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REVIEW

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Management of abnormal bleeding in etonogestrel-releasing implant users: *quo vadis*? An exploratory study on the attitudes of a cohort of Italian gynaecologists and review of the literature

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Abstract

Introduction Long-acting reversible contraceptives (LARCs) are increasingly gaining popularity due to their high efficacy and ease of use compared to short-acting reversible contraceptives (SARCs). Among available LARCs, the etonogestrel (ENG) subdermal implant represents a particularly effective contraceptive method. However, many patients request early removal of the device due to the persistence of unfavourable bleeding patterns.

Methods We developed a short, multiple-choice *ad hoc* questionnaire distributed online from October 2024 to March 2025 to investigate the attitude of Italian gynaecologists towards medical treatment of unfavourable bleeding in women using the ENG-releasing implant. A total of 141 physicians responded reporting their first- and second-line treatments for patients with and without a contraindication to combined oral contraceptives (COC). We discuss the results of our survey in the light of the existing literature, through a systematic review including studies evaluating medical treatments in ENG implant users experiencing troublesome bleeding.

Results and conclusion The results of our survey and the review of the literature highlight the diverse, sparse, and sometimes confused approaches to unfavourable bleeding in ENG implant users. In our survey, up to 19% of practitioners indicated they would not know what to do in different case scenarios. In order to help gynaecologists gain greater confidence in managing this symptom, large randomised controlled trials (RCTs) with long-term follow-up on which clinical guidelines and standardized training programs can be based, are needed.

Keywords Contraception, LARC, Subdermal implant, Etonogestrel, Irregular bleeding, Treatment

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Introduction

Long-acting reversible contraceptives (LARCs) are becoming increasingly popular, particularly among adolescents and young adults [1]. These methods have demonstrated exceptional effectiveness, carrying a risk of contraceptive failure 20 times lower than short-acting reversible contraceptives (SARCs) [2], and user satisfaction with LARCs at 12 months appears to be higher compared to SARCs [3].

The subcutaneous etonogestrel-releasing implant represents an intriguing alternative among the currently marketed LARCs. The release of the progestogen begins immediately after implantation with maximum values (813 pg/ml, range 364–1020 pg/ml) reached after approximately 96 h; a minimum plasma concentration of 90 pg/ml is necessary to inhibit ovulation [4], and a steady state etonogestrel (ENG) concentration of 200 pg/ml is reached after four to six months, remaining stable for at least the subsequent three years [5]. After implant removal, plasma ENG levels begin to decline, becoming undetectable within seven days [6]. With a Pearl Index ranging from 0.00 to 0.6 [7], it is currently the most effective contraceptive method. Its insertion is noninvasive, and its handling is seldom complicated [7]. Despite its ability to prevent ovulation, the implant does not appear to suppress ovarian activity completely. Evidence of follicular growth has been consistently reported in the literature [6, 8, 9], and plasma estradiol (E2) levels do not appear to decrease after implant insertion: in fact, E2 shows a tendency to increase during the course of treatment [5], possibly preserving its beneficial effects on bone mineral density, which does not worsen during the course of treatment with the implant [10, 11]. Recent evidence has also found the implant to be effective in managing dysmenorrhea and endometriosis [12, 13], as well as adenomyosis [14–16].

Unfortunately, all that glitters is not gold, and the implant does have some shortcomings. Adverse effects described in the literature include acne, weight gain, decreased libido, and unfavourable bleeding patterns [17–20].

Data from the CHOICE project revealed higher continuation rates in LARC users than in SARC users (67.2% versus 31%) after three years. However, among LARCs, ENG implants seem to have lower continuation rates when compared to intrauterine devices, with estimates of 56% versus 70% after three years of use [21]. Similarly, a recent systematic review found higher dissatisfaction among subdermal implant users when compared to LNG-IUS users, mainly due to side effects such as acne, weight gain and bleeding irregularities [22]. Unacceptable bleeding is, indeed, the most common side effect in implant users and a frequent cause of discontinuation [23], with removal for troublesome bleeding at 12 months, ranging from 7.6 to 13.8% [17, 18, 20].

Since there is currently no consensus on the management of irregular bleeding in implant users, we decided to investigate the attitudes of a cohort of gynaecologists towards the treatment of this adverse effect. We discuss the results of our survey considering the existing literature, assessing current evidence-based interventions, and identifying gaps in the literature that fail to address uncertainties of the clinicians.

Materials and methods

We developed a short, multiple-choice ad hoc questionnaire distributed online to gynaecologists from October 2024 to March 2025. The questionnaire consisted of a first section on personal data (age and workplace), and a second section with questions on their first- and second-line treatments of choice for unfavourable bleeding in implant users, both for patients with and without a contraindication to COC (combined oral contraceptive) (Supplementary A). Respondents who chose (1) contraindicated therapies, (2) the same therapy as both first- and second-line, and (3) watchful waiting despite patient request for medical assistance, as well as those who indicated non-medicinal dietary supplements, were classified as "unsure" as they all represent a reflection of the same latent construct of clinical uncertainty. Given the low number of participants who suggested dietary supplements or watchful waiting, no further sensitivity analysis was undertaken due to insufficient statistical power.

