CLINICAL ARTICLE

Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials

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Objective: To present efficacy, safety, and bleeding profile results from the clinical trials that supported the U.S. Food and Drug Administration filing for the approval of a single-rod etonogestrel (ENG) contraceptive implant (Implanon).

Design: Integrated analysis of 11 international clinical trials.

Setting: Contraceptive clinics in U.S., Chile, Asia, and Europe.

Patient(s): A total of 942 healthy women, aged 18 to 40 years.

Intervention(s): Insertion of an ENG implant. Most women were enrolled in studies lasting either 2 or 3 years.

Main Outcomes Measure(s): Efficacy was measured by the cumulative Pearl Index in women $\leq$35 years old. Safety was primarily assessed by incidence of adverse events. Bleeding profiles were analyzed via reference period analyses.

Result(s): No pregnancies were reported while the ENG implants were in place. Six pregnancies occurred during the first 14 days after ENG implant removal. Including these six pregnancies, the cumulative Pearl Index was 0.38 (year 1 and 2 Pearl Indexes were 0.27 and 0.30, respectively). Common drug-related adverse events were headache, weight gain, acne, breast tenderness, emotional lability, and abdominal pain. Bleeding pattern changes were observed, but no one pattern predominated.

Conclusion(s): The ENG implant is an efficacious and safe method of contraception which does not require patients' consistent action. (Fertil Steril® 2008;■:■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Contraceptive implant, etonogestrel, menstruation, desogestrel, levonorgestrel

Implanon (etonogestrel [ENF] implant) is a single-rod, subdermal, progestin-only, nonbiodegradable, long-acting, and reversible contraceptive implant that contains the progestin etonogestrel, the biologically active metabolite of desogestrel. When inserted subdermally, it provides contraceptive protection for up to 3 years (1, 2). The ENG implant is distinguishable from newer combined hormonal contraceptives (oral, transdermal, and intravaginal) in that it does not require daily, weekly, or monthly dosing and is estrogen free. Compared with shorter-term user-dependent methods which increase the risk of use-related method failure, long-acting reversible contraceptives can bring "typical use" failure rates more in line with "perfect use" failure rates. These new contraceptives give potential users a wider range of risk-benefit profiles from which to choose their contraceptive methods. The ENG implant, approved by the U.S. Food and Drug Administration (FDA) in July 2006, is manufactured for Organon USA (Roseland, NJ) by NV Organon, Oss, The Netherlands. The ENG implant was first marketed in Indonesia in 1998 and it is currently available in more than 30 countries. According to the manufacturer, more than 3.3 million ENG implants have been dispensed worldwide since 1998 (data on file, Organon International, Roseland, NJ).

The present report provides an overview of the efficacy, safety, and tolerability profile of this novel long-acting contraceptive and is based on a summary of the clinical data

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which were submitted, reviewed, and approved by the FDA in 2006. The data were derived from 11 clinical trials of the ENG implant which were the basis for the U.S.-approved product labeling and serve as the source of the clinical information used in the mandatory clinical training program for U.S. clinicians who wish to prescribe the ENG implant. Additionally, the bleeding profile of the ENG implant is presented and compared with that of Norplant, a 6-capsule progestin-only contraceptive implant releasing levonorgestrel (LNG implant). The LNG implant was marketed earlier in the U.S., and many U.S. clinicians are familiar with it. The bleeding profile comparison is intended to provide a frame of reference to aid prescribing clinicians in counseling prospective ENG implant users.

MATERIALS AND METHODS

Subjects

This report is based on an integrated analysis of the clinical data from 11 international Good Clinical Practice (GCP)–compliant studies. Studies were conducted in the U.S., Chile, Europe, and Asia. Study participants were healthy, sexually active women, 18 to 40 years of age, who were within 80% to 130% of their ideal body weight according to the Metropolitan Height and Weight Tables, 1983. Subjects were required to have normal menstrual cycles, i.e., recurring every 24 to 35 days, with an intraindividual variation of no more than 3 days. A negative pregnancy test and Pap test were required before implant insertion. Exclusion criteria included: 1) use of an injectable hormonal method of contraception within the preceding 6 months or other hormonal contraceptives within the preceding 2 months; 2) use of implantable contraception within the preceding 2 months; and 3) having had a delivery, abortion, or miscarriage within 2 months before study entry. For all centers, local institutional review boards or ethics committees approved the study protocol before the first subject was enrolled. All subjects provided written informed consent.

