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Review article

The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users☆

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Abstract

The aim of this guidance is to review the management of unacceptable vaginal bleeding patterns in etonogestrel (ENG)-releasing contraceptive implant users concentrating, where possible, on the evidence for pharmacological treatments and identifying a pragmatic approach where this is not possible.

This article was developed in accordance with methodology used for producing Royal College of Obstetricians and Gynaecologists' Green Top Guidelines.

The Cochrane Library (including the Cochrane Database of Systematic Reviews, DARE and EMBASE) and Medline (1966–2010) were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included "progestogen only contraceptives," "contraceptive implants," "progestogen implants," "etonogestrel implants," "irregular bleeding," "unpredictable bleeding," "bleeding irregularity" and "bleeding pattern," and the search was limited to humans and English language. Enquiries for relevant information were also made to the pharmaceutical industry and researchers for missing studies.

Although this is not a systematic review, two of the authors (D.M., I.S.F.), qualitatively assessed those papers reporting quantitative results involving treatments given either to stop or prevent bleeding in ENG or levonorgestrel contraceptive implants users.

Keywords: Progestogen only contraceptives; Contraceptive implants; Progestogen implants; Etonogestrel implants; Irregular bleeding; Unpredictable bleeding; Bleeding irregularity; Bleeding pattern

1. Introduction

ENG contraceptive implants are becoming an increasingly popular birth control choice with approximately six million women using this method worldwide (data on file, Merck, Sharp, Dohme). This safe, highly effective, long-acting and reversible contraceptive is suitable for most women of reproductive age, with recent guidelines supporting its use in women with a history of venous thromboembolism or congenital and acquired cardiovascular disease [1,2].

2. How effective is the ENG contraceptive implant?

Recent data have shown that the ENG implant is one of the most effective reversible contraceptives with a method failure rate of 0.01 per 100 implants fitted [3].

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Recent reanalysis of initial trial data and postmarketing reporting figures show ENG implants to be one of the most effective female contraceptives with overall typical failure rates of 0.049 per 100 implants fitted (method failure rate −0.01 per 100 implants fitted) [3]. This has led to some health insurance schemes fully reimbursing the cost of implant provision in a number of high resource countries and other governments subsidising or providing it free at health care facilities.

Most women find ENG contraceptive implants highly acceptable with first year continuation rates of approximately 80% in published studies [4].

Continuation rates for ENG implants are generally good, however there are marked differences depending on geographical area, with 90.4% continuation rate at two years in developing countries compared to 55.4% in developed populations [4].This may reflect a disparity in health care provision, cultural differences in perception of "nuisance" side effects and their acceptance or an ethnic variation in menstrual bleeding pattern experienced by users [4,5].

Reasons given for implant removal vary but almost one third of European women who discontinue state that "bleeding problems" have led to the early discontinuation [4]. There is also some evidence that nuisance side effects are less well tolerated by younger women using implants [6] and those attending urban health clinics [7]. Interestingly, women from Southeast Asia have less vaginal bleeding — about 5 to 7 days fewer bleeding-spotting days per 90-day reference period — compared to women from Europe and the United States [5]. Body weight may help explain these findings with Southeast Asian women in this study weighing, on average, 7.7 kg less than other women. A positive correlation was found between numbers of bleeding/spotting days and body weight with less bleeding/spotting occurring in lighter women [5].

There is, therefore, a need to review the management of "unacceptable" bleeding in ENG implant users taking into account these factors and providing a standardized approach in its management based on currently available evidence at all levels.

2.1. Bleeding pattern definitions

For the purpose of this paper, the characterization of bleeding descriptions and patterns were based on World Health Organization-recommended definitions and are shown in Table 1 [8].

