



# Faculty Aid to CPD Topics

## A CPD Self-Assessment Test

### REVIEW

*This review is intended as an educational exercise and reports the personal views of the authors*

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## Bleeding problems and progestogen-only contraception

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### How to use a FACT

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FACTs have three sections: a review, a true/false test, and discussion points. To use a FACT to earn CPD credits you should do the following:

1. **Working alone:** Read the review and do the test on page 181. The answers are provided on page 200 so you can mark yourself. If there are points you are unsure about, disagree with, or need further clarification on, make a note of these for use at a later date. This should take you no more than 1 hour. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).
2. **Working as a group:** Arrange a meeting of at least 1 hour with colleagues to discuss the discussion points given in the FACT (page 000) and any issues the participants have come up with as a result of reading the FACT. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).

### Introduction

The association between progestogen-only contraception and altered and irregular vaginal bleeding is well established yet remains poorly understood. It is the major reason for discontinuation of these otherwise safe and reliable contraceptive methods. There is both inter- and intra-individual variation in the extent of bleeding side effects encountered, with some women achieving complete amenorrhoea at very low doses of administered progestogen, while others have continuous unacceptable bleeding problems at the same dose. This review examines these problems, excluding other coincidental causes of altered bleeding.

All progestogenic methods of contraception affect ovulation to some extent. Some lead to anovulation, while others only partially suppress follicular activity. The bleeding patterns produced depend upon the progestogen used, the dose at which it is given and the circulating oestradiol levels priming the endometrium.

### Progestogens and the endometrium

Synthetic progestogens inhibit endometrial mitosis and induce secretory change within the endometrium. The extent of the change depends on the dose and type of progestogen administered.<sup>1</sup> Under the influence of progestogens there is an increase in the endometrial vascular density and increased fragility of superficial vessels.<sup>2</sup> This is associated with abnormality of the structure of the blood vessels and diminished spiral arteriolar development.<sup>2</sup> Direct visualisation of the endometrium has shown that bleeding appears to arise from superficial endometrial vessels which have been shown to lack endothelial vasoconstrictors. Under the influence of progestogen the thickness of the endometrial endothelial basal lamina is reduced, particularly in the early months of use, and this combination of impaired coagulation, increased vascular fragility and alterations in endometrial vascular structure may be involved in the induction of abnormal bleeding patterns. Individual progestogens

provoke different angiogenic responses, which may be dose dependent.<sup>3</sup>

### Progestogen-only pill (POP)

The POP as marketed in the UK contains a microdose of one of three progestogens: levonorgestrel, norethisterone, or its prodrug, ethynodiol acetate. Despite the extremely low dose (of the order of 1/1000 of that used in the treatment of dysfunctional bleeding) the POP can affect not only the production of cervical mucus, but has been shown to have variable effects on ovulation. These effects can vary both between women and between cycles, explaining the unpredictability of the bleeding pattern produced.

A total of 50–70% of cycles in women using the POP will be of 'normal' length, i.e. between 25 and 35 days;<sup>4</sup> 25% of cycles will be shortened and 5–10% of women will have persistent amenorrhoea. In those women where there is complete absence of menstruation, anovulation is assumed; therefore they have extremely good protection against pregnancy and can be reassured as long as they do not find the lack of bleeding worrisome. However, it is important to exclude pregnancy in women who have become amenorrhoeic after starting the POP and in those in whom there is a change of menstrual pattern. In those women with more erratic cycles, enhanced contraceptive protection may also be assumed. In anovulatory cycles in which follicles are produced but do not rupture, higher than normal levels of oestradiol may be produced, leading to endometrial thickening and erratic vaginal bleeding. However, as ovulation has not occurred, protection against pregnancy is better assured than in the woman who has a regular ovulatory cycle where the risk of pregnancy persists with each ovulation. For women using the POP, therefore, menstrual irregularity is theoretically advantageous as a marker of contraceptive efficacy.<sup>4</sup>

Despite the wide inter- and intra-individual bleeding patterns observed with different POPs, no link has been made between blood levels of progestogen and bleeding pattern. Similarly, body mass index (BMI) has not been shown to affect the likely bleeding pattern, which appears to be related to endometrial sensitivity.

