Progestogen-only pills and bleeding disturbances

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The progestogen-only pill (POP), minipill, is quite an effective second line contraceptive. Despite this, it is used relatively infrequently except during lactation. The main reason for this is that women on POP often have abnormal bleeding patterns, with an increased frequency of bleeding, lengthened cycles, breakthrough bleeding, spotting and prolonged bleeding. These menstrual disturbances are the most common quoted reason for discontinuation in up to 25% of users.

Key words: bleeding/minipill/progestogen-only pill/spotting

Although the minipill (progestogen-only pill; POP) was once hailed as a possible successor to the combined oral contraceptive, it has failed to live up to its expectations. By 1975 it was used by a few hundred thousand women out of the more than 50 million women using some form of oral contraception (Rinehart, 1975). POP were developed in the mid-1960s, when it was discovered that small doses of progestogens could prevent pregnancy, even though they did not always prevent ovulation. Its mechanism of action may include changes to the cervical mucus, endometrium, corpus luteum function and tubal motility, and in some cases prevention of ovulation (Graham and Fraser, 1982). The POP is less effective in preventing pregnancy than the combined pills, and forgetting just one or two pills may be enough to cause a loss of contraceptive efficacy.

Although the first orally active POP preparation that was shown to be effective was chlormadinone acetate (Martinez-Manautou et al., 1966), the first oral POP preparations to receive US Federal Drug Agency approval were the norethisterone preparations of 0.35 mg daily Micronor (Ortho) and Nor Q-D (Syntex), which were approved in December 1972. The dl-norgestrel preparation (0.075 mg) Ovrette (Wyeth) was approved in January 1973.

The first detailed review of POP was in 1975 (Rinehart, 1975). This review reported on three studies with norethisterone, and eight with norgestrel. The efficacy varied from 0.0 to 4.3 pregnancies per 100 woman years. This review highlighted the fact that although the side-effects associated with the combined pill, such as dizziness, nausea, headaches and breast tenderness, were decreased, this was heavily outweighed by the disadvantage of alterations and disturbances of menstrual flow. Of eight studies in which women used norethisterone (a total of 1253 women), it was found that between 30 and 50% of women maintained a normal cycle length, but that up to 70% complained of breakthrough bleeding/spotting in one or more cycles. With respect to duration of bleeding, one-third to one-half of women had prolonged menstruation. In a summary of 14 reports of norgestrel use in a total of 5500 women, it was found that 35–70% maintained normal cycles, with up to 39% of cycles having breakthrough bleeding and 17–35% having prolonged bleeding. The review concluded that <50% of women were still continuing with the method 12 months later, a continuation rate which is much lower than for combined pills, and that women more often abandoned POP use because of menstrual disturbances and less often because of non-menstrual side-effects.

The next major review of POP was in 1982 (Graham and Fraser, 1982). Although this review
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Table I. Studies on bleeding patterns and progestogen-only pills (norethisterone and levonorgestrel)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Countries study based in</th>
<th>No. of women</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korba et al. (1974)</td>
<td>USA</td>
<td>2202 norgestrel</td>
<td>14% discontinued because of bleeding; 70% had 21–45 day cycle</td>
</tr>
<tr>
<td>Lawson (1982)</td>
<td>UK, New Zealand, Jamaica</td>
<td>913 norethisterone</td>
<td>Breakthrough bleeding: 24% in cycle 1, 7.2% in cycle 12</td>
</tr>
<tr>
<td>Vessey et al. (1972)</td>
<td>Yugoslavia</td>
<td>74 norgestrel, 76 norethisterone</td>
<td>&lt;5% discontinued because of bleeding</td>
</tr>
<tr>
<td>Vessey et al. (1985)</td>
<td>England</td>
<td>1764 norethisterone, 555 norgestrel</td>
<td>More than half of discontinuations caused by bleeding</td>
</tr>
<tr>
<td>WHO (1982)</td>
<td>India, Yugoslavia</td>
<td>130 norethisterone, 128 levonorgestrel</td>
<td>One-quarter discontinued because of bleeding</td>
</tr>
<tr>
<td>Bell et al. (1991)</td>
<td>England</td>
<td>23 norethisterone, 23 levonorgestrel</td>
<td>No. of bleeds per month: 1.24 norethisterone, 1.28 levonorgestrel</td>
</tr>
<tr>
<td>Bisset et al. (1992)</td>
<td>Scotland</td>
<td>369 norethisterone, 146 levonorgestrel</td>
<td>15% discontinued because of bleeding; 35% had disturbed cycles</td>
</tr>
<tr>
<td>Broome and Fotherby(1990)</td>
<td>England</td>
<td>189 norethisterone, 27 levonorgestrel</td>
<td>Only 39% had regular cycles; 24% discontinued because of bleeding</td>
</tr>
<tr>
<td>Hawkins and Benster(1977)</td>
<td>England</td>
<td>200 norethisterone</td>
<td>23% discontinued because of bleeding</td>
</tr>
</tbody>
</table>