Table 1
Characterisations of bleeding descriptions and patterns [adapted from 8]

- Bleeding day — any day with vaginal discharge containing blood that required more than one sanitary towel or tampon per day
- Spotting-day — any day with vaginal discharge containing blood that required at most one sanitary towel or tampon per day
- Bleeding-free day — a day during which neither bleeding nor spotting was reported
- Bleeding-spotting episode — one or more consecutive days during which bleeding or spotting was entered in the diary, bounded by bleeding-free days
- Amenorrhea — no bleeding or spotting days throughout the 90-day reference period
- Infrequent bleeding — less than three bleeding-spotting episodes in a 90-day reference period, excluding amenorrhea
- Normal frequency — three to five bleeding-spotting episodes in a 90-day reference period
- Frequent bleeding — more than five bleeding-spotting episodes in a 90-day reference period
- Prolonged bleeding — any bleeding-spotting episode (uninterrupted) lasting more than 14 days in the 90-day reference period [as defined in 5]

2.2. What types of bleeding patterns occur in users of ENG implants?

Like other progestogen-only contraceptives, use of ENG implants is associated with unpredictable vaginal bleeding patterns [5].

Data from 923 women, in 11 clinical trials conducted around the world, were analyzed recently and this confirmed that ENG contraceptive implants were associated with unpredictable bleeding patterns [5]. Amenorrhea was reported in 22.2% of women, 33.6% had infrequent bleeding and 6.7% frequent and/or 17.7% prolonged bleeding [5]. A second integrated analysis of 942 women from the US, Chile, Asia and Europe (including some of the trial data in Mansour et al. [5]) reported that widespread changes in bleeding patterns were found in ENG implant users but that no one pattern predominated [9].

2.3. Do users of ENG implants experience less menstrual bleeding than women who have natural cycles?

Most ENG implant users report a reduction in frequency and volume of menstrual bleeding [10].

There are no published papers reporting quantitative blood loss measurements in ENG implant users but most women will experience a reduction in frequency and volume of menstrual bleeding [10]. A recent analysis of bleeding patterns in ENG implant users stated that the number of bleeding/spotting days was less in 75% of the 90-day reference periods compared to those observed during natural cycles. The analysis also reported that the median number of bleeding-spotting days was slightly lower in ENG users than in women experiencing natural cycles and comparable to those taking a combined oral contraceptive (COC) [5]. This analysis reported no change in hemoglobin concentration following ENG use [5].

2.4. Will these bleeding patterns improve over time and who is likely to discontinue early?

Initial studies suggested that the bleeding pattern experienced by ENG implant users would improve with time but two recent analyses concluded that individual patterns vary considerably [5,9].

One recent analysis stated that the bleeding pattern experienced in the first three months of ENG implant use was "broadly predictive" of future bleeding patterns [5].

Those ENG users who experience frequent and/or prolonged bleeding are more likely to request early removal [5].

Recent analysis of extensive clinical trial data suggest women who experience very little bleeding within the first 90 days of ENG implant use are very unlikely to discontinue prematurely due to bleeding irregularities (2.3%) [5]. However, 26.4% of women reporting 50 to 90 bleeding-spotting days in the first reference period will request early implant removal citing bleeding problems [5].

Those with more favorable initial bleeding patterns tend to stay within an acceptable range of bleeding/spotting of 28 days or less in any one reference period (90 days) but bleeding often increases over time [5]. Although 44% of women with unfavourable bleeding patterns will eventually discontinue prematurely, up to 50% of remaining women with unfavorable patterns will find an improvement over time [5]. These analyses did not look at individual women's bleeding patterns therefore those who are amenorrheic in one reference period may not necessarily be amenorrheic in the next.

2.5. Will dysmenorrhea improve following the insertion of an ENG implant?

Most women will report an improvement or absence of dysmenorrhea following the fitting of an ENG implant [5].

Dysmenorrhea was present in 48.7% of women joining these studies, with 77% reporting complete resolution of symptoms and 6% a decrease in severity following ENG implant insertion [5]. Dysmenorrhea appeared for the first time or worsened in 5.5% of subjects.

2.6. How does the bleeding pattern in ENG implant users differ from those using other progestogen-only contraceptive methods?

The total number of bleeding-spotting days in ENG implant users appears similar but more unpredictable than those experiencing natural cycles or taking a cyclical COC with a classic seven-day hormone-free interval [5].

