JOINT STATEMENT

Bleeding pattern changes with progestogen-only long-acting reversible contraceptives

This is a Joint Statement by the following expert consultants:

Dr Christine Read, Sexual Health Physician and Consultant in Family Planning, Reproductive and Sexual Health;

Dr Caroline Harvey, Medical Director, Family Planning Queensland;

Dr Deborah Bateson, Medical Director, Family Planning NSW;

Dr Kathy McNamee, Senior Medical Officer, Family Planning Victoria;

Dr Terri Foran, Sexual Health Physician and Lecturer, School of Women's and Children's Health, University of New South Wales.

Introduction

Long-acting reversible contraceptives (LARCs) are methods that require administration less than once per cycle or month.[1]

Progestogen-only LARCs in Australia include:[2]

- etonogestrel implant – Implanon®
- depot medroxyprogesterone acetate (DMPA) – Depo Provera®/Depo Ralovera®
- levonorgestrel intrauterine device (LNG-IUD) – Mirena®

Progestogen-only LARCs have the following advantages:

- They have a higher 'real life' efficacy than more easily reversible methods, such as oral contraceptives or barrier methods, because adherence is not patient dependent.[1] Failure rates associated with 'typical' use are virtually the same as those associated with 'perfect' use.[1]
- They are more cost effective than the combined oral contraceptive pill based on economic modelling in the United Kingdom.[1]
- They are listed on the Pharmaceutical Benefits Scheme (PBS) in Australia.[2] Hence, the cost to women is low and similar to, or less than, 4 months of oral contraceptive pill supply.

This statement is supported by an unrestricted educational grant from MSD.

MSD

Produced and published by ZEST Healthcare Communications ABN 81 115 828 941, Suite 1 (Ground Floor) 213 Miller Street, North Sydney, NSW 2060 on behalf of Schering-Plough Pty Limited, a subsidiary of Merck & Co. Inc. Level 4, 66 Waterloo Road, North Ryde NSW 2113.
MSDSY267 10/10

Sexual Health & Family Planning Australia
Leading the way in sexual and reproductive health

However, an important issue with progestogen-only LARCs is that they all disrupt the regular menstrual cycle. These resulting altered bleeding patterns have no serious effects on health but can interfere with daily activities.[3] Importantly, the changes in vaginal bleeding patterns – which may include amenorrhoea, infrequent, frequent or prolonged episodes – is the most common cause for discontinuation of these contraceptive methods, accounting for 40–70% of cases.[1,3,4]

Currently, there does not appear to be evidence for an effective treatment for these bleeding irregularities in the long term.[5] It has been suggested that providing counselling and support may be the most important way to help patients continue on progestogen-only contraception.[6–8] A study that examined the effect of pre-treatment counselling on discontinuation of DPMA found that the discontinuation rate was significantly lower in women who received intensive structured counselling than in women who received basic information about the method, with side effects only being discussed upon request.[9]

Why are bleeding patterns different with progestogen-only contraceptives?

The endometrium differs in users of hormonal contraceptives from that seen in women having physiological cycles.[1] With DMPA and implants, ovulation is completely suppressed, although variable amounts of oestrogen – produced for example by adipose tissue as well as the ovary – continue to circulate.[1] Both DMPA and implants supply a relatively constant level of exogenous systemic progestogen. With the LNG-IUD, many women still ovulate while the endometrium is exposed to high levels of local progestogen. This overrides influences from systemic ovarian oestrogen and progesterone on the endometrium.

It is apparent then that in none of these methods is the endometrium primed for regular cyclical bleeding. Any bleeding that does occur is more correctly described as 'breakthrough' bleeding.[10]

The mechanism behind 'breakthrough' bleeding is multifactorial and incompletely understood. Research indicates the involvement of a wide range of molecular disturbances contributing to unpredictable endometrial vessel breakdown including disturbed endometrial angiogenesis, increased fragility of blood vessels and a loss of integrity of the stromal supporting system.[11]

In bleeding associated with progestogen-only LARCs, these changes in the endometrium are possibly activated by exposure to the synthetic progestogens themselves.[3] Continuous exposure to a relatively constant progestogen dose while simultaneously being exposed to fluctuating low endogenous oestrogen levels appears to be an important causative factor.[11]

Changes in vaginal bleeding patterns

The progestogen-only LARCs tend to have different bleeding patterns, which are outlined below:

Etonogestrel implant (Implanon®)

About one in five women are amenorrhoeic (no vaginal bleeding) in the first year of use.[6] Others may experience infrequent, frequent or prolonged bleeding.

