the warnings and precautions stated are derived from clinical and epidemiological data for ethinyl estradiol-containing COCs.[11] It states that COCs should not be used in patients with any of the following:

- current or past venous thrombosis; arterial thrombosis (e.g. angina pectoris, transient ischaemic attack); stroke; severe hepatic disease (for as long as liver function test results have not returned to normal); or liver tumours (benign or malignant);
- severe or multiple risk factor(s) for venous or arterial thrombosis (e.g. diabetes mellitus with vascular symptoms; severe hypertension; severe dyslipoproteinaemia);
- hereditary or acquired predisposition to venous or arterial thrombosis (e.g. deficiencies of antithrombin-III, protein C or protein S; antiphospholipid antibodies);
- a history of migraine with focal neurological symptoms;
- known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast);
- undiagnosed vaginal bleeding;
- pancreatitis, or a history thereof if associated with severe hypertriglyceridaemia;
- hypersensitivity to the active substances or to any of the excipients.[11]

The SPC also states that should any of the above conditions appear for the first time during use of Qlaira, the contraceptive should be stopped immediately.[11]

Qlaira should not be used in pregnancy or lactation.[11] The SPC states that contraceptive steroids and/or their metabolites may be excreted in the milk and these amounts may affect the child; however, the potential effects of this exposure are not detailed in the SPC.[11]

Precautions

The SPC states that the use of any COC carries an increased risk of venous thromboembolism (fatal in 1–2% of cases) and arterial thromboembolism. These risks increase with age, a family history of thromboembolism, and obesity (body mass index over 30kg/m^2).[11]

Interactions

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure.[11] Contraceptive failure has been reported with antibacterials (e.g. penicillins, tetracyclines); the mechanism for this effect is unknown.

Dienogest is a substrate of cytochrome P450 (CYP) 3A4, and drugs that induce this enzyme can result in interactions with Qlaira (resulting in increased clearance of sex hormones and, therefore, reduced contraceptive efficacy).[11] Examples of such drugs include barbiturates, carbamazepine, phenytoin, primidone, rifampicin, and possibly felbamate, griseofulvin, nevirapine, oxcarbazepine, ritonavir, ▼topiramate, and the herbal remedy St. John's wort (*Hypericum perforatum*). The effect of enzyme induction may be sustained for at least 4 weeks after stopping drug therapy.The SPC advises that women on rifampicin should use a barrier method in addition to the COC during rifampicin therapy and for 28 days after its discontinuation. Those on short-term treatment (i.e. for up to 1 week) with any of the above drugs apart from rifampicin should use a barrier method in addition to the COC while using the drug and for 14 days after discontinuation. For women on chronic treatment with drugs that induce hepatic enzymes, the SPC recommends using another reliable, non-hormonal, method of contraception.[11]

The SPC also states that known CYP3A4 isoenzyme inhibitors (e.g. azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants, grapefruit juice) "may" increase plasma concentrations of dienogest; the clinical relevance of these interactions is unknown.[11] In addition, oral contraceptives may affect the metabolism of other drugs; concentrations of these other drugs may be increased (e.g. ciclosporin) or decreased (e.g. lamotrigine).[11]

Cost

The cost to the NHS of 1 year's treatment with Qlaira is around £109, compared to around £9–£85 for other COCs.

What do guidelines say?

For first-ever use of a COC, guidance from the Faculty of Sexual and Reproductive Healthcare (FSRH; formerly the Faculty of Family Planning and Reproductive Healthcare) advises that a monophasic COC containing 30µg EE with norethisterone or

levonorgestrel is a suitable first pill.[5] The stated rationale for this advice is as follows:

- there is no evidence to support preferential use of biphasic or triphasic COCs over monophasic COCs;
- norethisterone- and levonorgestrel-containing COCs may have a lower risk of venous thromboembolism than COCs containing desogestrel and gestodene; and
- efficacy of 20µg and 30µg EE COCs is similar but unscheduled bleeding is more common with 20µg COCs.[5]

The Faculty also states that "Other pills may be considered as second-line pills after trying a first pill", but gives no further advice. The guidance was published before Qlaira was available in the UK. In September 2009, the FSRH released a statement regarding Qlaira, which included the following:

- there is currently no evidence of clinically significant benefits over pills containing synthetic oestrogen, with failure rates, unwanted effects and tolerability being comparable to those of other COCs; and
- Qlaira has different missed-pill rules and is considerably more expensive than any of the COCs currently available in the UK.[3]

Conclusion

▼Qlaira is the first combined oral contraceptive (COC) in the UK to contain the oestrogen estradiol valerate (an ester of endogenously produced oestrogen) and the progestogen dienogest. Only one comparative study of Qlaira has been fully published, and this did not use contraceptive efficacy as a primary outcome measure. Also, the comparator COC in the trial did not contain the recommended starting dose of oestrogen; no advantages have been demonstrated for Qlaira over standard COCs in terms of efficacy or unwanted effects; and no long-term safety data are available for the drug. A pack for a single cycle of Qlaira contains five different types and colours of pills, with four different missed-pill instructions (including one colour of tablet that has two different missed-pill instructions, depending on whether it is before or after day 17). This is a potentially confusing regimen for regular pill-taking and particularly complicated for dealing with missed pills. Also, Qlaira is more expensive than other COCs.

For all of the above reasons, we cannot recommend Qlaira.

[R=randomised controlled trial; M=meta-analysis]

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What role for ?Qlaira in contraception?

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Notes