Faculty of Family Planning and Reproductive Health Care
Clinical Effectiveness Unit

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New Product Review (April 2003)
Desogestrel-only Pill (Cerazette)

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Evidence from a randomised trial has shown that a 75 µg (microgrammes) desogestrel pill inhibits ovulation in 97% of cycles. Thus, on theoretical grounds, we would expect the desogestrel pill to be more effective than existing progestogen-only pills (POPs). However, Pearl indices from clinical trials comparing it to a levonorgestrel POP were not significantly different. Therefore an evidence-based recommendation cannot be made that the desogestrel pill is different from other POPs in terms of efficacy, nor that it is similar to combined oral contraception (COC) in this respect. An evidence-based recommendation can be made that the desogestrel-only pill is similar to other POPs in terms of side effects and acceptability. The desogestrel-only pill is not recommended as an alternative to COC in routine practice, but provides a useful alternative for women who require oestrogen-free contraception.

In clinical trials:

- Ovulation was inhibited in 97% of cycles at 7 and 12 months after initiation.
- The Pearl index was 0.41 per 100 woman-years, which was not significantly different from a levonorgestrel-only pill. However, the trial providing these data was too small to detect a clinically important difference. Pearl indices of the desogestrel POP and of COC have not been compared directly.
- Variable bleeding was more common than with levonorgestrel-only pills but by 11–13 months of use almost 50% of women using desogestrel had infrequent bleeding or amenorrhoea compared to 10% in the levonorgestrel group.
- Despite relatively greater desogestrel concentrations being used, reported side effects were no different than with a levonorgestrel-only pill due to desogestrel's low affinity for androgen receptors.
- There were no significant alterations in metabolic or haemostatic parameters with desogestrel use, and volume and composition of breast milk were unchanged.

Women experiencing unacceptable bleeding patterns on conventional POPs are unlikely to fare any better on the desogestrel-only pill. The desogestrel-only pill should be taken as for other POPs, ideally no more than 27 hours after the previous dose and without a pill-free week

Background

Inevitably there are limited long-term safety data for any new contraceptive method. Detailed scientific studies, performed in a small number of women, provide evidence on mode of action. Larger clinical trials examine efficacy, side effects and acceptability. The number of women-years of exposure is less than for established methods and all available evidence should be considered before prescribing new products. Many existing products have, however, been licensed for many years and may have not have been the subject of recent evidence-based assessments.

In the paragraphs that follow, answers are provided to a number of key questions about desogestrel-only pills.

What is the desogestrel-only pill?

This new progestogen-only pill (POP) received its UK product licence in 2002. Each tablet contains 75 µg (microgrammes) of desogestrel, which is metabolised to etonorgestrel. Etonorgestrel is a selective progestogen with high affinity for progesterone receptors and low affinity for androgen receptors compared to other progestogens.[1] A high dose can be used to inhibit ovulation without increasing androgenic side effects.[2]

How does the desogestrel-only pill work?

Inhibition of ovulation

A randomised, double-blind trial performed over 13 cycles showed that 75 µg desogestrel daily was sufficient to inhibit ovulation in 97% of cycles, and this is its primary mode of action.[2] Ovulation was identified by luteal-phase progesterone >30 nmol/l and evidence of follicular rupture on ultrasound scan. Both follicular rupture and serum progestogen levels are used as an indicator of ovulation since neither assessment alone necessarily signifies fertility. Of 33 women starting desogestrel, 29 completed 12 months' treatment, and of 31 women starting levonorgestrel, 28 completed 12 months' treatment. The effects of these two progestogens on the inhibition of ovulation after 7 and 12 months of use were observed over a total of 59 cycles (desogestrel) and 57 cycles (levonorgestrel).[2]

Ovulation was inhibited with desogestrel in 58/59 cycles studied (98.3%). In the levonorgestrel group, ovulation was inhibited in 41/57 cycles studied (71.9%). When a more conservative measure of progesterone was used (10 nmol/l), together with evidence of follicular rupture, ovulation was inhibited in 57/59 cycles in the desogestrel group (96.6%) and in 39/57 cycles in the levonorgestrel group (68.4%). Desogestrel was significantly more effective at inhibiting ovulation than levonorgestrel. Inhibition of ovulation in this study, however, was better than that expected for conventional POPs which inhibit ovulation in up to 50% of cycles.[3] A dose-finding study showed that 75 µg of desogestrel daily inhibited progesterone levels to less than 10 nmol/l in all 14 women in the first 3 months of use. This effective inhibition was also seen in the sixth month of use.[4]