The present report focuses on the safety and efficacy of the ENG implant. However, three smaller comparative studies examining the effects of the ENG implant (n = 59) versus the LNG implant (n = 55) regarding bleeding patterns were also included. Observations regarding differences between the ENG implant and the LNG implant were limited to bleeding pattern differences, because the sample size was too small to make comparisons regarding safety and efficacy.

Treatment

The ENG implant is a single (coaxial) rod made up of an ethylene vinyl acetate (EVA) copolymer core (40% EVA) containing 68 mg ENG, surrounded by a 60-μm skin of EVA copolymer (100% EVA). The implant is 40 mm in length and 2 mm in diameter. The ENG implant was inserted subdermally in the inner aspect of the woman's nondominant arm. The implant was inserted during days 1 to 5 of a spontaneous menses and left in place throughout the course of the study for up to 3 years. A small number of subjects underwent longer durations of treatment as part of extensions that were added to certain studies, resulting in total exposure greater than the currently approved 3 years.

Assessments

Baseline assessments consisted of medical history, gynecologic history, recording of preexisting medical conditions, vital signs, physical examination (including a breast examination), and gynecologic examination (including pelvic examination, Pap smear, and pregnancy test). During the trials, each subject underwent clinical assessments every 3 months that recorded concomitant medications, adverse events (AEs, including occurrences of vaginal bleeding and pregnancy), vital signs, and implant site condition (assessed by clinicians). Subjects had gynecologic and detailed physical exams annually. Post-treatment evaluations 3 months after implant removal determined subjects' menses, pregnancy, use of contraceptive methods, and the occurrence of AEs.

Adverse events were categorized by the investigators based on their relationship to the study drug (none, unlikely, possible, probable, or definite) and whether or not they were serious (fatal or life threatening, permanently disabling, required hospitalization or prolonged hospitalization).

Bleeding Pattern Analyses

To assess the impact of the ENG implant on vaginal bleeding, the clinical trial program used the criteria proposed by the World Health Organization (WHO) in 1986 for assessment of bleeding patterns experienced while using progestin-only contraceptive methods (3). Because progestin-only methods interrupt the cyclicity of menses, this analysis assesses bleeding patterns with respect to 90-day reference periods (RPs).

Bleeding parameters All subjects were given diary cards to record by date occurrences of vaginal bleeding, spotting, or absence thereof. Bleeding was defined as any bloody vaginal discharge that required the use of >1 pad or tampon per day. Spotting was defined as any bloody vaginal discharge that required ≤ 1 pad or tampon per day. A bleeding or spotting episode was defined as ≥ 1 consecutive day in which bleeding or spotting was recorded, where each episode was bounded by at least 1 bleeding and spotting–free day on either side (note that by this definition 1 bleeding and spotting–free day ends an episode). Given a 28-day cycle, a 90-day RP would, therefore, be expected to contain 3.2 menses or bleeding episodes. Per WHO definitions, 3 to 5 bleeding/spotting episodes within a 90-day RP are considered to be a normal frequency of "menses" or bleeding episodes (3).

Bleeding pattern indexes Bleeding pattern indexes were calculated based on the diary entries. Per WHO definitions, amenorrhea was defined as no bleeding or spotting within a 90-day time interval, infrequent bleeding was defined as <3 episodes of bleeding/spotting within a 90-day RP, frequent bleeding was defined as >5 episodes of bleeding

within a 90-day RP, and prolonged bleeding was defined as ≥1 bleeding episode that began within a 90-day RP and lasted for >14 consecutive days.

Statistical Methods

All of the 942 women who were treated with the ENG implant were included in our analysis. Breastfeeding women were excluded from the contraceptive efficacy and bleeding analyses.

Contraceptive efficacy was assessed by calculating the Pearl Index (the expected number of pregnancies per 100 woman-years of exposure) and its exact 95% confidence interval (CI). Confidence intervals were calculated by assuming an underlying Poisson distribution.