The bleeding patterns in ENG implant users are unpredictable and, unlike other progestogen-only methods such as depot medroxyprogesterone acetate (DMPA) injectables, amenorrhea is not necessarily sustained [5].

Users of the levonorgestrel-releasing intrauterine system (LNG IUS) experience more bleeding-spotting days initially but this decreases to about 7.5 bleeding-spotting days per 90-day reference period at one year [11]. With continuing use some women experience a return of vaginal bleeding [12], probably associated with the LNG IUS releasing less levonorgestrel (LNG) over time (20 mcg/day when first inserted decreasing to 11 mcg/day at 5 years) [13]. One recent study investigating extended use of the LNG IUS demonstrated decreasing serum LNG levels associated with a fall in the incidence of amenorrhea from 41.8% at 84 months to 31.5% at 102 months [14]. The possibility that fluctuating estradiol (E_2) levels, related to the gradual return of ovarian follicular activity over time, may be an endocrine "trigger" to a return of increased bleeding episodes in some women needs further investigation.

For progestogen-only injectables, the prevalence of amenorrhea increases with time. The intramuscular dose of DMPA is such that ovarian quiescence results with mean E_2 levels of about 140 pmol/L [15]. About 12% of women report no bleeding or spotting in the first reference period of use, increasing to 46% after one year [16]. Following the last DMPA injection, menstrual bleeding slowly returns, often chaotically for some months, and we postulate that this is possibly as a result of increasing but erratic ovarian follicular activity.

2.7. Why do women who use progestogen-only contraceptives experience unpredictable bleeding patterns?

The underlying mechanisms leading to unpredictable vaginal bleeding in progestogen-only contraceptive users are not understood [17–21].

Over the last 30 years there have been five World Health Organization (WHO) workshops commissioned to investigate bleeding irregularities with steroid contraceptives [17–21]. The very first group concluded, "based upon the available published reports describing the influence of contraceptive steroids on circulating hormone levels and clinical trials reporting the incidence of spotting and breakthrough bleeding in relation to the use of low-dose steroidal contraceptives, it may be concluded that there is no simple relationship between the peripheral hormone levels (exogenous and endogenous) and intermenstrual bleeding in women using these contraceptives" [17]. They could not demonstrate a link between a fall in circulating E_2 or ethinyl estradiol (EE) levels and an episode of bleeding.

In the early 1990s, a similar group of experts considered irregular bleeding among progestogen-only contraceptive users occurred as a consequence of estrogen fluctuations or withdrawal [19]. This theory would not, however, explain the high incidence of irregular bleeding in DMPA users where there is marked ovarian suppression with E_2 levels falling initially and remaining low, in the early follicular range (about 140 pmol/L) [15].

By contrast, exposure to high-dose progesterone accompanied by high-dose estrogen (during pregnancy) produces a stable endometrium and amenorrhea. Within these extreme limits there is a minority of women in whom it is difficult to maintain a "stable" endometrium. In these women the mechanisms and the specific triggers leading to unpredictable and sometimes persistent bleeding are unclear. The authors of this paper suggest that progestogens with some androgenic properties (like LNG or danazol) may be more effective in inducing amenorrhea, but this requires further research.

Perhaps initial estrogen withdrawal followed by incomplete ovarian suppression leading to fluctuating E_2 levels may be important [22]. In a study reporting ovarian and endometrial changes in users of ENG implants, those with bleeding disturbances were more likely to have increased follicular diameter and endometrial thickness suggesting incomplete ovarian suppression with associated changes in E_2 levels [23]. This theory is supported by the finding that ENG serum levels fall by about 50% over 3 years of use with mean E_2 levels increasing from 241.7 pmol/L at 1 year to 313.9 pmol/L at 2 years [24].

Many groups have explored the molecular and cellular mechanisms underpinning endometrial bleeding with progestogen-only contraception. Much of our understanding about "trigger" mechanisms at the endometrial level is based on studies conducted in women using LNG subdermal implants and is summarized in a series of recent reviews [25–27].

