# Management of vaginal bleeding irregularities induced by progestin-only contraceptives

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As the use of progestin-only methods of contraception continues to increase worldwide, the problem of the vaginal bleeding disturbances these methods induce is becoming of increasing public health relevance. A number of approaches are used by clinicians to control these bleeding irregularities but few treatments have been adequately tested and, to date, none appears sufficiently effective. Better understanding of the mechanisms underlying vaginal bleeding as well as of the attitudes of women towards menstrual disturbances is needed, so that effective and acceptable therapies can be devised.
*Key words:* contraception/progestin/vaginal bleeding

## Introduction: the use of progestin-only methods of contraception

Over the past 30 years, the number of users of progestin-only methods of contraception has been increasing steadily worldwide and is currently estimated to be over 20 million women. The method most widely used is the injectable depot-medroxyprogesterone acetate (DMPA), first registered in the late 1960s in some countries. Its approval for contraceptive use by the US Food and Drug Administration in 1992 gave it increased access through new registrations and it is estimated that ~13 million women worldwide currently use DMPA for contraception. By contrast, the only other progestin-only injectable contraceptive available, norethisterone enanthate (NET-EN), is used by less than one million women worldwide.

Other progestin-only contraceptive methods include two levonorgestrel-releasing delivery systems: the six-rod implantable system, Norplant® (Leiras Oy, Turku, Finland), available since 1983 and currently used by about six million women, and the levonorgestrel-releasing intrauterine system, Mirena® (Leiras Oy), available since 1990 and currently used by about one million women. Use of progestin-only oral preparations remains limited. Other methods are becoming available, such as Implanon® (Organon, Oss, The Netherlands), the single-rod implantable system delivering etonogestrel, first registered in Indonesia in 1998, and other injectable and implantable systems are under development.

Progestin-only injectable and implantable methods have a number of features in common: they are highly effective and their long-acting properties facilitate their use. However, all induce major bleeding disturbances. In clinical trials, it was found that, at 1 year of use, less than 10% of DMPA and Mirena users and only 25% of Norplant users experience a regular monthly bleed, whereas others experience a variety of patterns ranging from infrequent bleeding and amenorrhoea to irregular and frequent/prolonged bleeding. These have been described in detail in previous publications (Newton *et al.*, 1994; Meng and Gu, 1996; Suvisaari and Lähteenmäki, 1996; Affandi, 1998; Fraser *et al.*, 1998). It is also well documented that this side-effect is the main reason given by

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women for discontinuing use of these methods, accounting for 40–70% of termination reasons in clinical trials (d'Arcangues *et al.*, 1992). It is also recognized that there are great variations in the tolerance that women have for these disturbances. In a multicentre clinical trial of DMPA (World Health Organization, 1987) for example, users in Egypt, Jamaica and Thailand reported similar experiences of amenorrhoea, yet 27% of women discontinued DMPA use for this reason in Egypt, against none in Thailand and Jamaica. Clearly, women make trade-offs between the different benefits and disadvantages of a contraceptive method when making their choice. Nevertheless, many women do not tolerate disturbances such as unpredictable, irregular, prolonged, infrequent or absent bleeding and need effective therapies.

### Treatment of progestin-induced vaginal bleeding irregularities

In the early 1980s, a survey was conducted on the management of progestin-associated menstrual disturbances among physicians and organizations (Fraser, 1983). A total of 35 responses was obtained from 20 countries, most of which were based on experience with DMPA, three with additional experience with NET-EN. Fourteen years later, a similar survey was conducted among family planning providers and researchers on the treatment regimens they used for progestin-associated bleeding disturbances (Nutley and Dunson, 1997). They received 64 responses from 32 countries, this time based on experience with injectable, implantable and oral progestin-only methods. Both surveys documented the wide variability of treatment regimens offered to women; these ranged from oestrogens, combined oral contraceptives (OC), progestins, non-steroidal anti-inflammatory agents, to vitamins, iron and anxiolytic agents. Notably, no significant change in practice could be observed between the two surveys. In some respects such a wide array of approaches reflects the limited understanding of the physiological process underlying these bleeding irregularities.

