EXHIBIT 1018

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

Table I. Studies on bleeding patterns and progestogen-only pills (norethisterone and levonorgestrel)

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

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

Table II. Bleeding patterns for breastfeeding women on progestogen-only pills

Reference	Country study based in	No. of women	Results
Apelo and Veloso (1973)	Philippines	99 levonorgestrel	3% discontinued because of bleeding
Dunson *et al.* (1993)	Multicentre	4088 norgestrel	4.9% discontinued because of bleeding
McCann *et al.* (1989)	Argentina	250 levonorgestrel	1.6% discontinued because of bleeding
Moggia *et al.* (1991)	Argentina	241 norgestrel	36% with intermenstrual bleeding
West (1983)	Scotland	84 norethisterone	1.8% discontinued because of irregular bleeding

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.

Acknowledgement

I would like to thank Lee McLaren for typing the manuscript.

References

Apelo, R. and Veloso, I. (1973) Clinical experience with microdose D-norgestel as an oral contraceptive. *Fertil. Steril.*, **24,** 191–197.

Ball, M.J., Ashwell, E. and Gillmer, M.D.G. (1991) Progestagen-only oral contraceptives: Comparison of the metabolic effects of levonorgestrel and norethisterone. *Contraception*, **44,** 223–233.

Bissett, A.M., Dingwall-Fordyce, I. and Hamilton, M.I.K. (1992) The progestogen only pill: Acceptability and continuation rates. *Br. J. Fam. Plann.*, **18,** 47–49.

Broome, M. and Fotherby, K. (1990) Clinical experience with the progestogen-only pill. *Contraception*, **42,** 489–495.

Dunson, T.R., McLaurin, V.L., Grubb, G.S. and Rosman W.W. (1993) A multicenter clinical trial of a progestin-only oral contraceptive in lactating women. *Contraception*, **47,** 23–25.

Graham, S. and Fraser, I.S. (1982) The progestogen-only mini-pill. *Contraception*, **26,** 373–388.

Hawkins, D.F. and Benster, B. (1977) A comparative study of three low dose progestogens, chlormadinone acetate, megestrol acetate and norethisterone, as oral contraceptives. *Br. J. Obstet. Gynaecol.*, **84,** 708–713.

Hourihan, H.M., Sheppard, B.L. and Bonnar, J. (1986) A morphometric study of the effect of oral norethisterone or levonorgestrel on endometrial blood vessels. *Contraception*, **34,** 603–612.

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.

Kim-Bjorklund, T., Landgren, B.M. and Johannisson, E. (1991) Morphometric studies of the endometrium, the fallopian tube and the corpus luteum during contraception with the 300 µg norethisterone (NET) minipill. *Contraception*, **43,** 459–474.

Korba, V.D. and Paulson, S.R. (1974) Five years of fertility control with microdose norgestrel: An updated clinical review. *J. Reprod. Med.*, **13,** 71–75

Lawson, J.P. (1982) Experience with norethisterone 0.35 mg daily as an oral contraceptive. *Br. J. Fam. Plann.*, **8,** 84–89.

Martinez-Manautou, J., Giner-Velazquez, J., Cortes-Gallegos, V. *et al.* (1966) Fertility control with microdoses of progestogen. In Gual, C. (ed.), *Proceedings of the Sixth Pan-American Congress of Endocrinology, Mexico City, 10–15 October 1965.* Excerpta Medica, Amsterdam, The Netherlands, International Congress Series No. 112, pp. 157–165.

McCann, M.F., Moggia, A.V., Higgins, J.E., Potts, M. and Becker, C. (1989) The effects of a progestin-only oral contraceptive (levonorgestrel 0.03 mg) on breast-feeding. *Contraception*, **40,** 635—648.

McCann, M.F. and Potter, L.S. (1994) Progestin-only oral contraception: a comprehensive review. *Contraception*, **50** (Suppl. 1), S9–S195.

Moggia, A.V., Harris, G.S. and Dunson, T.R. (1991) A comparative study of a progestin-only oral contraceptive versus non-hormonal methods in lactating women in buenos Aires, Argentina. *Contraception*, **44,** 31–43.

Paulsen, M.L., Varaday, A., Brown, B.W. and Kalman, S.M. (1974) A randomised contraceptive trial comparing a daily progestogen with a combined oral contraceptive steroid. *Contraception*, **9,** 497–508.

Rinehart, W. (1975) Minipill — a limited alternative for certain women. *Population Rep.*, **3,** A53–A65.

Vessey, M.P., Mears, E., Andolsek, L. and Ogrinc-Oven, M. (1972) Randomised double-blind trial of four oral progestogen-only contraceptives. *Lancet*, **i,** 915–922.

Vessey, M.P., Lawless, M., Yeates, D. and McPherson, K. (1985) Progestogen-only oral contraception. Findings in a large prospective study with special reference to effectiveness. *Br. J. Fam. Plann.*, **10,** 117–121.

West, C.P. (1983) The acceptability of a progestagen-only contraceptive during breast-feeding. *Contraception*, **27,** 563–569.

World Health Organization Task Force on Oral Contraceptives (1982) A randomized, double-blind study of two combined and two progestogen-only oral contraceptives. *Contraception*, **25,** 243–252.