Statistical analysis

Data were collected anonymously and subsequently analysed using Fisher's exact test to compare categorical variables; a p-value of <0.05 was considered significant. Demographic data were reported as means +/- standard deviations and ranges. Statistical analysis was performed using Stata SE version 18.0 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Literature review

We conducted a systematic search in PubMed, Scopus, Google Scholar and Cochrane Library to identify all the studies evaluating medical treatment in ENG implant users experiencing troublesome bleeding. We evaluated studies published up to December 2024. The following terms were used as search criteria: "contraceptive implant," "bleeding", "treatment", "etonogestrel", "abnormal bleeding", and "etonogestrel implant". Duplicates, reviews, evidence-based practice and articles not written in English were excluded. In addition, the reference list of all the articles that qualified for inclusion was examined to identify studies not captured by electronic searches.

Table 1 Number of implants inserted per month and workplace of respondents

Number of ENG-implants inserted per month	Private facility	Public-affiliated private facility	Public	Total (insertions)
None	25 (17.7%)	3 (2.1%)	42 (29.8%)	70 (49.7%)
Less than 1	5 (3.6%)	0 (0.0%)	23 (16.3%)	28 (19.9%)
Between 1 and 3	7 (5.0%)	0 (0.0%)	14 (9.9%)	21 (14.9%)
More than 3	2 (1.4%)	0 (0.0%)	20 (14.2%)	22 (15.6%)
Total	39 (27.7%)	3 (2.1%)	99 (70.2%)	141 (100%)

Table 2 The table describes the treatment options for first- or second-line choice in the absence of contraindications to COC. Options are listed in alphabetical order

Treatment options	First-line treatment	Second-line treatment
COC	49 (34.8%)	44 (31.2%)
NSAIDs	17 (12.1%)	13 (9.2%)
Oestradiol	27 (19.2%)	24 (17.0%)
POP	14 (9.9%)	8 (5.7%)
Removal	6 (4.3%)	37 (26.2%)
Tamoxifen	1 (0.71%)	2 (1.4%)
Unsure	27 (19.2%)	13 (9.2%)

Table 3 The table describes the treatment choices as first or second line choice in the presence of contraindications to COC. Choices are listed in alphabetical order

Treatment options	First-line treatment	Second-line treatment
IUD	4 (2.8%)	3 (2.1%)
NSAIDs	24 (17.0%)	16 (11.4%)
POP	26 (18.4%)	8 (5.7%)
Removal	22 (15.6%)	77 (54.6%)
Tamoxifen	2 (1.4%)	4 (2.8%)
Transdermal oestradiol	38 (27.0%)	20 (14.2%)
Unsure	25 (17.7%)	13 (9.2%)

We excluded studies that did not specify the treatment for bothersome bleeding or failed to report data separately for the analysed interventions. To evaluate the quality of the selected articles, we adopted the GRADE system [24].

Results

The questionnaire was administered to 217 gynaecologists, and a total of 141 responses were collected. Demographics are reported in Table 1. The vast majority (70.2%; 98) reported practising in a public healthcare facility, 2.1% [3] in a public-affiliated private facility, and 27.7% [25] in a private facility. Regarding the use of ENG implants, 70.2% [26] of respondents reported performing either none or less than one insertion per month, 14.9% [21] reported inserting between one and three implants per month, and 15.6% [22] reported inserting more than three devices per month. No statistically significant differences in prescription attitudes were found between these groups ($P > 0.05$).

First and second-line treatment choices for unfavourable bleeding in ENG implant users are reported in Tables 2 and 3. As the first line for individuals without a contraindication to COC, most clinicians indicated COC (34.8%), 19.2% transdermal estradiol, 12.1% non-steroidal anti-inflammatory drugs (NSAIDs), 9.9% the progestogen-only pill (POP), 4.3% would remove the implant and 0.7% Tamoxifen. However, 19.2% [27] would not know how to manage the symptoms. As a second-line option, 31.2% chose COC, 26.2% [28] would remove the implant, 17% oestradiol, 9.2% NSAIDs, 5.7% POP, 1.4% Tamoxifen. 11.3% would not know how to manage the symptoms.

In the presence of contraindications to COC, as a first line of treatment, 27% chose transdermal estradiol, 18.4% POP, 15.6% would remove the implant, 17% NSAIDs, 2.8% [4] IUD and 1.4% Tamoxifen. 17.7% would not know how to manage unfavourable bleeding. As a second-line, the majority (54.6%) indicated they would remove the implant, 14.2% chose transdermal estradiol, 11.4% [16] NSAIDs, 5.7% POP (progestin-only pill), 2.8% Tamoxifen and 2.1% [3] IUD. 20% per cent would not know how to proceed.

No statistically significant ($p > 0.05$) differences in preferred treatments were found when the facility or the number of insertions per month were factored into the analysis.

Discussion

The results of our survey highlight the difficulties experienced by clinicians in managing unfavourable bleeding during treatment with ENG-releasing implants: attitudes are far from unanimous, and up to 19% of practitioners have indicated they would not know what to do in different case scenarios.

This prompted us to further explore this issue with a review of the literature.

