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REGIONAL DRUG AND THERAPEUTICS CENTRE

DRUG UPDATE

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WHICH PROGESTOGEN-ONLY PILL?

The progestogen-only pill (POP) is an alternative oral contraceptive to the combined oral contraceptive pill. 'Established' POPs must be taken at the same time each day with contraceptive efficacy declining if a dose is more than three hours late. A desogestrel-containing POP has been shown to be more effective at inhibiting ovulation than levonorgestrel and it has contraceptive efficacy if a dose is up to 12 hours late. Comparisons of desogestrel with other POPs are lacking and there are no data confirming that these factors confer improved contraception. Desogestrel is expensive compared with the other POPs and therefore should be reserved for women who find it difficult to adhere to the strict regimen of the 'established' POPs. Parenteral or intra-uterine progestogen-only contraceptives may also be considered as an option for this group.

What are they?

Progestogen-only pills (POPs) contain synthetic progestogens and no oestrogen. Five POPs are licensed in the UK for contraception: four 'established' POPs (Micronor® and Noriday® both containing norethisterone 350 micrograms; Norgeston® containing levonorgestrel 30 micrograms and Femulen® containing etynodiol diacetate 500 micrograms), and Cerazette® (desogestrel 75 micrograms),[1] available since 2002. The older POPs exert their contraceptive action mainly by thickening cervical mucus, inhibiting ovulation in approximately 50% of cycles, and may delay ovum transport and reduce uterine receptivity[2] whereas the primary mechanism of desogestrel is to inhibit ovulation.[3] All POPs are taken continuously without any break between packets.

How effective are they?

With all contraceptive methods the failure rate is highest within the first year of use.[4] Data from clinical trials demonstrate an incidence of 0.3% with POPs and combined oral contraceptives (COCs).[4] However, in the general population the contraceptive failure rate rises to 8% in this first year (including cases of incorrect use and non-use).[4] Desogestrel inhibits ovulation in addition to thickening cervical mucus.[3] Theoretically this would lead to an improvement in contraceptive efficacy compared with the 'established' POPs.

However the limited evidence comparing desogestrel and levonorgestrel suggests that contraceptive efficacy is not significantly different.[5] The available trial data are not robust enough to prove a statistically significant difference in pregnancy rates between these POPs. No comparative data are available for desogestrel, norethisterone and etynodiol.

In order to maintain their contraceptive properties, the 'established' POPs must be taken at the same time each day. If a dose is more than three hours late, contraceptive efficacy cannot be relied upon.[1] Reported data suggest that desogestrel continues to inhibit ovulation when the dose has been taken up to 12 hours late.[3] In one 56 week, open label study 103 women were randomly allocated to a regimen during which tablets were to be taken 12 hours late on days 39, 42 and 49 (n = 53) or days 11, 14 and 21 (n = 50).[6] Ovulation was defined as serum progesterone concentrations > 16 nmol/L, sustained for at least five consecutive days. One subject ovulated twice during treatment and there was no apparent relationship between these ovulations and the scheduled late tablets on days 11, 14 and 21. Overall, the ovulation incidence amounted to 1.0% (95% CI 0.02% to 5.29%).[6]

Prescribers should be aware that double dosing (using two tablets as a single daily dose) of the 'established' POPs in women weighing >70kg is unlicensed. Concerns over the correlation between weight and contraceptive failure have been extrapolated from studies evaluating levonorgestrel-containing implants.[7] Direct evidence to support this practice is not currently available, however it does form part of the Faculty of Family Planning and Reproductive Health Care (FFPRHC) recommendations.[7] Women using the desogestrel-only pill are advised to take only one pill per day regardless of weight.[7]

How safe are they?