Only a few of these treatments have been systematically evaluated in randomized placebo-controlled clinical trials. Table I summarizes the findings from these trials. Although investigators have tested different regimens of oestrogens, ethinyl oestradiol is shown consistently to be effective in shortening the length of bleeding/spotting episodes experienced by Norplant and DMPA users; however, it does not alter the frequency of bleeding/spotting episodes and has little mid-term and no long-term effect. In one trial in Norplant users (Diaz *et al.*, 1990), ibuprofen was shown to have a similar effect, although of lesser magnitude, but this was not confirmed in a subsequent study. In that same trial, only a weak response was obtained by giving additional levonorgestrel. The use of a combined OC for 3 weeks by Norplant users was possibly the most effective, particularly if a high-dose preparation was used; however, the women's perception of the advantages of using two contraceptive methods simultaneously needs to be evaluated. Furthermore, oestrogen treatments negate the advantages of oestrogen-free methods, an important factor for some women, particularly those who have developed nausea, breast tenderness, hypertension or severe headaches while taking combined oestrogen–progestin methods, those who are breast-feeding and those at risk of venous thrombophlebitis and pulmonary embolism. Addition of an oestrogen may also jeopardize the high efficacy of progestin-only methods.

Clearly, alternative, more effective therapies are needed. There is some debate among researchers as to the desired goal of these treatments. Experience to date suggests that restoring a regular bleeding pattern may not be easily feasible and that achieving induced amenorrhoea and providing appropriate counselling and reassurance to women may be more realistic. However, to make this choice requires better understanding of women's perceptions of menstruation and of the acceptability of different menstrual patterns in various socio-cultural and religious contexts.

### Women's perceptions of menstruation and acceptability of menstrual patterns

In the late 1970s, a landmark 10-country comparative study was conducted on the patterns and perceptions of menstruation (Snowden and Christian, 1983). It was found that women are very aware of their menstrual pattern, that they perceive an increase or decrease in bleeding days as being

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**Table I.** Randomized placebo-controlled clinical trials of treatments given for progestin-induced menstrual irregularities

| Reference | Contraceptive method | No. of subjects | Conditions of treatment | Treatment | Treatment effect, in comparison to placebo |
|---|---|---|---|---|---|
| Johannisson et al. (1982) | NET 300 µg daily | 13 | Given at onset of bleeding | • EO 50 µg ×7 days | No effect |
| Diaz et al. (1990) | Norplant | 80 | B/S episode >7 days. Possibly up to 5 treatments per year | • EO 50 µg ×20 days<br><br>• Ibuprofen 800 mg t.i.d. ×5 days<br><br>• LNG 30 µg b.i.d. ×20 days | • 40% ↓ in B/S (mostly S) days, B/s episodes as frequent<br>• 30% ↓ in B/S (mostly S) days, B/S episodes as frequent<br>• 20% ↓ in B/S (mostly S) days, B/S episodes as frequent |
| Alvarez-Sanchez et al. (1996) | Norplant | 134 | B/S episode >7 days, or B/S-free interval <15 days | • EO 50 µg ×20 days<br><br>• LNG 250 µg + EO 50 µg ×20 days | • B/S episode stopped in 6 days, 40% ↓ in B/S days during tx<br>• B/S episode stopped in 3 days, 80% ↓ in B/S days during tx next B-free interval longer |
| Archer et al. (unpublished) | Norplant, past the first month of use | 106 | B/S episode >7 days, or >10 B/S days out of 14 days | • EO 20 µg ×10 days<br><br>• Ibuprofen 800 mg t.i.d. ×5 days | • ↓ in S days within first 30 days after treatment<br>• no effect |
| Witjaksono et al. (1996) | Norplant, past the first 3 months of use, not beyond 1 year of use | 180 | B/S episode >10 days, or ≥5 B/S episodes in past 90 days, or range of B/S-free intervals >17 days in last 90 days | • EO 50 µg ×21 days<br><br>• LNG 150 µg + EO 30 µg ×21 days | • B/S episodes as frequent, but shorter; effect over 6 months<br>• B/S episodes as frequent, but shorter; effect over 3 months |
| WHO (1996) | DMPA, first 6 months of use | 278 | B/S episode >7 days; first 6 months of DMPA use | • EO 50 µg ×14 days<br><br>• OS 2.5 mg ×14 days | • episode ↓ by 1B/3S days, then more irregular bleeding<br>• no effect |