Bleeding patterns in implant users

Several studies have described bleeding patterns in implant users. At three months after ENG-implant insertion, amenorrhea was reported by 0–69,8% of participants, infrequent bleeding from less than 5–39.1%, frequent bleeding from less than 2.5–11.5%, and prolonged bleeding by 2.2 to 66% [8, 21, 29–35]. Two studies also identified patterns of irregular bleeding (defined as three to five bleeding/spotting (B/S) episodes and fewer than three B/S-free intervals equal to or more than 14 days) in 17.1% [31] and 34.1% [18] of participants. In another study by Diedrich and colleagues, participants were regularly interviewed by phone and asked whether

their blood flow had changed in volume or frequency: no change in volume or frequency was reported by 28.6% and 23.1% of participants respectively, a decrease in volume or frequency by 58.3% and 41.7%, and an increased volume or frequency by 13.1% and 35.1% [21].

In other studies, one year after insertion 23–28.5% of implant users reported amenorrhea, 4.8–39% referred normal bleeding pattern, 28–32% infrequent, 6–10% had frequent bleeding and 2–44% presented with prolonged bleeding [18, 20, 33, 36]. After two years, 53–77% presented amenorrhea or infrequent bleeding [20, 34].

It appears that bleeding days are generally more frequent during the first three to six months following implant insertion. In a study involving 212 patients experiencing unfavourable bleeding during the first 28 days after insertion, 51% reported a transition to favourable bleeding patterns after 12 months [35]. However, it is important to mention that the majority of drop-outs in the studies that we analysed reported dissatisfaction with bleeding patterns as the main reason for implant removal, which raises the question as to whether bleeding patterns do in fact improve or if it is just a question of sampling bias. It is indeed possible that patient pools at six months predominantly include women who exhibited favourable bleeding patterns from the outset of the study.

In any case, how and why bleeding patterns change after the insertion of ENG implants is yet unknown. Higher ENG plasma concentrations have been found to be correlated with unfavourable bleeding in a study by Lazorwitz and colleagues [37]; this resonates with the work of Tsevat and Di Carlo, who found that amenorrhea and infrequent bleeding were more common in individuals with a higher BMI, with a difference of three to four points observed between women with favourable and unfavourable bleeding patterns 12 months after insertion [33, 38]. However, further and more robust research is required before drawing any conclusions.

Aetiology of bleeding

There is insufficient evidence regarding the causative mechanism(s) underlying unfavourable bleeding in individuals using ENG-releasing implants. Irregular bleeding patterns in other progestin-only contraceptive methods are not infrequent, and its pathophysiology has been characterised more extensively, even though each molecule produces its own pattern of gene expression and biofunctions [28], warranting scrutiny in the interpretation of available data.

Long-term progestin therapy induces changes in the morphological and hemodynamic properties of the endometrial vasculature, notably increased fragility of superficial endometrial vessels [39] and decreased endometrial perfusion [25], which in turn establishes an alternating hypoxia-reperfusion state that favours the release of ROS, altering angiopoietin expression profiles [40]. Several studies have demonstrated increased expression of Ang-2, an antiangiogenic and permeability factor, at the expense of Ang-1, which is pivotal to vessel stabilisation. Ultimately, this process eventuates in aberrant angiogenesis [41], giving rise to enlarged, thin-walled superficial endometrial vessels, whose aberrant morphology renders them prone to bleeding.

Other mediators implicated in this aberrant neoangiogenic process include members of the Matrix Metalloprotease (MMP) family, known to play a role in endometrial decidualization [42]. The increase in their expression following progesterone withdrawal is a key event in the initiation of endometrial shedding and, thus, menses [43]. Attempts to characterise MMP expression profiles in women experiencing irregular bleeding exist in the literature [44, 45]; however, further research is required to fully elucidate their functions, considering also that not all progestins appear to exert an effect on MMP expression [46, 47].

Haemostatic mediators, notably prothrombin (FII) and thrombin, have also been implicated in unfavourable bleeding in long-term users of POCs. FII extravasates from the abnormal microvasculature and is then converted into its activated form, thrombin, by tissue factor (TF). The excess thrombin will further disrupt angiogenesis by induction of Vascular Endothelial Growth Factor (VEGF) [48], chondroitin sulphate proteoglycan 4 [49], and interleukin 8 [50], eventuating in the establishment of a vicious circle of increased thrombin production, inflammation and aberrant neoangiogenesis.

Furthermore, it is now known that long-term POC also acts at a genetic level, modifying the expression of key stress-response mediators such as FKBP51, which downregulates glucocorticoid and progesterone receptor expression [51], and *ZBTB16*, a steroid-responsive transcription factor whose sustained upregulation enhances decidualization and induces proinflammatory and procoagulant mediators, including IL-8, PTGS2, and TF [52]. These alterations contribute to functional steroid withdrawal, impaired receptor signalling, and an inflammatory, prothrombotic endometrial milieu underlying unfavorable bleeding. Torelli and colleagues also demonstrated peculiar expression profiles of various proteins, including chemokines and bone morphogenetic proteins, associated with an increased risk of experiencing bleeding irregularities in ENG-implant users [53].

Further research is needed to fully explicate the nature of unfavourable bleeding in ENG-implant users, which could be beneficial for our understanding and management of these discomforting events.

Treatment options

As there is currently no consensus or standardised treatment for the management of unfavourable bleeding in ENG implant users, we chose to include all pharmacological options discussed in the literature, providing a tentative pathophysiological rationale for each of them. The selected articles have been summarised in Table 4.