The bleeding pattern experienced in the first 3 months is broadly predictive of future bleeding patterns for many women though there is at least a 50% chance that women with an unfavourable pattern during this period will subsequently improve.[6]

Depot medroxyprogesterone acetate (Depo Provera®/ Depo Ralovera®)

About 50% of women become amenorrhoeic in the first year of use. The initial bleeding pattern can include irregular, prolonged or frequent bleeding.[10,12] Amenorrhoea is increasingly likely with continued use.[12]

LNG- IUD (Mirena®)

In general there is a reduction of blood loss within a few months of insertion.[13] Amenorrhoea occurs in about 50% of women after 12 months of use.[13] Spotting occurs in 25% of users at 6 months and decreases over time.[13] Some women may experience prolonged bleeding in the first month but this decreases over time.[14] (Note: Mirena is listed on the PBS for treatment of idiopathic menorrhagia where oral treatments are ineffective or contraindicated.)

Managing changes in vaginal bleeding patterns

If the contraceptive method is considered to be the likely cause for unacceptable bleeding there is some evidence for the use of certain interventions to control bleeding episodes in the short term. A summary of these interventions and the evidence for their use is provided in a table at the end of this document. However, there is **no** evidence at this time that any of these interventions are successful in the long-term management of bleeding and none have been shown to increase the likelihood of continuation of the method.[5]

Amenorrhoea or infrequent bleeding

The woman should be advised that some women have no bleeding or very infrequent bleeding for the duration of the method, and reassured that this is not harmful and that no investigations are required. There is no physiological need to lose blood every month. There is no loss of fertility or 'build–up' of blood. In fact, once reassured many women prefer to be free from monthly bleeding.[2,15,16]

Frequent, heavy or prolonged bleeding

Again, explanation and reassurance is important. The bleeding often reduces in frequency or ceases with time.[10,16] Some woman may wish to trial one or more of the short-term interventions listed. If the bleeding pattern remains unacceptable, it may be necessary to consider a change of contraceptive method.[2,16]

As a clinical practice point, it is important not to assume that changes in vaginal bleeding patterns are always the result of the contraceptive method used, particularly in women presenting with persistent spotting or bleeding, or bleeding after a period of amenorrhoea.[2]

Sexual history and Pap smear history should be reviewed. If clinically indicated, exclude chlamydial infection, pregnancy or other gynaecologic problems unrelated to the contraceptive method as a possible cause of bleeding.[2] In the case of the LNG-IUD, it may also be important to ensure correct placement of the device. However, as bleeding pattern changes are an expected consequence of these methods, a balance must be struck between over- and under-investigation.

Table 1 Interventions for managing frequent/prolonged bleeding and evidence for effectiveness[5]

Proposed intervention	Implant*	DMPA	LNG-IUD†
Combined oral contraceptive pill‡ (COCP)	A 3-month study in women using Norplant showed reduced length of bleeding/spotting episodes, but not the number of episodes, with a 21-day course of a 30 mcg ethinyl oestradiol and 150 mcg levonorgestrel COCP[17] *Level of evidence: II*	No trials currently available	No trials currently available
Nonsteroidal anti-inflammatory drugs (NSAIDs) –commenced when bleeding starts	Two small studies in Norplant users: 1) Mefenamic acid 500 mg bd for 5 days reduced the number of bleeding/spotting days and reduced the number of women with irregular bleeding[18] *Level of evidence: II* 2) Oral ibuprofen 800 mg tds for 5 days decreased the mean number of bleeding/spotting days in the treatment interval[19] *Level of evidence: III-1*	Mefenamic acid – Significantly more women in the group taking mefenamic acid 500 mg bd for 5 days stopped bleeding within 7 days of treatment compared with the placebo group.[20]	No trials currently available
Salicylic acid (aspirin)	No evidence of benefit[21] *Level of evidence: II*	No trials currently available	No trials currently available
Tranexamic acid - commenced when bleeding starts	A small trial in women using Norplant showed significantly more women stopped bleeding within 7 days of using tranexamic acid 500 mg bd for 5 days compared with women using placebo[22] *Level of evidence: II*	Tranexamic acid 250 mg qid was more effective than placebo in short-term treatment of irregular uterine bleeding/spotting associated with DMPA use.[23] *Level of evidence: II*	No trials currently available
Vitamin E	No evidence of benefit[21] *Level of evidence: II*	No trials currently available	No trials currently available

Table 2 Level of evidence based on NHMRC guidelines

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test/post-test.