Cervical mucus changes
Cervical mucus changes in women using 75 µg desogestrel daily are evident (by Insler score for hostility to sperm) but this is likely to be less important for contraception than with other POPs.[4]

How should the desogestrel-only pill be taken?
All studies investigating the effects of desogestrel-only pills on ovulation have commenced treatment on Day 1 of the menstrual cycle. Recent recommendations from the World Health Organization (WHO), however, have suggested that POPs can be started up to Day 5 without the need for barrier methods, as the risk of ovulation is acceptably low.[5] Steady-state levels of hormone are achieved within 4–5 days, and maximal cervical mucus effects occur in about 2 days. Barrier contraception should be advised for 48 hours following pill starts after Day 5 or following missed pills. The half-life of desogestrel is about 30 hours and pills should be taken every day without omission. A delay of more than 3 hours (27 hours since the last dose) should be treated as a missed pill and barrier contraception used until two consecutive pills have been taken. Although ovulation inhibition appears to be the primary mode of action, in the UK the product licence presently advises tablets to be taken daily within 3 hours of the same time every day.[6]

How effective is the desogestrel-only pill?
A double-blind, randomised, multicentre trial investigated the efficacy of desogestrel (used by 989 women) compared to levonorgestrel (used by 331 women) over 13 cycles.[7] This trial was powered to compare acceptability and bleeding profiles but not to compare efficacy. The overall failure rate of desogestrel (including those women who were breastfeeding and poor compliers) was 0.41 per 100 women-years (95% CI 0.085–1.204), and for levonorgestrel 1.55 per 100 woman-years (95% CI 0.422–3.96). The Pearl indices of desogestrel and levonorgestrel were not significantly different because the trial was not powered to detect differences in contraceptive efficacy. Failure rates for desogestrel in this trial appear to be lower than for a levonorgestrel pill and, on theoretical grounds because ovulation is more reliably inhibited, we would expect the desogestrel pill to have lower failure rates. We do not have trial evidence to support this. One-third of women recruited to this trial were breastfeeding, which may itself improve contraceptive efficacy – Pearl indices calculated in women who were not breastfeeding were 0.17 (95% CI 0.004–0.928) for desogestrel and 1.41 (95% CI 0.290–4.116) for levonorgestrel.[7]

What are the contraindications for use of the desogestrel-only pill?
WHO Medical Eligibility Criteria for all POPs suggest few absolute contraindications for use. A WHO Classification 3 (theoretical risks outweigh benefits) is given for current deep vein thrombosis or pulmonary embolism; past history of breast cancer; severe active liver disease; malignant hepatoma; and liver enzyme inducing drugs (due to reduced efficacy).[8] There is no reason to suppose that desogestrel-only pills will be any different from conventional POPs in terms of safety.

What are the side effects of the desogestrel-only pill?
Disruption of bleeding pattern
Overall discontinuation rates in the study were high: 44.8% for the desogestrel group and 39.4% for the levonorgestrel group.[7] Discontinuation rates due to abnormal bleeding however were similar: 22.5% for desogestrel and 18% for levonorgestrel. In order to compare bleeding patterns between women using these two POPs menstrual bleeding diaries from women who continued the study to completion were analysed. Descriptions of abnormal bleeding are described over a 90-day reference period (RP): the first RP includes Months 2–4 and the fourth RP includes Months 11–13. A variable pattern of bleeding was almost twice as common in desogestrel users than levonorgestrel users in the first RP. Bleeding problems decreased with increasing duration of use and by the fourth RP almost 50% of desogestrel users had infrequent bleeding (one or two bleeding/spotting episodes) or amenorrhoea, compared to 10% of the levonorgestrel users. The incidence of prolonged bleeding (a bleeding/spotting episode lasting for more than 14 days) and frequent bleeding (more than six bleeding spotting episodes) also decreased with increasing duration of use.

As a rough guide, women considering desogestrel-only contraception can be advised that by 12 months of use, over a 3-month interval: 5 in 10 women can expect to be amenorrhoeic or have infrequent bleeding; 4 in 10 women can expect to have three to five bleeding spotting/episodes; and 1 in 10 women can expect more than six bleeding/spotting episodes or prolonged bleeding/spotting episodes. Individual women may have bleeding patterns which alter during desogestrel use, but these changes in bleeding patterns are not dramatic.