Combined oral contraceptives

COCs have long been a cornerstone for the treatment of unfavourable bleeding. At the level of the endometrium, the estrogen component plays a stabilising role whilst the progestogen simultaneously induces atrophy of the lining.

We found three randomised controlled trials (RCTs) analysing COC versus placebo or other treatment options in ENG implant users with unfavourable bleeding [54–56].

Upawi et al. [54] randomised 84 patients, at least 90 days after implant insertion, to treatment with ethinylestradiol (EE) 20 mcg/desogestrel (DSG) 150 mcg for 42 days continuously or to treatment with mefenamic acid 500 mg three times a day for two courses, five days each and 21 days apart. Therapy with COC was associated with higher and faster regression of bleeding compared to mefenamic acid. However, COC use was associated with a more frequent and rapid return of unacceptable bleeding patterns, notably with 14% experiencing bleeding seven days after discontinuation of COC compared to 7% experiencing bleeding after the interruption of mefenamic acid.

Hou et al. [55] randomised 28 patients to COC or placebo to assess bleeding improvement after a 28-day therapy. The COC group received continuous therapy with EE 30 mcg/ LNG 150 mcg. All individuals in the COC group reported a significant improvement in bleeding patterns. However, the majority of patients in the placebo group (8 out of 12) also experienced improvement: this is possibly due to recruitment bias, since patients in the placebo group had their implant inserted at an average of 109 days prior, whereas the COC group had the implant in place for an average of 343 days. After three months, 38% (6 out of 16) of patients in the COC group reported a recurrence of unscheduled bleeding.

Guiahi et al. [56] randomised 32 patients who had experienced at least seven consecutive days of bleeding to receive either a 14-day treatment with EE 30 mcg/LNG 150 mcg or placebo. The authors opted for a short-term course of therapy to meet patient needs, as women who choose implant contraception typically favoured a non-daily method and sought to avoid estrogen-related side effects. During treatment, patients in the COC group had fewer bleeding days (9 vs. 3.5 days); however, 85% of subjects experienced a recurrence within 10 days after discontinuing therapy, with a mean time to bleeding recurrence of five days.

Tamoxifen

Tamoxifen is a selective receptor estrogen modulator (SERM) that acts as a non-steroidal antiestrogen in breast tissue while exhibiting agonistic effects in other tissues. In the endometrium, in the presence of endogenous ovarian estrogen, SERM acts as a competitive inhibitor of oestrogen receptors. This action appears to reduce endometrial growth and vascular proliferation, possibly leading to fewer bleeding events in women with long-acting progestin therapies [57]. Additionally, in vitro studies have shown that Tamoxifen promotes remodelling of the endometrial vasculature by modulating mRNA expression of VEGF and PLGF, leading to an overall reduction in angiogenic activity [58].

Our review identified four studies investigating treatment with Tamoxifen in women with ENG implants experiencing unfavourable bleeding [59–62]. All studies concluded that a 7 to 10-day course of oral Tamoxifen 10 mg twice daily could be an effective option for managing troublesome bleeding in ENG implant users. No adverse effects were observed, even after repeated treatment cycles, up to three courses within six months, and no decrease in contraceptive effectiveness.

Friedman et al. [60] conducted a retrospective chart analysis including 67 adolescents (12 to 21 years of age) who reported troublesome bleeding and had been treated with Tamoxifen. The median time from implant insertion was nine months. The study reported continuation rates higher than or comparable to those observed in other studies evaluating the adolescent population (81.7% at 12 months, 54.7% at 24 months, and 22.5% at 36 months). However, no additional outcomes were analysed, and no placebo was included in this study.

Edelman et al. [61] conducted a double-blind RCT involving 80 patients who received either 10 mg twice daily for seven days or a placebo. The instructions were to start therapy after experiencing three consecutive days of bleeding or spotting. In the second stage, all participants entered an open-label phase in which Tamoxifen treatment could be repeated up to three times, with a minimum 30-day interval between courses. Women randomised to tamoxifen experienced 9.8 more consecutive days of amenorrhea compared to placebo. Secondary outcomes showed that the tamoxifen group had a longer time to bleeding resumption after the first treatment (12 days vs. 6 days in the placebo group).

Simmons et al. [62] conducted a double-blind retrospective randomised trial involving 56 ENG-implant users experiencing frequent or prolonged bleeding. Participants were randomised to receive either Tamoxifen 10 mg twice a day for seven days or a placebo. Tamoxifen