**Most interventions only trialled in women using an earlier contraceptive (levonorgestrel) implant Norplant® which has never been commercially available in Australia; it may be clinically inappropriate to extrapolate the findings to Implanon, which contains a different hormone (etonogestrel).*

†Mirena is listed on the PBS for treatment of idiopathic menorrhagia where oral treatments are ineffective or contraindicated.

‡There is a limited evidence base for the effectiveness of the combined oral contraceptive pill (COCP) in the management of unacceptable bleeding patterns in implant users and no evidence in DMPA users. There is no evidence the COCP will have any effect on subsequent bleeding patterns. Although the trial in Norplant users used a LNG COCP, there is no available evidence to suggest that one type of COCP is superior in this regard.

Notes:

- Much of the available clinical trial-based evidence is several years old and of a relatively low level due to the small numbers of participants and study design flaws.[5]
- There are a number of other interventions, such as mifepristone (RU486) and high-dose oral oestrogens which may be of some use in controlling bleeding in women using LARCs.[5] These have not been included on the above list since they are presently not readily available in Australia.
- Tamoxifen has been shown to reduce the incidence of bleeding episodes in Norplant users,[5, 24] but its side-effect profile limits its use in a clinical context.
- A small pilot study indicated that doxycycline 100 mg bd for 5 days was effective at stopping a single episode of bleeding[5,25] but a subsequent larger RCT did not confirm this effect.[26]

Practical suggestions for managing frequent/prolonged bleeding

In clinical practice, women commonly seek help with management of frequent/prolonged bleeding episodes related to use of the implant or DMPA. Evidence for successful long-term management of frequent/prolonged bleeding is lacking. However, based on the authors' clinical experience and review of available evidence, the following treatments may be offered:

- **Any COCP[§] for women with no contraindications to its use.**
- **A 5-day course of an NSAID (mefenamic acid 500 mg bd or oral ibuprofen 800 mg tds)**
- **A 5-day course of tranexamic acid 500 mg bd**

[§]Women may remain amenorrhoeic as long as they take active hormone pills and will experience a withdrawal bleed on ceasing active pills. The COCP is given either cyclically or as continuous active hormone pills to manage bleeding problems related to the implant or DMPA. Generally women are offered a 1–3 month trial of a COCP to bring relief from an unacceptable bleeding pattern. Some women choose to use COCP continuously or intermittently to manage their bleeding and leave their implant in situ.

Any interventions should be trialled in consultation with women and repeated courses of an intervention may be helpful to assist them in 'self-managing' their own bleeding patterns. In practice, these methods will most commonly be used to terminate episodes of prolonged bleeding, or used at the start of a bleeding episode. Despite a lack of evidence, these interventions may be used multiple times as required for the duration of the method. If bleeding patterns remain unacceptable, it may be necessary to consider an alternative contraceptive method.

Women who experience an unacceptable bleeding pattern where pathology has been excluded towards the expiration of the implant may be offered an early change of implant if they would like to continue with this contraceptive method. Anecdotally, some women may have an improved bleeding profile with the new implant but this cannot be guaranteed.

Conclusion

Progestogen-only LARCs offer many benefits in relation to contraceptive efficacy and cost-effectiveness but the effective management of unacceptable bleeding patterns in some women using these methods remains a clinical dilemma.

Provision of information including a specific explanation about the expected patterns of bleeding changes for women considering or commencing one of these methods should be a standard part of contraceptive choice consultations and assessments. Explanation about the mechanism behind these patterns may be helpful for some women in accepting the changes they experience.[2,16]

If the bleeding pattern is unacceptable the woman may choose to trial one of the reviewed interventions but it is important to inform her that the evidence base for these interventions is limited.

Finally, providing counselling and support is important to increase patient compliance, continuation, and satisfaction with any contraceptive methods.