In women using continuous progestogens, the endometrium appears to be inherently unstable, with a tendency for small surface blood vessels to break down and bleed unpredictably. The covering surface epithelium also tends to come easily free of its attachments to underlying stroma, allowing subepithelial bleeds to become overt and detectable in the vagina. Epithelial repair mechanisms also may be defective, permitting light bleeding often to persist for many days.

These tissue disturbances occur on a basis of disturbed endometrial angiogenesis resulting in the development of thin-walled, distended and fragile superficial microvessels. These fragile microvessels bleed easily when subjected to minor stretching stresses. The cause of the increased vascular fragility is not entirely clear, but deficiencies in endometrial microvessel pericytes and composition of basement membrane have been reported [25–27].

A range of endometrial cellular and molecular disturbances have been described, all of which may contribute to disturbed angiogenesis, increased spontaneous tissue breakdown or defective repair. These include increased local matrix metalloproteinase (MMP) release, endothelial cell dysfunction, disturbed vascular endothelial growth factor expression, reduced epithelial cytokeratin expression, increased tissue factor expression and multiple alterations in the concentrations and functions of migratory endometrial leukocytes [28].

2.8. What are the benefits of pre-insertion counselling?

Providing informed and realistic information prior to the fitting of an ENG implant may improve acceptance and continuation [29].

It is good practice to discuss the expected bleeding patterns with women who wish to use an ENG implant [30].

Counselling prior to contraceptive provision is an essential component of family planning. Clinicians consider that the resultant choice, along with adherence and satisfaction with a contraceptive method, depends heavily on the counselling experience [29]. The basis of this statement is reviewed below.

A recent Cochrane review assessed the effectiveness of counselling techniques to improve adherence to, and continuation of, client-dependent hormonal methods of contraception [30]. Unfortunately, the literature is scarce about this issue. Just one randomized controlled trial showed that structured counselling prior to receiving a method — DMPA in this case — and repeated counselling support improved overall continuation and women were less likely to discontinue due to menstrual disturbances [31].

A further study [32] reported that those receiving intensive counselling about family planning methods were less likely to discontinue due to dissatisfaction with the contraceptive method, but overall continuation was not affected.

The authors of the Cochrane review concluded that enhanced counselling appeared to have a "limited effect on contraceptive continuation" but "may change the reasons why women stop using contraception. Intensive counselling interventions with multiple contacts may be needed to improve adherence and acceptability of contraceptive use" [30].

2.9. Will a "trial" of taking a desogestrel progestogen-only pill (POP) predict the future bleeding pattern for prospective ENG implant users?

There are no data to suggest that bleeding patterns with one progestogen-only method will predict future bleeding patterns with another progestogen-only method. This includes administration of a desogestrel POP prior to fitting of an ENG implant.

2.10. How should we manage ENG implant users presenting with unacceptable vaginal bleeding?

A detailed clinical history from women complaining of unacceptable vaginal bleeding using ENG implants may be helpful in identification of the underlying cause and determine if a pelvic examination and/or further investigations are required [33].

The ENG contraceptive implant's "Summary of Product Characteristics" [24] states that, "evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynaecological pathology or pregnancy." Many clinicians find this advice rather vague and have requested clarification. The Clinical Effectiveness Unit (CEU) of the Faculty of Sexual and Reproductive Healthcare in the UK has responded and produced guidance [33] although fails to define "unacceptable" bleeding and when bleeding has "settled." It should also be noted that all bleeding that occurs with progestogen-only methods may be viewed as "unscheduled," and this term should not be used in this context. Some feel that the CEU guidance is excessive in recommending a pelvic examination after just three months of "persistent bleeding" therefore the authors have altered this guidance for worldwide use. The authors define

"unacceptable bleeding" as prolonged and/or frequent bleeding, judged by the woman, and "persistent" bleeding to be prolonged and/or frequent bleeding for more that 6 months. When "bleeding has settled," this suggests it is more acceptable to the user (Fig. 1).