### Progestogen implants

Two subdermal implants have been widely used in the UK, namely Norplant<sup>®</sup> (which releases levonorgestrel) and Implanon<sup>®</sup> (which releases etonogestrel). They give more constant blood levels of progestogens than do oral methods, but even when ovulation is more reliably abolished as with Implanon<sup>®</sup>, erratic bleeding patterns can result.

Norplant<sup>®</sup> was the first of the commercially available implants. During the first year of use with this method 25% of women were found to have regular 25–35 day cycles, 66% had irregular bleeding and 7% amenorrhoea. By Year 5, however, bleeding irregularities had improved with 66% of women having regular cycles and only 33% having erratic bleeding.<sup>5</sup> This pattern of long-term improvement probably occurs with other progestogen-only methods, but no long-term studies of bleeding with POP have been done. However, improvement with time may also be a reflection of a higher withdrawal rate for women with erratic bleeding patterns using these methods of contraception.

It is useful to note that the mean number of 'bleeding days' also reduces with time.<sup>6</sup> With Norplant<sup>®</sup>, the number of bleeding days in the first year of use was on average 54, decreasing to 44 days after 5 years.<sup>6</sup> Heavy vaginal bleeding with Norplant<sup>®</sup> was also uncommon, with a measured menstrual loss significantly less than the mean for women not using contraception.

Implanon<sup>®</sup> is now the only available contraceptive implant in the UK. It has more marked and predictable effects on ovulation than previous implants, and an extremely good record in pregnancy prevention.<sup>5</sup> With increased anovulation, as would be expected, the rate of amenorrhoea is increased as compared with Norplant<sup>®</sup>: 20.8% as compared with 7% in the first year of use. Otherwise the bleeding patterns observed have been similar when analysed in 90-day periods.

A total of 35% of women using implanted etonogestrel have 'normal' cycles and 26% erratic bleeding. Again it is important to note that heavy bleeding is uncommon and that overall measured menstrual loss is likely to be less than with regular menstruation. Nuisance value is, however, less measurable and a more likely cause of dissatisfaction and requests for removal.

### Injectable progestogens

Depot injections of either medroxyprogesterone acetate (DMPA, Depo-Provera<sup>®</sup>) or norethisterone enantate (NET EN, Noristerat<sup>®</sup>) provide higher doses of progestogen. As a result they act in contraceptive terms rather like the combined oral contraceptive (COC) in preventing ovulation at a pituitary level and suppressing gonadotrophin release. This has advantages in terms of efficacy when compared with the orally administered progestogens, but anovulation is associated with an increased rate of nuisance bleeding. With Depo-Provera<sup>®</sup> only 10% of cycles are regular and 10% of women will become amenorrhoeic after their first injection. The 'no bleeding' rate increases to 40% after the fourth injection and up to 67% after 2 years of use – assuming that the injections are given at regular intervals of 77–84 days. In women who continue to experience bleeding, increased follicular activity is noted as progestogen levels decline towards the date for the next injection, allowing oestradiol levels to rise and stimulate endometrial change. This explains the rationale for early repeat depot injections in women who experience erratic vaginal bleeding using this method of contraception.

Blood levels of progestogen decline more slowly in thin women but this has not been evidentially linked to bleeding patterns.<sup>7</sup>

NET EN produces similar bleeding patterns to Depo-Provera<sup>®</sup>, but with a lower rate of amenorrhoea and less spotting as its action in the prevention of ovulation is less reliable.