Table 4 Summary of the reviewed articles

Authors, publication year	Title	Study type	Population	Treatment	Results	Grade
Upawi S.N. et al., 2020	*Management of bleeding irregularities among etonogestrel implant users: Is combined oral contraceptive pills or nonsteroidal anti-inflammatory drugs the better option?*	RCT	84 patients ENG implant users with prolonged or frequent bleeding	EE 20 mcg /DSG 150 mg for two continuous cycles vs. Mefenamic acid 500 mg TDS for 5 days, 21 days apart for 2 cycles	The percentage of women who stopped bleeding within 7 days after the initiation of therapy was significantly higher in the COCP group as compared to the NSAID group.	High
Hou M.Y. et al., 2016	*Combined oral contraceptive treatment for bleeding complaints with the etonogestrel contraceptive implant: a randomised controlled trial*	Double-blind, placebo, multicentre RCT	26 patients experiencing troublesome bleeding related to their ENG contraceptive implant	EE 30mcg/LNG 150mcg 1pill for 28 days	Women may experience improvement with no treatment, but women who use COCs are more likely to report significant improvement	Low
M. Guiahi et al., 2015	*Short-Term Treatment of Bothersome Bleeding for Etonogestrel Implant Users Using a 14-Day Oral Contraceptive Pill Regimen*	RCT	32 patients ENG implant users with reported bleeding as extremely or very annoying	COC (EE 30 mcg/LNG150 mcg) 1 pill a day for 14 days	Women are more likely to have a temporary interruption of bleeding and fewer days of bleeding during a 14-day course of OCPs as compared with placebo.	Moderate
Friedman JC et al., 2022	*Tamoxifen for the Treatment of Etonogestrel Implant-Associated Bleeding in an Adolescent Gynecology Practice*	Retrospective chart review	67 patients ENG implant users with bleeding	10 mg twice daily, for 7 days (1 to 3 courses)	Tamoxifen was well-tolerated; it can be considered a treatment option to manage bothersome implant bleeding in adolescents.	Low
Edelman A.B. et al., 2020	*Treatment of Unfavorable Bleeding Patterns in Contraceptive Implant Users. A Randomized Controlled Trial*	Double-blind RCT and open-label phase	112 patients ENG implant users with frequent or prolonged bleeding or spotting	10 mg twice daily, for 7 days	Tamoxifen temporarily stop troublesome bleeding in etonogestrel implant users.	High
Ahmed N. Feith et al., 2019	*Tamoxifen for treatment of abnormal uterine bleeding in etonorgestrel implant users: a randomized clinical trial*	RCT	200 pz ENG implant for at least 3 months with frequent or prolonged bleeding or spotting	Tamoxifen 10 mg twice daily for 10 days vs. EE 30mcq/LNG 150mcq daily for 21days	Oral administration of tamoxifen 10 mg twice daily for 10 days is effective in stopping bleeding attacks in Implanon users.	High
Simmons K.B. et al., 2017	*Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: a randomized controlled trial*	Double-blind RCT	56 patients ENG implant for at least 30 days with frequent or prolonged bleeding or spotting in the last month	10 mg twice daily, for 7 days (1 to 3 courses)	First use of tamoxifen by ENG implant users reduces bleeding/spotting days and provides a longer cessation of bleeding/spotting than placebo. Without compromising ovulation suppression.	Low
Weisberg et al., 2009	*A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users*	Double-blind, placebo RCT	204 patients Women who had used Implanon for at least 3 months and were experiencing prolonged or frequent bleeding	Mifepristone 25 mg twice daily + EE 20 mg vs. Doxycycline 100 mg twice daily vs. Doxycycline 100 mg twice daily + mifepristone 25 mg vs. Doxycycline 100 mg twice daily + EE 20 mg	Mifepristone combined with either EE or doxycycline was significantly more effective than placebo in terminating an episode of bleeding in Implanon users. No improvement in subsequent bleeding patterns.	Moderate

Table 4 (continued)

Authors, publication year	Title	Study type	Population	Treatment	Results	Grade
Weisberg et al., 2006	*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*	RCT	179 patients Women who had used Implanon for 3 months and were experiencing prolonged or frequent bleeding patterns	Mifepristone 25 mg vs. Doxycycline 100 mg vs. mifepristone 25 mg plus EE 20 µg (10 µg twice daily) 4 days treatment	Reduction in the number of bleeding days by almost 50% compared to placebo in both the mifepristone combination group and the doxycycline group	High
Zigler et al., 2018	*Ulipristal Acetate for Unscheduled Bleeding in Etonogestrel Implant Users: A Randomized Controlled Trial*	Double-blind, placebo RCT	63 patients ENG implant in place for greater than 90 days and less than 3 years who reported greater than one bleeding episode in a 24-day period.	15 mg ulipristal acetate daily for 7 days	Ulipristal acetate is well-tolerated and reduces the number of bleeding days in etonogestrel implant users	Low
Phaliwong et al., 2004	*The Effect of Mefenamic Acid on Controlling Irregular Uterine Bleeding Second to Implanon Use*	Double-blind, placebo RCT study	50 patients Implanon users with irregular bleeding who attended the Family Planning Clinic	Mefenamic acid, 500 mg per oral three times a day for 5 days	Mefenamic acid was more effective than placebo in short–term treatment of irregular bleeding and spotting associated with Implanon use.	Moderate
Casey et al., 2014	*Management of Etonogestrel Subdermal Implant–Related Bleeding*	Retrospective cohort study	391 patients Women who had received ENG-releasing implants for contraception from June 2007 to April 2011	Reassurance alone or Reassurance plus one or more between doxicycline, ibuprofen or oestradiol	Reassurance plus doxycycline is associated with lower removal rates than reassurance alone.	Low

therapy was initiated after three consecutive days of bleeding, and patients had the possibility of repeating the treatment up to three times within 180 days. During the first 30 days of follow-up, the Tamoxifen group had fewer bleeding and spotting days and a longer duration of consecutive bleeding-free days (mean difference 15.2 days). However, there was no significant difference between the two groups in the time to the first bleeding-free day (five to six days). Although the follow-up lasted six months, data at 180 days could not be reliably interpreted due to sample bias.