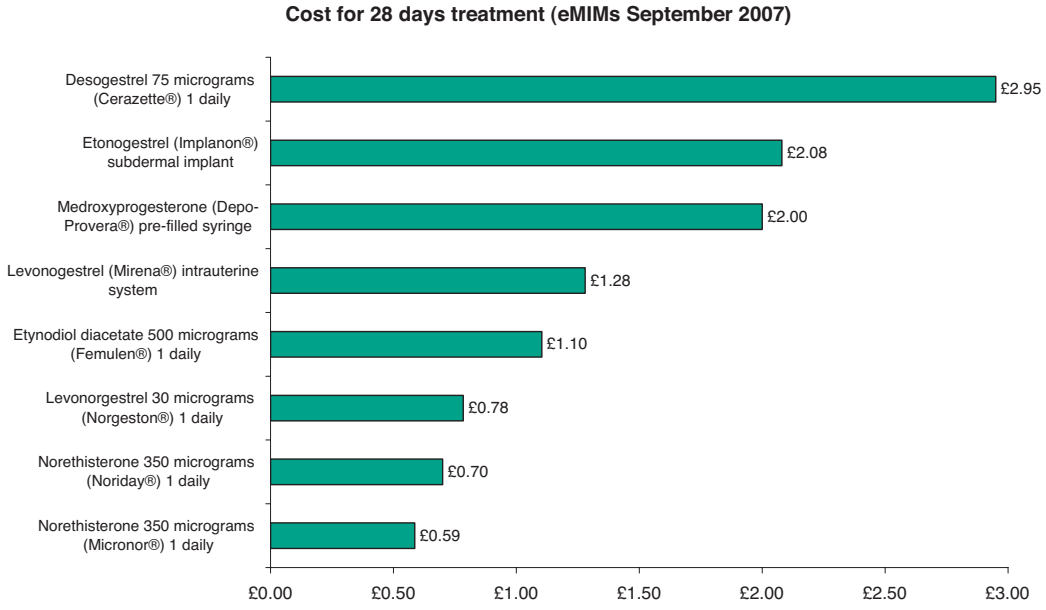
Menstrual irregularities are associated with all POPs[3] and the proportion of women discontinuing due to 'irregular bleeding' was not significantly different between the two groups in one double-blind study (22.5% for desogestrel and 18.0% for levonorgestrel).[8]

The risk of cardiovascular disease associated with POPs, parenteral progestogen-only and parenteral combined contraceptives has been evaluated in one case control study. No significant increase in overall risk for stroke, venous thromboembolism or acute myocardial infarction was demonstrated.[9] However, the number of cases and control subjects using these contraceptive methods was relatively small. In one study investigating acceptability and efficacy, the proportion of women reporting adverse and serious adverse events were comparable for desogestrel 75 micrograms/day (41.8% and 1.4%, respectively) and levonorgestrel 30 micrograms/day (41.3% and 1.8%, respectively).[8] The most common adverse events were acne, headache, nausea, breast pain, dysmenorrhoea and vaginitis.

When should they be used?

POPs may be appropriate alternatives for women who have cautions or contraindications to COCs, such as those over 35 years of age, breastfeeding mothers, heavy smokers, migraine sufferers, hypertension, valvular heart disease, and a history of, or risk factors for, thromboembolism. [1,4] The desogestrel-containing POP may be more effective than older POPs at preventing ovulation, but this has not yet been shown to improve contraceptive efficacy in practice.[4] There are no published studies comparing efficacy or ovulatory inhibition between desogestrel-containing POPs and COCs. In the financial year 2006/07, desogestrel accounted for 48% of POP items and 76% of net ingredient cost (NIC) for the former Northern and Yorkshire region. As desogestrel is more expensive than other POPs it should be reserved as an alternative for women who find it difficult to keep to the strict regimen of the 'established' POPs. Parenteral and intra-uterine progestogen-only contraceptives may also be considered as options for women with particular compliance problems.

How much do they cost?



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, CT-controlled trial, G-Guidelines

Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax 0191 260 6192
E-mail: nyrdtc.di@ncl.ac.uk Website: www.nyrdtc.nhs.uk