Monthly combined injectables combining norethisterone enantate or medroxyprogesterone acetate with a short acting 'natural oestrogen' are being developed. Comparison with a COC found less breakthrough bleeding but more amenorrhoea.<sup>8</sup>

### Locally active progestogens

The levonorgestrel-releasing intrauterine system (IUS) Mirena<sup>®</sup> releases levonorgestrel locally in the uterus enabling it to have a direct effect on the endometrium. The majority of women continue to ovulate normally and the device can significantly reduce the volume of menstrual blood flow. Initially, as with all progestogen-only methods, erratic bleeding can be troublesome, with a mean of 8 days of bleeding and 10 days of spotting reported over the first cycle.<sup>9</sup>

By 6 months, however, the duration and frequency of bleeding is generally much reduced, with an average of 2 days bleeding and 4 days of spotting. The overall reduction in menstrual volume is reported to be 60% at 3 months and 75% in the first year, and a significant number of women

will have complete amenorrhoea (20% at 6 months, rising to 50% at 5 years).<sup>10</sup>

The main mechanism of action of the IUS in reducing menstrual blood loss is by rendering the endometrium atrophic and by direct vascular changes due to the high endometrial levonorgestrel concentration.<sup>4</sup>

Management of bleeding problems

As bleeding problems are encountered so frequently with progestogen-only methods of contraception, appropriate counselling of the user is essential. With Implanon<sup>®</sup> insertion it has been reported that the procedure takes only 1.1 minutes but that 30 minutes of counselling are required prior to the procedure.<sup>11</sup> It is helpful to reassure women taking the POP that menstrual disturbance is a side effect of improved contraceptive efficacy, and that for all progestogen-only methods data show that bleeding patterns tend to improve with time.

When reassurance fails, ethinylloestradiol (EE, 30–50 µg) has been used to halt bleeding with Norplant<sup>®</sup>.<sup>12,13</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or mefenamic acid taken continuously for three cycles also appear to be effective, but not as good as EE. Similarly, levonorgestrel-containing POPs, again taken over 3 months, can be helpful. Levonorgestrel-containing COCs can also significantly reduce bleeding side effects in women using Norplant<sup>®</sup>.

The use of COCs containing desogestrel (Marvelon<sup>®</sup>, Mercilon<sup>®</sup>) has been suggested for women with troublesome bleeding with Implanon<sup>®</sup>, providing that there is no contraindication to the use of synthetic oestrogens.

EE can be used to abate bleeding in women using Depo-Provera<sup>®</sup> and has been found to stop bleeding episodes in up to 93% of cases.<sup>14</sup> Oestrone has been shown to be less useful, resulting in improvement for 76%, while placebo was found to improve blood loss in 74%.<sup>14</sup> Mefenamic acid (500 mg, three times daily) has also been suggested as a useful agent to help with troublesome bleeding with DMPA, but no evidence exists for its effectiveness.

The use of EE in women using the POP is more controversial as the oestradiol may theoretically negate the progestogenic mucus effect making pregnancy more likely. Traditionally swapping between brands and doses has been used when women complain of erratic bleeding but evidence that this is effective is anecdotal, as is the doubling of POP dose. The use of Femulen<sup>®</sup>, containing ethynodiol diacetate, a prodrug of norethisterone, may be helpful. However, other switches of dose and brand are unlikely to be of benefit, and as long as pregnancy and other causes of abnormal vaginal bleeding have been excluded, patience or a change of method are the most reliable options.

Other strategies that have been considered for the reduction of bleeding side effects in users of progestogen-only contraceptives include cyclical mifepristone (50–200 mg) (Table 1). The use of this anti-progestogen led to significantly shorter episodes of vaginal bleeding in women using Norplant<sup>®</sup> without any effect on contraceptive efficacy.<sup>15</sup> Mifepristone is not licensed for this use in the UK. The role of selective oestrogen modulators in the control of bleeding with progestogen-only contraception may also merit further attention,<sup>16</sup> as may the use of antioxidants such as vitamin E (recommended daily allowance 10 mg).<sup>17</sup> Other lifestyle measures such as stopping cigarette smoking may also improve bleeding patterns with progesterone-only methods of contraception and, anecdotally, phyto-oestrogens such as red clover may be helpful.

The difficulty with using any of these interventions is that on stopping therapy, bleeding problems will tend to recur. Adequate counselling, support and patience are therefore likely to be just as helpful.