Clinicians are advised to take a careful history from women complaining of unacceptable bleeding when using a progestogen-only contraceptive method and should address the questions outlined in Table 2. A detailed drug history and inquiry about the number of units of alcohol consumed each week and cigarettes smoked each day should be ascertained. Although there is little in the literature suggesting that these factors increase bleeding episodes in ENG implant users, they have been linked with reports of unscheduled bleeding among combined hormonal contraceptive users [34–36].

Table 2
Points to cover when seeing users of ENG implants complaining of unscheduled vaginal bleeding (adapted from Clinical Effectiveness Unit guidance, 2009 [33])

What are the woman's main concerns?
Ask about her bleeding pattern prior to having the ENG implant fitted
Ask the user to describe the number of days each month she bleeds plus the number of episodes. Does the bleeding or pain occur during or after sex or is it associated with abdominal pain or urinary symptoms?
When was the implant fitted? Is the implant palpable? Is there any risk of pregnancy?
Have any other drugs or medication been taken, e.g., antiepileptic drugs? Does she smoke and, if so, how many?
Is the user at risk of an STI? Is the user in a new sexual relationship, under 25 years, or has had more than one partner in the last year?
When was her last cervical screening test?

2.11. What clinical investigations are required prior to offering treatment for unacceptable vaginal bleeding?

Those at risk (under 25 years old, or have a new sexual partner, or more than one partner in the last year) should be offered an STI screen. This should always include testing for *Chlamydia trachomatis*. Ideally, a full STI screen should be offered but this will depend on local prevalence, cost and the availability of laboratory testing [33].

A pelvic examination is required in women with unacceptable bleeding using ENG implants if there are risk factors for an STI, if there are concurrent symptoms or the woman requires routine cervical cytology screening as indicated by National/professional guidelines [33].