Fetih et al. [59] conducted an RCT in two Egyptian family planning clinics, enrolling 200 women with irregular vaginal bleeding at least 30 months after ENG implant insertion. Patients were randomised to Tamoxifen 10 mg twice daily for 10 days, or EE 30 mcg/LNG 150 mcg, once daily for 21 days, starting the first day of a bleeding or spotting episode. Over a three-month follow-up period, a higher proportion of women in the COC group achieved bleeding cessation during treatment compared to the Tamoxifen group (92% vs. 84%). However, Tamoxifen appeared to have a more sustained effect after three months, while bleeding disorders in the COC group returned to baseline within two months post-treatment.

NSAIDs

NSAIDs reduce prostaglandin synthesis and favour thromboxane production by inhibiting cyclo-oxygenases, eventuating in an increased tendency towards platelet aggregation and vasoconstriction, which in turn contribute to a decrease in uterine bleeding [63]. In the literature, ibuprofen and acid mefenamic appear to reduce the occurrence of bleeding irregularities in POP [64].

Our review identified a single trial by Phaliwong et al. [65], who conducted a double-blind placebo-controlled study in a Thai family clinic, enrolling 50 women complaining of irregular bleeding, after at least two months of implant use. Bleeding cessation four weeks after treatment was more common in the group treated with mefenamic acid (65.2% vs. 21,7%), with a reduction of B/S days during follow-up.

Mifepristone

Mifepristone is a steroidal anti-progestin that acts by competitively binding progesterone receptors, leading to a rapid drop of progesterone levels in the endometrium. Studies using murine models of long-term ENG exposure suggest that Mifepristone induces endometrial fragility that triggers repair mechanisms and re-epithelialization [66]. Additionally, mifepristone has demonstrated a significant induction of estrogen receptors in

the endometrium of Depot medroxyprogesterone acetate (DMPA) users seven days after exposure [67]. The differential expression of ER may justify an adjuvant effect of estradiol in promoting endometrial proliferation when combined with mifepristone.

Weisberg et al. published two studies comparing different treatment regimens for managing unfavourable bleeding in implant users [68, 69]. In 2006, they published a multicenter RCT comparing three different five-day treatments: mifepristone (25 mg twice daily for one day), mifepristone + EE (25 mg twice daily for one day and 4 subsequent days of EE 20 mcg once a day) and doxycycline (100 mg twice a day for 5 days) versus placebo. Mifepristone alone was not more effective than placebo in controlling bleeding, but treatment with mifepristone + EE and doxycycline was more effective than placebo in stopping the bleeding episode (4.2 days mifepristone + EE, 4.8 days doxycycline, 5.9 days mifepristone, 7.5 days placebo) and was associated with fewer B/S days. A greater reduction of B/S days in the mifepristone + EE group (14.5%) compared to the other study groups (8% doxycycline, 6.1% mifepristone, 1.5% placebo) was also reported.

In 2009 Weisberg et al. [69] randomized 204 women to 5 different 5-day courses of therapy: (a) mifepristone 25 mg given twice on day 1 followed by 4 days of EE 20 mg; (b) doxycycline 100 mg twice daily for 5 days; (c) mifepristone 25 mg given twice on day 1 plus doxycycline 100 mg twice daily for 5 days; (d) doxycycline 100 mg twice daily with EE 20 mg daily; and (e) placebo twice daily for 5 days. This study found that the more effective treatments in terminating the bleeding were the mifepristone combined either with doxycycline 100 mg 72%) or EE 20 mcg (92%).

Ulipristal acetate

Ulipristal acetate (UPA) has been used for a long time to manage bleeding irregularities, especially when caused by fibroids [70]. Although its action mechanism remains unknown, it appears to have both a direct and indirect effect on the endometrium through alteration of receptor expression or suppression of the hypothalamic-pituitary-gonad axis [71].

Zigler et al. [72] randomised 65 women to a seven-day therapy with UPA or placebo. During the 30-day follow up patients in the UPA group reported fewer bleeding days than the placebo group (five days). Even though the follow-up was short, and the authors did not collect data on pre-therapy bleeding patterns, a significant result is that 72% of women treated with UPA were "very happy" with their bleeding pattern versus 26.7% in the placebo group.

Doxycycline

Doxycycline, an antibiotic belonging to the tetracycline class, is an inhibitor of MMPs, which have been implicated in endometrial decidualization and bleeding irregularities. Additionally, doxycycline down-regulates proinflammatory cytokine expression in the endometrium, which may contribute to reducing unfavourable bleeding. Both MMP inhibition and anti-inflammatory effects can be achieved with low doses without reaching antimicrobial activity [73, 74].

Casey and colleagues conducted a retrospective chart review and particularly analysed 128 implant users who referred to their physicians for bleeding-related complaints. They compared 86 subjects who were offered either reassurance alone [53] or reassurance associated with five days of doxycycline treatment [34].

Results showed fewer bleeding complaints in women who received reassurance plus doxycycline (45.5%) versus reassurance alone (75.5%) [75].