Table 1 Suggested strategies for alleviation of troublesome bleeding with progestogen-only methods of contraception

	POP	Injectables	Implants	IUS
Time alone	+	+	+	+
Switch brands		±		NA
Less frequent intervals	NA	+		
Double dose	Anecdotal; some benefit	NA	NA	NA
Add EE (30–50 µg daily for 3 months)		+	+	+
Add COC (continuously for 3 months)		+ (LNG)	+ (Desogestrel for Implanon <sup>®</sup> , or LNG for Norplant <sup>®</sup> )	+ (LNG)
Mefenamic acid (500 mg three times daily)	+	+	+	+

COC; Combined oral contraceptive; EE, ethinylloestradiol; IUS; intrauterine system; LNG; levonorgestrel; NA, not applicable; POP; progestogen-only pill.

New developments

Cerazette<sup>®</sup>, a desogestrel-containing POP, is likely to be launched in the UK in October 2002. The dose of 75 mg desogestrel is designed to inhibit ovulation, and pre-marketing studies suggest that 50% of women will become amenorrhoeic. The use of different delivery systems such as vaginal rings is also a possibility, with the levonorgestrel ring having a reported 1% amenorrhoea rate.

Conclusions

Troublesome bleeding accounts for 25% of premature discontinuation of progestogen-only contraception. With increasing worldwide use of these safe contraceptive options, it is important to counsel women appropriately about likely bleeding side effects prior to starting them. A variety of treatment options have been explored, but none appear as reliable as time in reducing the extent of bleeding side effects.

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with those of women using Ortho-Novum 7/7/7 (norethindrone/ethinylestradioltriphasic) or other oral contraceptives. *Contraception* 2000; **62**: 289–295.

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Discussion points

- 1. What information should be given to women taking the progestogen-only pill about bleeding side effects and contraceptive efficacy?
- 2. Does body mass index (BMI) affect the incidence of bleeding side effects with progestogen-only contraception and, if so, how?
- 3. Is the endometrium adequately protected when oestradiol is used with depot contraception?
- 4. What guidance would you issue to your department to ensure a standardised and pragmatic approach to women using progestogen-only methods who experience bleeding as a problem?
- 5. What agents have been found to be helpful in the treatment of bleeding side effects with progestogen-only contraceptives?

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A CPD Self-Assessment Test

QUESTION SHEET

Review No. 2002/04

To be reviewed not later than 31<sup>st</sup> December 2007

Bleeding problems and progestogen-only contraception

Indicate your answer by ticking the appropriate box for each question	True	False
1. Progestogen induces proliferative change in the endometrium.	<input type="checkbox"/>	<input type="checkbox"/>
2. Under the influence of synthetic progestogens, endometrial bleeding comes from the spiral arterioles.	<input type="checkbox"/>	<input type="checkbox"/>
3. Circulating progestogen levels are linked to the bleeding pattern.	<input type="checkbox"/>	<input type="checkbox"/>
4. When abnormal bleeding patterns are produced by the POP there is evidence to suggest that changing brands is helpful.	<input type="checkbox"/>	<input type="checkbox"/>
5. Bleeding problems with progestogen-only methods improve with time.	<input type="checkbox"/>	<input type="checkbox"/>
6. Implanon® produces a higher rate of amenorrhoea than Depo-Provera®.	<input type="checkbox"/>	<input type="checkbox"/>
7. Women using the Mirena® IUS will ovulate normally in the majority of cycles.	<input type="checkbox"/>	<input type="checkbox"/>
8. Ethinylloestradiol is more effective than placebo in reducing bleeding side effects with Norplant®.	<input type="checkbox"/>	<input type="checkbox"/>
9. Oestrone is no better than placebo in reducing bleeding side effects with Depo-Provera®.	<input type="checkbox"/>	<input type="checkbox"/>
10. The use of oestrogen with the POP may affect contraceptive protection.	<input type="checkbox"/>	<input type="checkbox"/>

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