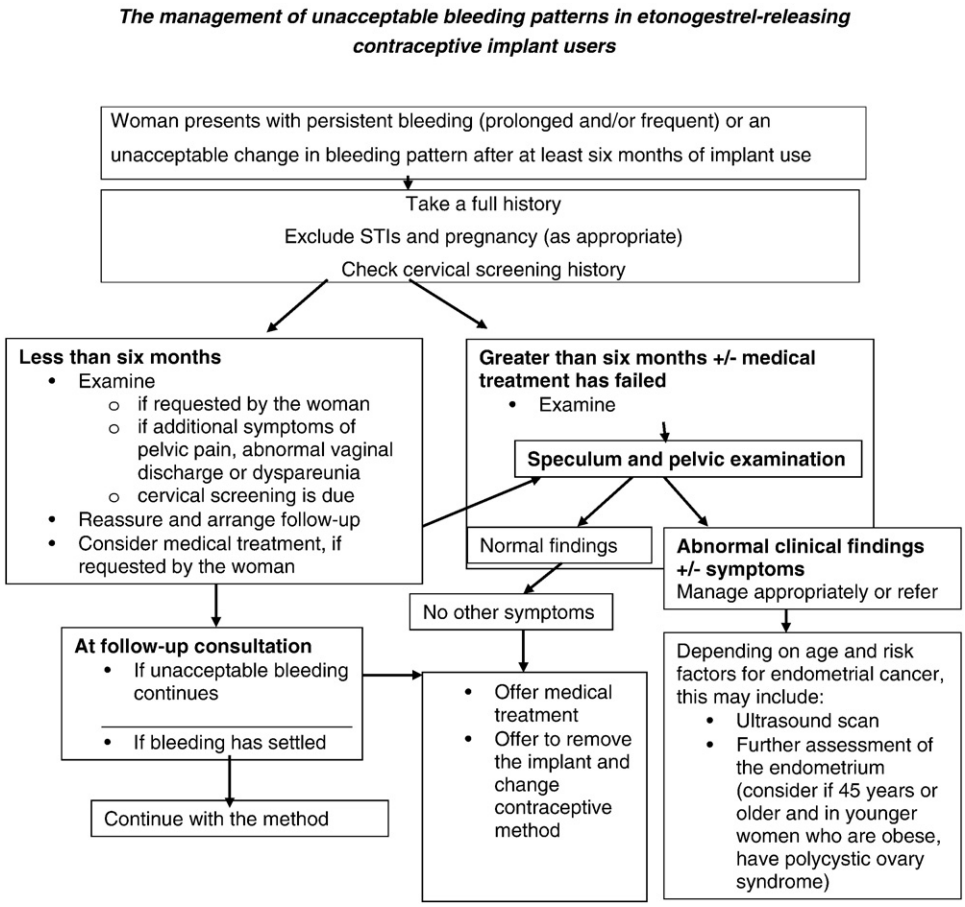

Fig. 1. Management pathway for ENG implant users with persistent vaginal bleeding (based on the UK's Clinical Effectiveness Unit, Faculty of Sexual and Reproductive Health Care guidelines 2009 [33]).

A pregnancy test may be indicated if there are concerns that the woman was pregnant when the implant was inserted or there was non-insertion of the implant or concurrent drug interactions may have occurred [33].

2.12. When is a pelvic examination required?

Examination of the cervix using a speculum is required (adapted from Ref. [33]):

- If requested by the woman
- If there is persistent bleeding after at least six months of implant use (prolonged and/or frequent bleeding)
- If new symptoms occur or there has been an unacceptable change in bleeding after at least 6 months of implant use
- If the user requires cervical cytology screening as indicated by National/professional guidelines
- If medical treatment of unacceptable bleeding fails
- If the woman complains of concurrent symptoms then a bimanual examination is also indicated.

There are just three published papers investigating therapeutic options to help improve bleeding patterns in ENG implant users [37–39]. Clinicians have, therefore, advised easily prescribed drugs based on data extrapolated from LNG contraceptive implant studies.

A recent Cochrane systematic review of randomized controlled trials compared various treatments to control unscheduled bleeding in women using progestogen-only methods [40]. Twenty-three randomized controlled trials containing 2,674 women were included. Studies exploring preventative as well as active treatments for bleeding irregularities in progestogen-only contraceptive users were included. The discussion below will concentrate on active treatments as the Cochrane systematic review, along with a subsequent publication [41], do not support the routine use of any preventative regimens.

Estrogen is thought to help with the endometrial repair process following menstruation and is therefore a suitable treatment option to investigate [42,43]. The systematic review stated that treatment with estrogen alone, or as a COC, reduced the number of days of an ongoing bleeding episode and this effect lasted for several months after treatment when compared to placebo in LNG implant users [40]. However, its use may lead to individuals discontinuing treatment because of nausea [44,45].

Selective progesterone receptor modulators (SPRM) such as mifepristone inhibit the actions of progesterone. Administration of SPRM is reported to up-regulate endometrial estrogen receptors, thereby inducing endometrial proliferation and reducing vaginal bleeding [46]. One study reported shorter episodes of unscheduled bleeding among women taking a single monthly dose of mifepristone (50 mg) when using the LNG contraceptive implant [47]. A subsequent pilot study in ENG implant users has failed to show medium- or long-term benefit of mifepristone over placebo [38].

Progestogens have often been used in high dosage to control spontaneous heavy menstrual bleeding [48] but appear to be of little use when given in low dose to LNG implant users. Only one small study has looked at administration of low-dose oral progestogen (0.03 mg LNG twice daily for 20 days and up to 5 occasions in one year) in LNG implant users. The number of bleeding/spotting days was reduced but discontinuation and nonuse rates were high [49].

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) to treat irregular bleeding has been encouraged because arachidonic acid metabolism in the endometrium of progestogen-only contraceptive users may be disturbed [50] NSAIDS, however, have shown variable efficacy in LNG implant users. Different NSAIDs (ibuprofen, mefenamic acid, aspirin) were used in regimens lasting 5–10 days without clear benefit [49-52]. A further study randomized women complaining of irregular bleeding with ENG implants to taking either 500 mg mefenamic acid or placebo three times a day for five days [37]. About 65% of women stopped bleeding within one week of taking NSAID treatment compared with 21.7% who had taken placebo. Over the next 4 weeks, there were about six less bleeding/spotting days among women who had taken mefenamic acid [37]. Although UK guidance from the National Institute for Health and Clinical Excellence [53] recommend NSAID use in this situation, clarity over which NSAID to give, the appropriate dose and regimen needs to be established.