B/S = bleeding/spotting; DMPA = depot-medroxyprogesterone acetate; EO = ethinyl oestradiol; OS = oestrone sulphate; LNG = levonorgestrel; NET = norethisterone; tx = treatment.

more important than a change in the number of bleeding-free days and that they strongly associate amount and duration of menstrual bleeding. They also found that over two-thirds of women expressed preference for having one monthly bleed and that the majority were not prepared to accept induced amenorrhoea, this majority ranging from 53% of respondents in the UK to 91% in India.

Their work clearly illustrated the positive and negative perceptions associated with menses. In many societies, menstruation is seen as a sign of feminity, fertility, youth and purification, but at the same time, it is tainted by associations with vulnerability, pollution, disgust and shame. In some cases, these negative attributes translate into limitations imposed on the menstruating woman's religious, social and household activities. They went on to conclude that 'Menstruation is not simply a physiological process but is linked with psychological, social and cultural variables. These interactions act differently upon the perception of menstruation and upon its sequelae, both symptomological and behavioural. As all women menstruate they are all subjected to the same cultural taboos of restriction, segregation and discrimination. [...] a woman has two perceptions of bleeding: one from the actual experience and the other from her position as a member of society which has attached certain meanings to menstruation. The interaction of these two perceptions will affect her attitudes to [...] the event.'

Twenty years later, some investigators question whether these findings would still be valid and suggest that there has been a change in women's attitudes towards menstruation. A number of studies have explored and tested the preference of women for different patterns of vaginal bleeding, mostly in the context of OC use. The acceptability of a 3 month withdrawal bleed was tested by administering a combined OC for periods of 84 days followed by 6 pill-free days to a group of 196 Scottish women (Loudon et al., 1977). The majority (82%) liked having infrequent periods and 91% of those who completed the year of follow-up refused to return to the standard monthly OC regimen after the study was completed. However, 45% of volunteers withdrew early from the study, mostly because of medical reasons and,

interestingly, the clinic staff were not entirely favourable to the new regimen. The acceptability of a 7 week pill cycle was tested among a group of 100 women and it was concluded that this was 'not a promising alternative since the majority of the volunteers preferred the inconvenience of a monthly withdrawal bleeding' (Hamerlynck et al., 1987). In a similar study conducted in Sweden (Cachrimanidou et al., 1993), 198 women used a 9 weeks on/1 week off low-dose OC regimen; despite some breakthrough bleeding and spotting early on, 63% of them preferred having a withdrawal bleed every 3 months and 26% preferred the traditional monthly bleed.

A study in Australia based on interviews of 158 women (Rutter et al., 1988) revealed that 83% believed that it was necessary to bleed monthly when taking an OC but, given a choice, 54% preferred to bleed monthly, 27% every 3 months, 4% every 6–12 months and 15% preferred amenorrhoea. In a large study conducted in France, Germany and the UK (Fuchs et al., 1996), 1005 women were asked to rank the choices of bleeding monthly, 3-monthly, 6-monthly or none at all. The most preferred pattern was 'every 3 months' and the least preferred was 'none at all'. However, in terms of individual ranking, there was a polarization between 44% of the women who gave 'monthly' as their first choice and 34% who preferred amenorrhoea above all. In a study conducted in The Netherlands, based on telephone interviews of 1301 women (Den Tonkelaar and Oddens, 1999), two-thirds of the women between the ages of 15 and 49 years preferred a bleeding frequency of less than 1 per month or never and the proportion of women expressing a preference for amenorrhoea increased with age, from 36% in the 15–19 year age group to 54% in the 45–49 year age group. When asked which would be their preferred pattern while using an OC, 71% of the women aged 15–49 years expressed a preference for a bleeding frequency of less than once a month, and in the youngest age group (15–19 years), the most preferred frequency was once every 3 months.