Other side effects
Other side effects, which have been identified by women using the desogestrel-only pill, are listed in the manufacturers' product characteristics.[6] In a randomised trial the most commonly reported side effects were headache, acne, breast pain, nausea, vaginitis and dysmenorrhoea.[7] The incidence of these side effects was similar in desogestrel and levonorgestrel users. Other common complaints associated with desogestrel use occurring in more than 1 in 100 women include mood changes and decreased libido. Side effects occurring in more than 1 in 1000 women include ovarian cysts, vomiting, alopecia, fatigue, and problems with contact lenses. Side effects occurring in less than 1 in 1000 women include rash urticaria and erythema nodosum.

Ectopic risk
No ectopic pregnancies were identified in more than 700 women-years of use of desogestrel compared to one ectopic pregnancy in 250 women-years of use of levonorgestrel.[7] This non-significant difference may well be due to more effective ovulation inhibition than with other POPs.

Metabolic effects
Randomised, double-blind studies have not shown clinically significant differences between desogestrel and levonorgestrel users in: carbohydrate metabolism;[9] thyroid or adrenal function;[9] lipid parameters;[10] or coagulation factors.[11] An open, non-randomised comparative study in breastfeeding women did not identify any differences in breast milk volume or composition compared to women using an intrauterine device.[12]

Is the desogestrel-only pill cost effective?
Presently there are insufficient data to be able to assess the cost-effectiveness of desogestrel-only pills compared to other methods of contraception. Prices from the *British National Formulary* (BNF)[13] are included for information in Table 1. Many existing contraceptive products have been licensed for many years – combined oral contraceptives (COCs) containing second-generation progestogens since

Table 1 *Price of desogestrel-only pill (Cerazette, Organon) compared to* British National Formulary *approximate net prices for other contraceptive methods per month of use*[13]

Contraceptive method	Net price per month of use
Progestogen-only pill (POP)	
Cerazette	£2.95
Microval	£0.90
Micronor	£0.65
Femulen	£0.90
Neogest	£0.95
Norgeston	£0.95
Noriday	£0.70
Combined oral contraceptive (COC)	
Cilest	£2.15
Eugynon 30	£0.80
Microgynon 30	£0.85
Ovranette	£0.80
Logynon	£1.30
Loestrin 30	£1.30
Trinordiol	£1.45
Trimunulet	£3.20
Minulet	£2.30
Femodene	£2.30
Marvelon	£2.20
Mercilon	£2.85
Loestrin 20	£0.85
Femodette	£2.75
Yasmin	£4.90
Injectible	
Depo-Provera	£1.70
Implant	
Implanon	£2.50
Intrauterine device (IUD)	
Nova T380	£0.20
Intrauterine system (IUS)	
Mirena	£1.50

the 1970s and those containing third-generation progestogens (desogestrel) since the early 1980s, which is reflected in their lower price.

What does this new desogestrel-only pill add to current contraceptive choice for women?

A survey of oral contraceptive prescribed in the UK identified that POPs are used by only 5% of women.[14] POPs may be the method of choice for older women.[14] Women who are breastfeeding also commonly use the POP. In randomised trials this new desogestrel-only pill has been shown to reliably inhibit ovulation in 97% of cycles, Pearl index 0.41. In a direct comparative study, levonorgestrel-only POP inhibited ovulation in 71% of cycles, Peal index 1.55. On theoretical grounds, therefore, the desogestrel-only pill should have greater efficacy than other POPs. This possible improved contraceptive efficacy may not provide further benefit to women whose natural fertility is already reduced (breastfeeding or aged over 40 years). The Pearl index of desogestrel in women who are not breastfeeding is 0.17 (95% CI 0.004–0.928), however, suggesting that the desogestrel-only pill may provide an alternative to women who require oestrogen-free contraception and wish to use an effective oral method. Conventional POPs may be associated with higher failure rates, poor compliance and irregular bleeding than COCs and, as with other POPs, irregular bleeding and androgenic side effects may limit the acceptability of desogestrel-only contraception.

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The Faculty of Family Planning and Reproductive Health Care (FFPRHC) Clinical Effectiveness Unit (CEU) team comprising Susan Brechin (Unit Co-ordinator), Gillian Penney (Director) and Alison de Souza (Researcher) has prepared the advice given in this New Product Review. It is based on a structured search and review of published evidence available at the date of preparation. The advice given here should be considered as guidance only. Adherence to it will not ensure a successful outcome in every case and it may not include all acceptable methods of care aimed at the same results. This response has been prepared as a service to FFPRHC members, but is not an official Faculty Guidance product; a different and lengthier process produces Faculty Guidance. It is not intended to be construed or to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances. Members are welcome to reproduce this document by photocopying or other means, in order to share the information with colleagues.

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