References

1. NHS National Institute for Clinical Excellence CG30 Long-acting reversible contraception. October 2005. Available at www.nice.org.uk/CG030. [Accessed 29 August 2010].
2. Sexual Health & Family Planning Australia. Contraception: An Australian clinical practice handbook. 2nd edition. November 2008.
3. Hickey M, d'Arcangues C. Vaginal bleeding disturbances and implantable contraceptives. *Contraception* 2002; 65:75–84.
4. Harvey C, Seib C, Lucke J. Continuation rates and reasons for removal among Implanon® users accessing two family planning clinics in Queensland, Australia. *Contraception* 2009; 80(6):527–32.
5. Abdel-Aleem H, d'Arcangues C, Vogelsong KK *et al.* Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No: CD003449. DOI:10.1002/14651858.CD003449.pub3.
6. Mansour D, Korver T, Marintcheva-Petrova M *et al.* The effects of Implanon on menstrual bleeding patterns. *Eur J Contracept Reprod Health Care* 2008; 13(1):13–28.
7. Belsey EM. The association between vaginal bleeding patterns and reasons for discontinuation of contraceptive use. *Contraception* 1988; 38(2):207–25.
8. Davie JE, Walling MR, Mansour DJ *et al.* Impact of patient counseling on acceptance of the levonorgestrel implant contraceptive in the United Kingdom. *Clin Ther* 1996; 18(1):150–9.
9. Lei ZW, Wu SC, Garceau RJ *et al.* Effect of pretreatment counseling on discontinuation rates in Chinese women given depo-medroxyprogesterone acetate for contraception. *Contraception* 1996; 53(6):357–61.
10. Hickey M, Fraser IS. The causes and management of endometrial breakthrough bleeding. *Reproductive Medicine Review* 2001; 9(2):153–71.
11. Livingstone M, Fraser IS. Mechanisms for abnormal uterine bleeding. *Human Reproduction Update* 2002; 8(1):60–67.
12. Sangi-Haghpeykar H, Poindexter AN 3rd, Bateman L *et al.* Experiences of injectable contraceptive users in an urban setting. *Obstet Gynecol* 1996; 88(2):227–33.
13. Hidalgo M, Bahamondes L, Perrotti M *et al.* Bleeding patterns and clinical performance of levonorgestrel releasing intrauterine system (Mirena) up to two years. *Contraception* 65(2):129–32.
14. Mirena® Product Information. Bayer Australia. 23 September 2009.
15. Glasier AF, Smith KB, van der Spuy ZM *et al.* Amenorrhea associated with contraception – an international study on acceptability. *Contraception* 2003; 67:1–8.
16. World Health Organisation. Family Planning: A global handbook for providers. 2007. Available at: www.who.int/entity/reproductivehealth/publications/family_planning/en. [Accessed August 2010].
17. Witjaksono J, Lau TM, Affandi B *et al.* Oestrogen treatment for increased bleeding in Norplant users: preliminary results. *Human Reproduction* 1996; 11:109–14.
18. Kaewrudee S, Taneepanichskul S, Jalsamruan U. The effect of mefenamic acid on controlling irregular uterine bleeding secondary to Norspan® use. *Contraception* 1999; 60:25–30.
19. Diaz S, Croxatto HB, Pavez M *et al.* Clinical assessment of treatments for prolonged bleeding in users of Norplant Implants. *Contraception* 1990; 42:97–109.
20. Tantiwattakaul P, Taneepanciskul S. Effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. *Contraception* 2004; 70:277–9.
21. D'Arcangues C, Piaggio G, Brache V *et al.* Effectiveness and acceptability of Vitamin E and low-dose aspirin in combination, on Norplant-induced prolonged bleeding. *Contraception* 2004; 70:451–62.
22. Phupong V, Sophonsritsuk A, Taneepanichskul S. The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use. *Contraception* 2006; 73:253–6.
23. Senthong, AJ, S. Taneepanichskul. The effect of tranexamic acid for treatment irregular uterine bleeding secondary to DMPA use. *J Med Assoc Thai* 2009; 92(4):461–5.
24. Abdel-Aleem H, Shaaban OM, Amin AF *et al.* Tamoxifen treatment of bleeding irregularities associated with Norplant use. *Contraception* 2005; 72(6):432–7.
25. Weisberg E, Hickey M, Palmer D *et al.* A pilot study to assess the effect of three short-term treatments on frequent and/or prolonged bleeding compared to placebo in women using Implanon. *Human Reproduction* 2006; 21(1):295–302.
26. Weisberg E, Hickey M, Palmer D *et al.* A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. *Human Reproduction* 2009; 24:(8):1852–61.