Zoely: new COC with a higher rate of amenorrhoea

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KEY POINTS

- Zoely is a combined oral contraceptive containing estradiol 1.5mg and nomegestrol 2.5mg per tablet, plus 4 placebo tablets per pack of 28 tablets
- 1 pack (3 x 28 tablets) costs £16.50
- Nomegestrol acetate is structurally similar to progesterone, with selectivity for the progesterone receptor and modest antiandrogenic activity
- In 2 similar trials lasting 1 year, Zoely was associated with a lower rate of pregnancy than Yasmin but the difference was not statistically significant
- Zoely was associated with shorter and lighter withdrawal bleeding than Yasmin, and a higher incidence of amenorrhoea
- It was also associated with a higher frequency of adverse effects notably acne, irregular withdrawal bleeding and weight gain
- The higher chance of amenorrhea will be regarded as a benefit by many women, especially when reassured that amenorrhoea from COCs is not harmful

Zoely is a new COC containing estradiol and nomegestrol, a novel progestogen. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse events and Dr Stephen Searle discusses its place in therapy.

Combined oral contraceptives (COCs) contain different oestrogens, usually ethinylestradiol but also mestranol (Norinyl-1) and estradiol valerate (Qlaira), and progestogens, ie norethisterone acetate, levonorgestrel or norgestimate, and the newer alternatives desogestrel, drospirenone (Yasmin), dienogest (Qlaira) and gestodene. They are considered to have broadly similar efficacy but they differ in tolerability, partly due to the effects of the progestogen.²

Nomegestrol is a new progestogen derived from and structurally similar to progesterone, which is selective for the progesterone receptor and has modest antiandrogenic activity.³

Zoely (MSD) is a COC containing estradiol 1.5mg and nomegestrol 2.5mg per tablet. Each pack contains 24 tablets of estradiol/nomegestrol and four placebo tablets.

Clinical trials

The efficacy and tolerability of Zoely have been compared with that of Yasmin (ethinylestradiol/drospirenone) in two randomised nonblinded trials.⁴ Both recruited women aged 18–50 and had a duration of 13 cycles. The primary end-point in both trials was the Pearl Index (number of pregnancies per 100 woman-years of use).

In the trial conducted in Europe, Asia and Australia (n=2126),⁴ 18 per cent of women taking Zoely discontinued use prematurely due to adverse events, mainly unacceptable bleeding (4 per cent) and unspecified events (14 per cent). Of women assigned to Yasmin, 11 per cent withdrew from the trial due to adverse events, with a lower incidence of unacceptable bleeding (0.7 per cent) and unspecified events (10 per cent).

There were no pregnancies among women aged over 35. In women aged 35 or younger there were four pregnancies during 1058 woman-years of exposure to Zoely, giving a Pearl Index of 0.38 (0.31 for all women; see Table 1). There were three pregnancies during 372 woman-years of use of Yasmin, giving a Pearl Index of 0.81 (0.66 overall).

Cumulative one-year pregnancy rates were 0.40 (0.33 overall) and 0.77 (0.64 overall) respectively. Neither difference was statistically significant.

In the North and South American trial (n=2281),³ 17 per cent of women discontinued Zoely due to adverse events
(unacceptable bleeding in 4 per cent) compared with 10 per cent of those assigned to Yasmin (unacceptable bleeding 2 per cent). Among women taking Zoely there were 25 pregnancies in 2092 woman-years of use; the Pearl Index was 1.27 among women aged 18–35 and 1.13 overall. For Yasmin, there were 13 pregnancies in 700 woman-years, giving a Pearl Index of 1.89 in women aged 18–35 and 1.83 overall.

Cumulative one-year pregnancy rates among young women were 1.22 with Zoely and 1.82 with Yasmin. These differences were again not statistically significant.

The incidence of unscheduled bleeding or spotting was higher with Zoely during the first six cycles, after which there were no differences. Zoely was associated with shorter and lighter scheduled bleeding episodes (see Figure 1) and the incidence of amenorrhoea increased to about 30 per cent after one year compared with less than 10 per cent throughout the year with Yasmin.

**Adverse effects**

The overall frequency of treatment-related adverse reactions was higher with Zoely (49–51 per cent) than Yasmin (37–39 per cent). The most frequently reported adverse reactions were acne (15–16 per cent with Zoely vs 7–9 per cent with Yasmin), irregular withdrawal bleeding (9–12 vs 0.4–0.5 per cent) and weight gain (8–10 vs 5–6 per cent).

**References**

2. Combined hormonal contraceptives. BNF 64. September 2012.

**Declaration of interests**

None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.
Place in therapy

Any contraceptive that improves acceptability, adherence and continuation rates by reducing side-effects or by adding noncontraceptive benefits is to be welcomed and may assist reduction of unwanted pregnancy and abortion rates.

COCs remain among the most popular forms of contraception and often give better menstrual control than other methods. They also have many noncontraceptive benefits, e.g. COCs with stronger antiandrogen activity often improve acne and some reduce fluid retention so are less likely to raise blood pressure.

In recent years most experts have recommended offering women a no-bleed continuous COC regimen. These are currently unlicensed and may lead to breakthrough bleeding. Pharmaceutical companies have responded by launching Pills with shorter hormone-free intervals.

Ideally, for a step-change improvement women and clinicians would like to see the availability of a licensed no-bleed continuous COC (although absence of bleeding cannot be 100 per cent guaranteed).

Two randomised, nonblinded clinical trials have compared Zoely with Yasmin. The cumulative one-year pregnancy rates did not differ statistically. Acne, irregular withdrawal bleeding and weight gain were more commonly reported in Zoely users.

The incidence of amenorrhea increased to about 30 per cent in women taking Zoely for one year. Although reported as an ‘adverse event’ many women may see this as an advantage, especially when reassured that amenorrhea on COCs is not harmful.

Newer pills, particularly those with stronger antiandrogen effects (including Zoely), tend to be more expensive than older brands. Zoely is comparable in cost to Yasmin. The higher chance of amenorrhea, though, will be regarded as a benefit by many women. Clinicians eagerly await ‘no-bleed’ contraceptive Pills.

Declaration of interests
Dr Searle has received lecture fees, expenses, sponsorship for educational events and honoraria for advisory board work from several pharmaceutical companies producing oral contraceptives, including MSD.

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