Few studies have been carried out among users of injectable or implantable contraceptive users. Gold and Coupey (1998) interviewed 328 young

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women in three different clinical sites in the USA to discover their attitudes to these methods: with regard to menstrual changes, 74% indicated they would stop a contraceptive method that caused irregular menses and 66% would stop a method if it caused amenorrhoea. These responses were unrelated to education, sexual, menstrual or pregnancy history, previous contraceptive use or history of sexually transmitted diseases. Two-thirds indicated their preference for a method that would decrease flow and this was associated with sexual experience.

Fewer studies still have been conducted in the developing world. In China, a study (Lei *et al.*, 1996) confirmed the important role of counselling: among 421 DMPA users, half received detailed pretreatment and ongoing counselling, half received routine counselling only. Although the main reason for discontinuing DMPA use remained menstrual changes, significantly more women (42% versus 11%) were still using DMPA at 1 year who had received the more intensive counselling. In a recent study conducted in Thailand (Supanee, 1998), it was found that amenorrhoea was perceived negatively and was associated with poor health as well as with a negative effect on appearance, and this finding was sustained regardless of age and education. This is indeed the experience of local health care providers and it led a group of Thai investigators to offer DMPA users complaining of amenorrhoea the choice of switching to the combined monthly injectable Cyclofem (Aplicaciones Farmaceuticas, Mexico City, Mexico) in order to bring on their menses. Because Cyclofem contains 25 mg DMPA and 5 mg oestradiol cypionate, this option avoids increasing the body burden of synthetic steroid, while continuing with a similar form of contraception. This was tested in a controlled clinical trial (Manee *et al.*, 1998) conducted in a group of 100 amenorrhoeic DMPA users; by 6 months, 82% of those who had switched to Cyclofem had experienced some vaginal bleeding but nearly all complained of associated hormonal side-effects; at the end of the study a third of these women opted to continue using Cyclofem despite the more demanding schedule of administration.

Thus, while the inducement of amenorrhoea may appear a more reachable target for the treatment of progestin-induced menstrual disturbances, further research is needed to test whether this would be readily accepted by women of different socio-cultural and religious backgrounds.

In conclusion, women perceive their menstrual pattern as the 'pulse' of their reproductive health and of their heath in general. Furthermore, the natural process of menstruation has been given socio-cultural and religious dimensions which impact on women's lives. It is therefore not surprising that women do not tolerate vaginal bleeding disturbances induced by contraception and expect help from the medical community. To meet their needs, better understanding of the mechanisms underlying vaginal bleeding as well as of the attitudes of women towards menstrual disturbances is needed, so that effective and acceptable therapies can be devised.

## References

Affandi, B. (1998) An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon®. *Contraception*, **58**, 99S–107S.

Alvarez-Sanchez, F., Brache, V., Thenevin, F. *et al.* (1996) Hormonal treatment for bleeding irregularities in Norplant implant users. *Am. J. Obstet. Gynecol.*, **174**, 919–922.

Cachrimanidou, A.-C., Hellberg, D., Nilsson, S. *et al.* (1993) Long-interval treatment regimen with a desogestrel-containing oral contraceptive. *Contraception*, **48**, 205–216.

d'Arcangues, C., Odlind, V. and Fraser, I.S. (1992) Dysfunctional uterine bleeding induced by exogenous hormones. In Alexander, N.J. and d'Arcangues, C. (eds), *Steroid Hormones and Uterine Bleeding*. AAAS Press, Washington, pp. 81–105.

den Tonkelaar, I. and Oddens, B.J. (1999) Preferred frequency and characteristics of menstrual bleeding in relation to reproductive status, oral contraceptive use, and hormone replacement therapy use. *Contraception*, **59**, 357–362.

Diaz, S., Croxatto, H.B., Pavez, M. *et al.* (1990) Clinical assessment of treatments for prolonged bleeding in users of Norplant implants. *Contraception*, **42**, 97–109.