Additional small therapeutic studies cited in the Cochrane Review suggest that the following treatments were more effective than placebo for terminating an episode of bleeding among women using progestogen-only contraceptive implants: mifepristone plus an estrogen or doxycycline for ENG implant users [38], tamoxifen or tranexamic acid in LNG implant users [54,55].

Since the Cochrane review, there have been a small number of other studies published looking at short-term treatment options for the management of troublesome bleeding in contraceptive implant users. A recent double-blind, randomized trial, involving 40 Thai women, showed that irregular bleeding with a LNG implant (Jadelle®) ceased completely in 70% of those treated with a cyclooxygenase 2 (COX-2) inhibitor, celecoxib (200 mg once daily for 5 days), compared with 0% of women in the placebo arm [56].

Another recent randomized trial found that mifepristone, combined with EE or doxycycline, was significantly more effective than placebo in ending an episode of bleeding in ENG implant users. No improvement was seen, however, in subsequent bleeding patterns, and improvement with treatment, compared with placebo, amounted to a decrease of only two days out of 90 days [39].

Overall, it appears that some women with persistent bleeding benefit from some treatments, particularly when an EE-based COC is prescribed (see Table 3).

However, the authors of the Cochrane Review caution that until there is more published evidence, their findings do not support the routine clinical use of any of the regimens

Table 3
A pragmatic approach to the use of currently available therapies in stopping unscheduled bleeding in users of ENG contraceptive implant

	Therapy regimen	Supportive evidence
First choice	COC taken daily for 21 days followed by a 7-day break. Use for up to three months.	Little published evidence. Anecdotally, appears to help in practice
Second choice	High-dose cyclical progestogen for up to 3 months (medroxyprogesterone acetate 10 mg twice daily or norethisterone 5 mg twice daily for 21 days with a 7-day break)	No published evidence. Anecdotally, appears to help in practice
Third choice	POP, particularly a desogestrel POP, taken daily for up to three months	No published evidence. Anecdotally, may work in some cases
Fourth choice	NSAIDS, especially COX-2 inhibitors, taken daily for 5-10 days	Some published evidence. Anecdotally, may work in practice
Fifth choice	Tranexamic acid 500 mg twice daily for 5 days	Limited published evidence. Anecdotally, may work in practice

included in the trials, particularly for obtaining a long-term effect [40].

In practice, a clinician's first choice medication to control persistent bleeding in ENG implant users is a COC. It is inexpensive and there is some limited evidence to suggest benefit in the short term. Preventative management of recurrent unscheduled bleeding is a greater challenge. Most studies suggest that the benefit of any therapeutic intervention is short-lived and that unpredictable bleeding usually returns. Careful counselling is required, with some women choosing to take the pill if bleeding returns at an inappropriate time, i.e., just before a holiday. Other women will desire more predictable bleeding and change their contraceptive method. There are a few women who will choose to keep the contraceptive implant but are intolerant of the bleeding pattern and who also find other contraceptive methods unacceptable or potentially ineffective. In this situation, a number of clinicians now prescribe long-term COC to regulate bleeding patterns while the implant continues to provide highly effective contraception. It does seem counterintuitive to administer two contraceptive methods, particularly in women who have a history of forgetting pills but in practice this regimen provides effective contraception and reduces unscheduled bleeding. Although there are no data to support this "off-licence" prescribing of the pill in ENG implant users, theoretically, the dose of EE and progestogen should be safe. Most clinicians prescribe a 30 mcg EE COC in this situation.