Current treatment schemas

Medical therapy has been posited as a powerful aid in reducing unfavourable bleeding in implant users [76], yet no standardised indications are currently available.

As of now, the World Health Organisation (WHO) and the Centre for Disease Control and Prevention (CDC) are the only health organisations to propose treatment protocols. In 2016, the WHO published the third edition of selected practice recommendations for contraceptive use, issuing indications for both hormonal and non-hormonal (NSAIDs) treatment for spotting, light, heavy and prolonged bleeding [77]. These, however, present several limitations such as a lack of indication on which COC should be preferred, the dosage of EE, the duration of add-on treatment and whether the hormonal or non-hormonal treatment should be preferred. In addition, the recommendations are derived from information on LNG-releasing implants, and the extent to which they apply to ENG-releasing implants is unclear. Conversely, the recommendations issued by the CDC in 2024 are drawn from evidence on ENG-releasing implants [78]. However, due to the paucity of high-quality evidence, the authors opted for issuing general recommendations instead of specific regimens. In particular, based on patient preferences and history, the CDC essentially distinguishes between treatments where bleeding is likely to recur after cessation (hormones such as 20–30 μg EE COCs or estrogen, or antifibrinolytics such as tranexamic acid for five days) and treatments whose effects might persist for some time after treatment cessation (NSAIDs such as celecoxib, ibuprofen, or mefenamic acid for five to seven days, or Tamoxifen for seven to 10 days). If needed, treatment may be repeated. Whilst questions about the duration of certain treatments and the type of

Table 5 Available treatment schemas proposed for unfavourable bleeding in ENG implant users

	Mansour, 2011	CDC 2024	Grandi, 2024
COC	21 days and 7 days break, up to 3 months	EE 20–30 mcg, unspecified duration	3 cycles, not containing DSG/ENG
Oestrogen	NR	unspecified	Transdermal or oral oestradiol, 1-2 mg/die for 7 days, 1–3 weeks per month, to repeat for 3 cycles
Progestogen	Up to 3 months (DMPA, NET, DSG)	NR	NET, DNG, NOMAC, DRSP. 3 cycles
Tamoxifen	NR	7–10 days	10 mg BID, 7 days, 1–3 weeks per month, repeat for 3 cycles
NSAIDs	COX-2 inhibitors daily for 5–10 days	Celecoxib, ibuprofen, or mefenamic acid, 5–7 days	NR
Tranexamic acid	500 mg BID for 5 days	NR	NR

COC to be chosen remain unanswered, these guidelines represent a favourable evolution compared to their predecessors. Two notable scholars have also proposed their regimens based on their clinical experience, and these are reported in Table 5.

And in clinical practice?

The results of our survey show diverse, sparse, and sometimes confused approaches that reflect the paucity of guidelines and high-quality studies on the management of unfavourable bleeding in ENG implant users.

In the absence of contraindications, COC appears to be the most popular first line of treatment. This finding is coherent with available treatment schemes and resonates with the well-established role of COC in the management of bleeding irregularities. However, in the case of ENG-related unfavourable bleeding, some additional considerations should be made. Firstly, the rapid and frequent return of unfavourable bleeding after its interruption makes it a palliative rather than a curative approach. In addition, many individuals opt for the implant as it is a non-daily contraceptive method, which raises the question as to whether it is appropriate, within this context, to prescribe a pill that needs to be taken every day.

A possible answer to this problem, which was not contemplated by any of the scrutinised protocols nor the clinicians who answered our survey, is the vaginal ring. Its advantages are intuitive: it has been found to yield better bleeding patterns in women with bleeding irregularities when compared to COCs with the same [79] or different [80, 81] hormonal combinations, and it is a non-daily method, possibly responding to one of the primary needs of individuals opting for the implant, ultimately favouring better compliance. Whilst concerns about the additive effect of the progestogen component of the ring on the serum concentrations of ENG are understandable, considering also that plasma ENG concentrations do not vary significantly with respect to oral EE/DSG formulations, the local action of the contraceptive ring should be considered in this context. In particular, Bulten et al. analysed endometrial histology after 12 and 24 months of therapy with a vaginal contraceptive ring and found adequate suppression of endometrial activity, with biopsy samples showing endometrial atrophy or minimal proliferation in most cases [82]. An alternative to bypass the caveat of ENG, which, however, is not available in our country (Italy), is the EE/segesterone acetate ring [83], although its cost could represent another significant limitation in its use. It should be noted that this treatment remains speculative, as no studies are currently available in the literature evaluating the use of the vaginal ring for the management of unfavorable bleeding associated with ENG. Further investigation into this treatment is warranted.

An additional intervention not contemplated by any of the scrutinised protocols nor the clinicians who answered our survey, is the use of combined injectable contraceptives. Only one study in the literature has evaluated this approach [84]. Sinthuchai et al. conducted a randomized, double-blind, placebo-controlled trial in women experiencing troublesome bleeding during LNG or ENG contraceptive implant use. Patients who received a single injection of 25 mg of medroxyprogesterone acetate (MPA) and 5 mg of estradiol cypionate were more likely to experience at least 7 days without bleeding during the month after injection compared with women in the placebo group (87% vs. 48%): therefore, similarly to the vaginal ring, injectable contraception may satisfy users as it does not require daily administration. However, bleeding patterns 21 days after injection where not significantly different between the two study groups, suggesting that the beneficial effect of monthly injectable may last less than 21 days. In addition, the small sample size prevented the authors from discerning the bleeding effect of ENG and LNG separately. Larger studies are needed to confirm the efficacy of this therapeutic option.