Fraser, I.S. (1983) A survey of different approaches to management of menstrual disturbances in women using injectable contraceptives. *Contraception*, **28**, 385–397.

Fraser, I.S., Tiitinen, A., Affandi, B. *et al.* (1998) Norplant consensus statement and background review. *Contraception*, **57**, 1–9.

Fuchs, N., Prinz, H. and Koch, U. (1996) Attitudes to current oral contraceptive use and future developments: the women's perspective. *Eur. J. Contracept. Reprod. Health Care*, **1**, 275–284.

Gold, M.A. and Coupey, S.M. (1998) Young women's attitudes toward injectable and implantable contraceptives. *J. Pediatr. Adolesc. Gynecol.*, **11**, 17–24.

Hamerlynck, J.V., Vollebregt, J.A., Doornebos, C.M. *et al.* (1987) Postponement of withdrawal bleeding in women using low-dose combined oral contraceptives. *Contraception*, **35**, 199–205.

Johannisson, E., Landgren, B.-M. and Diczfalusy, E. (1982) Endometrial morphology and peripheral steroid levels in women with and without intermenstrual bleeding during contraception with the 300 μg norethisterone (NET) minipill. *Contraception*, **25**, 13–30.

Lei, Z.W., Wu, S.C., Garceau, R.J. *et al.* (1996) Effect of pretreatment counselling on discontinuation rates in Chinese women given depo-medroxyprogesterone acetate for contraception. *Contraception*, **53**, 357–361.

Loudon, N.B., Foxwell, M., Potts, D.M. *et al.* (1977) Acceptability of an oral contraceptive that reduces the frequency of menstruation: the tri-cycle pill regimen. *Br. Med. J.*, **2**, 487–490.

Manee, P.-A., Suporn, K., Nuanchan, P. *et al.* (1998) Effectiveness of Cyclofem in the treatment of depot medroxyprogesterone acetate-induced amenorrhea. *Contraception*, **57**, 23–28.

Meng Fan and Gu Sujuan (1996) Menstrual bleeding patterns in Chinese women using the Norplant subdermal implant. *Hum. Reprod.*, **11** (Suppl. 2), 14–19.

Newton, J.R., d'Arcangues, C. and Hall, P.E. (1994) 'Once-a-month' combined injectable contraceptives. *J. Obstet. Gynaecol.*, **14** (Suppl. 1), S1–S34.

Nutley, T. and Dunson, T.R. (1997) Treatment of bleeding problems associated with progestin-only contraceptives: survey results. *Adv. Contracept.*, **13**, 419–428.

Rutter, W., Knight, C., Vizzard, J. *et al.* (1988) Women's attitudes to withdrawal bleeding and their knowledge and beliefs about the oral contraceptive pill. *Med. J. Austr.*, **149**, 417–419.

Snowden, R. and Christian, B. (eds) (1983) *Patterns and Perceptions of Menstruation*. St Martin's Press, New York, 339 pp.

Supanee, J.-A. (1998) *The Effects of Perceived Change in the Menstrual Pattern on the Acceptability of Fertility Regulating Methods*. Ph.D. Thesis, University of Exeter, UK, 275 pp.

Suvisaari, J. and Lähteenmäki, P. (1996) Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. *Contraception*, **54**, 201–208.

Witjaksono, J., Lau, T.M., Affandi, B. *et al.* (1996) Oestrogen treatment for increased bleeding in Norplant users: preliminary results. *Hum. Reprod.*, **11** (Suppl. 2), 109–114.

World Health Organization, Task Force on Long-acting Systemic Agents for Fertility Regulation, Special Programme of Research, Development and Research Training in Human Reproduction (1987) A multicentred Phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100mg or 150mg: II. The comparison of bleeding patterns. *Contraception*, **35**, 591–610.

World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation. (1996) Clinical evaluation of the therapeutic effectiveness of ethinyl oestradiol and oestrone sulphate on prolonged bleeding in women using depot medroxyprogesterone acetate for contraception. *Hum. Reprod.*, **11** (Suppl. 2), 1–13.