The safety analysis was restricted to descriptive statistics. Bleeding irregularities were excluded as AEs, because they are an expected and common side effect of progestin-only methods (4). The following conventions were used in the safety analysis:

The in-treatment period was defined as the period from the first day of implant insertion up to and including 5 days after implant removal, except for pregnancies, where this period included the 2-week period after implant removal.

Last measurement was defined as the last value obtained during the in-treatment period.

A 3-month (90-day) evaluation period was allowed for each scheduled assessment of physical, gynecologic, and laboratory parameters. Assessments taking place outside this time, or not during the in-treatment period (for post-baseline assessments) were excluded from the analysis of that particular visit. These 90-day periods were only used in the presentation of summary statistics.

A 1.5-month (45-day) evaluation period was allowed for each scheduled assessment in vital signs.

In cases where there were multiple results per evaluation period, the event with maximum severity was included. If severities were judged to be equal, then the most recent assessment was included in the analysis.

All AEs described by the investigators were coded based on the WHO Adverse Reaction Terminology (version 1994/2).

The bleeding pattern analysis is based on the RP analysis group, which consisted of all treated subjects who contributed at least one evaluable RP for the analysis of vaginal bleeding patterns. If a bleeding episode started in one RP and continued into the next one, it was counted in the RP in which it started.

An RP was considered not evaluable and was excluded from analysis if diary data with bleeding information were missing for 3 or more consecutive days or if concomitant medications that were not permitted were used. If missing data were spread across two RPs, then both RPs were excluded. If diary data were missing for ≤2 consecutive days, the missing values were replaced with the same bleeding-spotting response reported on the day immediately preceding the missing values. If the data were missing on the first 1 or 2 days of treatment, then the day immediately following the missing data was used.

Bleeding patterns during the first 2 years (eight RPs) of treatment were analyzed using descriptive statistics. These analyses included subjects who completed treatment as well as those who discontinued owing to bleeding irregularities. Overall means of bleeding parameters and bleeding pattern indexes were calculated for RPs 2–8. Reference period 1 was excluded from the calculation of overall means because it included the menstrual period during which the implant was inserted.

RESULTS

Subjects

A total of 946 subjects were enrolled in the clinical studies: 923 made up the group for which for efficacy was determined, and 942 subjects comprised the group for which safety data were determined (Fig. 1). Of the 946 subjects enrolled, 330 (34.9%) were in North America, 279 (29.5%) were in Asia, 215 (22.7%) were in Europe, and 122 (12.9%) were in South America.

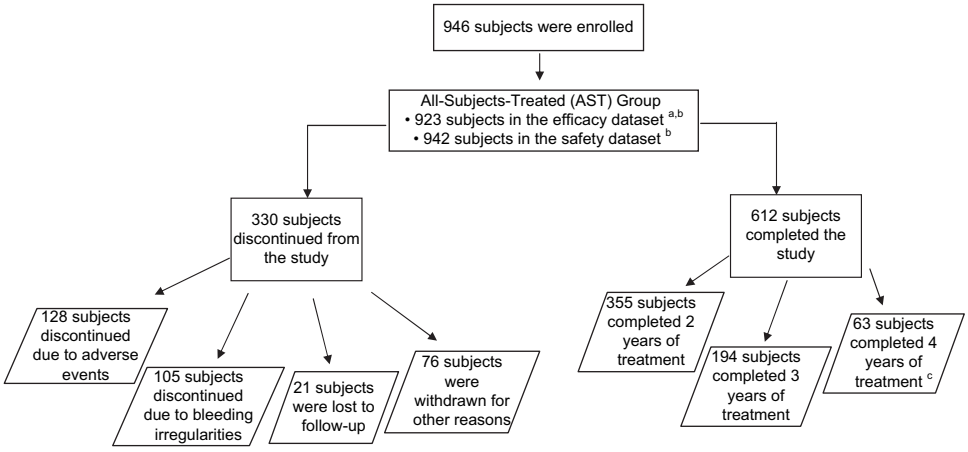
Demographic and other subject characteristics are summarized for the entire dataset in Table 1. The mean age of this population was 27.7 years, with most subjects ranging in age from 21 to 35 years. The mean body mass index was 23 kg/m^2. Most subjects had at least one prior pregnancy and delivery. The most common contraceptive methods used previously were foam, condoms, diaphragm, or spermicide (39.1%), followed by oral contraceptives (24.3%). The mean duration of menstrual bleeding at screening was 4.6 days. Since subjects could not use hormonal methods in the two months prior to enrollment, use of barrier methods was increased.