Another frequently reported option, with and without contraindications to COC, was the administration of a progestin. Whilst the rationale behind this choice is understandable, the specificities of the molecule that one wants to adopt are to be kept in mind. Given the association of higher plasma ENG concentrations and irregular bleeding [37] and considering that pre-treatment with DSG does not improve bleeding patterns, nor does it

reduce early removal rates [85], clinicians should refrain from prescribing oral DSG. This attitude is shared by Grandi and colleagues [86] but not by Mansour [87], who proposes other options, among which DMPA can be found. The popularity of this potent progestogen for managing unfavourable bleeding in low-income countries is due to its effects on the endometrium and relatively low cost [88, 89]. However, its potential side effects, particularly those related to its glucocorticoid activity [90], weigh against recommending it when other options are available. These include norethisterone (NET; suggested by both Grandi and Mansour) and drospirenone (DRSP; suggested by Grandi). NET has repeatedly demonstrated its efficacy in the management of unfavourable bleeding and menstrual suppression [91–93], to the point where it has also been suggested for the management of irregular in guidelines published by major societies and consensus groups [94, 95], and it was also found to be effective in reducing bleeding during use of a POP [96]. However, NET is a substrate of aromatase, which catalyses a fraction of it into a small amount of EE: in particular, 5 mg of NETA are converted into 20–30 mcg of EE, thereby warranting caution in prescription to people with a contraindication to COC [91]. Regarding DRSP, we believe it could be another interesting option to manage irregular bleeding, given that both pre- and post-marketing studies have demonstrated a favourable bleeding pattern, even better than that of DSG alone [26, 97]. Ultimately, as said earlier, a question of opportunity on the prescription of a daily contraceptive add-on remains.

Furthermore, many gynaecologists identified transdermal oestradiol as a valid treatment option, especially in the presence of a contraindication to COC [98]; this option has also been put forward by Grandi and colleagues. This finding is particularly interesting, as there are currently no studies assessing its efficacy in the context of ENG implant-related bleeding, nor is oestrogen alone indicated in the management of bleeding irregularities in other settings. Whilst the pathophysiological rationale is understandable, more evidence is needed prior to fully support this recommendation.

Among all respondents, 19.2% [27] reported uncertainty in managing the symptoms. Implant removal was selected as the first-line option by 4.3% (six) of participants, a percentage that increased to 26.2% [28] if first-line treatments failed. In patients with contraindications to COCs, 17.7% [99] of all respondents reported difficulties in symptom management and implant removal was considered a first-line treatment by 15.6% [22] of specialists, and this percentage rose to 54.6% [77] when initial treatment attempts were unsuccessful.

This limited understanding of unfavourable bleeding management in the context of contraceptive implants is particularly concerning in individuals with contraindications to COC, as the choice of a LARC is also frequently secondary to this caveat. The predominant use of COCs and POPs over other therapeutic options is likely influenced by gynaecologists' greater familiarity with these treatments. Limited knowledge of other drugs, rarely used in routine gynaecological practice, such as Tamoxifen, may discourage physicians despite existing evidence in the literature.

Our survey has some limitations. We used a short questionnaire to encourage participation and recruited gynaecologists regardless of their clinical experience and area of expertise. As a result, most respondents (69.7%) had little or no experience with this contraceptive device. Nevertheless, even gynaecologists who do not insert the device may still come across patients experiencing adverse effects associated with this contraceptive method, which warrants thoughtful and competent management.

Conclusions

Managing unfavorable bleeding caused by ENG-releasing implants is a key challenge in routine clinical practice, as well as a major source of discomfort for implant users. The literature is scarce, with only a few high-quality studies indicating that COCs, tamoxifen, and mifepristone are the most effective treatments. Our survey's findings indicate that bleeding abnormalities in ENG-implant users are addressed in a diverse, sparse, and sometimes confusing manner. Indeed, our findings demand higher quality evidence, such as larger multi-centric RCTs with long-term follow-up, on which clinical guidelines and standardized training programs can be based. This would help gynecologists gain greater confidence in managing this symptom, improving patient adherence, compliance and satisfaction with the method.

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization: A.S., M.A., M.C.M.Distribution of the survey: A.S., M.A., E.S., A. L., R.S., M.C.M.;Statistical Analysis: M.A.;Review of the literature: A.S., M.A., M.C.M.;Data curation : A.S., M.A., E.S., A. L., R.S., M.C.M.;Writing—original draft preparation : A.S., M.A., M.C.M.;writing—review and editing : A.S., M.A., E.S., A. L., R.S., M.C.M.;All authors have read and agreed to the submitted version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Given that the survey was addressed only to practising gynaecologists, the local Ethics Committee (*Comitato Etico Area Vasta Emilia Centro*) waived its requirement for approval; all participants freely gave their consent to participate to the survey.

Competing interests
The authors declare no competing interests.

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