Options are limited for women who use ENG implants because of a contraindication to estrogen-containing contraceptives. Despite the absence of evidence, additional progestogen, in the form of a POP or higher dose cyclical oral progestogen regimens, is often prescribed. Other clinicians suggest a NSAID such as ibuprofen, mefenamic acid, celecoxib or an antifibrinolytic agent (tranexamic acid), and anecdotal evidence suggests that some women may benefit [37,51–53,55,56].

2.13. When should an implant be removed?

If a user of an ENG contraceptive implant requests its removal — for whatever reason — it should be removed as soon as possible.

An ENG implant should be removed if medical treatment for persistent bleeding fails and the user wishes to use another contraceptive method.

The implant should be removed if vaginal bleeding is heavy and cannot be managed by therapeutic intervention.

3. Future directions and areas for research

Future research aimed at understanding the disturbed endometrial mechanisms in women with more extreme, persistent and troublesome symptoms (compared with those who develop amenorrhea or light, infrequent periods) will be critical to eliminate this common cause of premature discontinuation of implant use. A number of theories have been proposed including estrogen withdrawal or estrogen fluctuation but most have concentrated on molecular and cellular mechanisms at the endometrial level. It is known that progestogen-only contraceptives alter the expression of steroid receptors, the morphology of blood vessels and epithelial attachment of the endometrium. Agents that will "repair" the endometrium by restoring blood vessel resilience and epithelial integrity need to be explored with the ultimate aim of achieving amenorrhea.

Since the 1980s, WHO has sponsored five international workshops on this topic, publishing extensive information about the potential mechanisms, but they failed to address the concept of possible "triggers." There must be local fluctuations of unknown regulatory molecules, for example MMPs in the endometrium, around the small superficial blood vessels and the epithelium resulting in intermittent localized breakdown. These local mechanisms are yet to be determined. It has so far proven impossible to exclude localized fluctuations in the availability of steroid ligands at an intracellular level within the endometrium. It has not been possible to show changes within systemic circulating levels that precede a bleeding episode. Further research in this area continues to be necessary.

After undertaking this review, we were surprised at the paucity of data investigating different treatment regimens to prevent unscheduled bleeding when an ENG implant is first inserted or to help control unacceptable bleeding in the long-

term, thereby improving user acceptance and continuation rates. Further well-designed randomized controlled studies should explore preventative and therapeutic options. It is likely that simple interventions to stop a particular bleeding episode will be recommended in the near future, but discovering an effective longer-term preventative treatment will prove a far greater challenge. This is mainly because no one has yet clarified all the mechanisms and thus target(s) for therapeutic strategies to prevent spontaneous endometrial breakdown in the presence of continuous progestogen exposure. Studies of potential candidate drugs will also be difficult because study recruitment will need to include a large number of new ENG implant users with random assignment of half to active therapy and half to placebo, ideally for at least one year, since there is no way of predicting which subset of women is at risk of troublesome unscheduled bleeding [41]. For initial studies aimed at changing clinical practice, easily prescribed medications such as a COC, progestogen-only pill, cyclical oral progestogen therapy, an antifibrinolytic agent and a COX-2 selective inhibitor should be investigated.

Finally, women complaining of spontaneous heavy menstrual bleeding have been successfully treated with DMPA and the LNG IUS [57]. There is one study that suggests menstrual blood loss (even in heavy bleeders) is significantly reduced in women using a LNG implant [58] with data to also support a marked improvement in dysmenorrhea for ENG implant users [5]. Additional studies to investigate the therapeutic benefits of the ENG implant in women with heavy and painful menstrual bleeding are needed.

4. Conclusion

This guidance has reviewed the practical management of unacceptable vaginal bleeding in ENG contraceptive implant users and provided an approach to investigating and stopping a specific episode of troublesome bleeding. Preventing such episodes is more difficult. If progestogen-only implants are to be more widely accepted and continuation rates improved, research must focus on understanding the underlying mechanisms provoking unscheduled endometrial breakdown. This must be allied with the study of easily prescribed therapies and novel regimens both to prevent and to treat unpredictable vaginal bleeding.

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