duplicated some of the 1975 review, it again made the point that menstrual cycle lengths were more variable in women taking POP than in those taking no form of hormonal contraceptive (and women on the combined pill were even more regular). Graham and Fraser (1982) also reported that 20–30% of women using minipills experienced breakthrough bleeding and that 5.8–16.2% of cycles in women using minipills had breakthrough bleeding. Their review of continuation rates was based on a comparison of the number of women using Ovulen (combined pill) and ethynodial diacetate (a progestogen-only preparation) (Paulsen et al., 1974). This study showed that although there was a better continuation rate for the combined pill at 6 months (~80 versus 70%), the rates were similar, at ~65%, at 13 months. One of the conclusions of Graham and Fraser (1982) stated that the progestogen only pill ‘(iii) minimises the menstrual disturbance seen with all progestogen-only methods’, but it is unclear on what evidence this conclusion is based.

The most comprehensive review of progestin-only contraception was prepared by McCann and Potter (1994) from Family Health International (FHI). The report included 521 references with regard to progestogen-only contraception and a whole section on bleeding disturbances. The studies on bleeding patterns that relate to norethisterone and norgestrel preparations are summarized in Table I. Their studies summarized nine series where the POP was used by non-breastfeeding women. Their results showed that menstrual disturbances were common, and were also the most often quoted reason for discontinuation of POP use, although there was quite a bit of variation in the incidence of menstrual disturbances, with the best results coming from a study in Yugoslavia in 1972 with a <5.5% discontinuation rate (Vessey et al., 1972). Interestingly, a World Health Organization (1982) study in Yugoslavia found more than half of the participants discontinuing because of menstrual abnormalities. This highlights the difficulty of any meaningful analysis of results originating from different centres, sometimes involving small numbers and having different end-points.

Interestingly, when breastfeeding women using POP are considered, and there are five series in the FHI review (Table II), four out of the five series had discontinuation rates of <5%, which is understandable because most of these women would have some degree of lactational amenorrhoea. This also highlights the fact that the POP has been widely accepted and marketed for lactational contraception.

The mechanism of action of the POP on the endometrium is poorly understood, and the menstrual response is unpredictable. It is generally said
that the POP interferes with the cyclic development of the endometrium, making it unsuitable for receiving the fertilized ovum, but histological findings are confusing. A study by Vessey et al. (1972) found that of 25 women sampled, most had proliferative changes early in the cycle. A study of 24 women who underwent endometrial biopsy (Johannisson et al., 1982) found that proliferative activity was suppressed compared with pretreatment cycles, and that patients with intermenstrual bleeding had a greater endometrial glandular diameter. Further morphometric studies of endometrial biopsies from 35 women using POP (Kim-Bjorklund et al., 1991) have shown a varied distribution of irregular secretory endometrium in one-third, a lack of proliferation in one-quarter and suppressed proliferation in a further quarter, with secretory and atrophic changes in all three groups. This confirms that the response of the endometrium to POP is variable and unpredictable. To better understand the causes of bleeding, Hourihan et al. (1986) studied the vascular patterns within the endometrium in POP users. They concluded that whereas the arteries at the endometrial–myometrial junction were decreased, the total and dilated veins were increased in POP users. How this affects the disturbance of bleeding patterns is not understood.

In conclusion, it is apparent that the greatest disadvantage of POP is its unpredictable effect on menstrual bleeding. This is responsible for many women abandoning it as a method of contraception. This is a pity because it is an excellent second line method of contraception, with efficacy only surpassed by the combined pill, sterilization and intrauterine devices. It also has no contraindications because it contains no oestrogen, and can therefore be used by women in whom oestrogens are contraindicated. Therefore new strategies must be developed to try to improve cycle control.

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References