A total of 16 subjects were excluded from the efficacy and RP analyses because they were breastfeeding and were thus at a lower risk for pregnancy and vaginal bleeding. Three additional subjects did not have any post-baseline assessments, resulting in 923 subjects for whom efficacy was determined. These women, who were 18–35 years old at study entry, represented a drug exposure of 20,648 treatment cycles. Some subjects were also treated for a longer period of time than the recommended 3-year period because 2 of the 11 trials were of 4 years' duration.

Of the subjects included, 612 (65%) completed the study in which they were enrolled, whereas 330 (35%) discontinued prematurely for any of several reasons (Fig. 1). The various studies ranged in duration from 2 to 4 years, and 355 (58.0%), 194 (31.7%), and 63 (10.3%) subjects completed 2, 3, and 4 years of treatment, respectively. A total of 128 subjects (13.6%) discontinued from the studies, citing AEs other than bleeding irregularity as their primary reason for discontinuation, 105 subjects (11.1%) discontinued

FIGURE 1

Disposition of subjects.



a: 16 subjects were excluded from the efficacy dataset because they were breastfeeding, and 3 additional subjects did not have any post-baseline assessments.

b: 4 randomized subjects were excluded from the AST population because they had no implant inserted.

c: Subjects completing more than 3 years of treatment were those included in extension studies.

Darney. ENG implant clinical experience. Fertil Steril 2008.

owing to a bleeding irregularity, 21 subjects (2.2%) were lost to follow-up, and 76 subjects (8.1%) discontinued for other reasons.

Duration of ENG Implant Use

The mean duration of exposure to the ENG implant in the entire group of 946 was 727.1 days. Most subjects were exposed for 1 to <3 years (58.9%), and 21.8% of subjects were exposed to the ENG implant for ≥3 years.

Efficacy

Cumulative Pearl Indexes for all subjects treated with the ENG implant as well as for those who were ≤35 years old at entry are presented in Table 2. No pregnancies were reported with the ENG implant in situ. There were six pregnancies with a conception date within 14 days after the ENG implant removal. The FDA requires that any pregnancies occurring within 14 days of cessation of a hormonal method of contraception be considered as possible method failures. Thus defined, the resulting cumulative Pearl Index for subjects ≤35 years old was 0.38.

Incidence of Adverse Events

All AEs experienced by subjects throughout the duration of the 11 clinical trials are presented here. These AEs include all events, related and not related to study drug, with the exception of bleeding irregularities, which are described separately. The most commonly occurring AEs were female reproductive disorders (378 of 942 subjects [40.1%]), with vaginitis (14.5%), breast pain (12.8%), leukorrhea (9.6%), and dysmenorrhea (7.2%) being the most frequent. The next highest incidence of AEs was observed in the group of events classified by the organ system affected: central and peripheral nervous system disorders (30.3%), body as a whole/general disorders (28.3%), respiratory system disorders (27.9%), skin and appendages disorders (25.7%), gastrointestinal system disorders (26.8%), psychiatric disorders (21.4%), and metabolic and nutritional disorders (16.0%). The incidence of AEs in all other system-organ classes was ≤10%.

A number of AEs were considered by the investigators to be possibly, probably, or definitely related to study drug and occurred in ≥5% of subjects. These drug-related AEs were headache (15.5%), weight increase (12.0%), acne (11.8%), breast pain (10.2%), emotional lability (5.8%), and abdominal pain (5.2%).

Incidence of Serious Adverse Events and Discontinuations Due to Adverse Events (Not Including Vaginal Bleeding)

A total of 56 of 942 (5.9%) subjects experienced a total of 77 serious AEs (SAEs). Most common were gastrointestinal (ten subjects, or 1.1% of those enrolled); seven subjects (0.7%) had neoplasms, and six subjects (0.6%) had liver and biliary system disorders. The vast majority of subjects recovered from their SAEs, with the exception of five whose variety of SAEs were either still present at the end of the study or had an unknown outcome. These included heart disorder, abdominal pain, and three subjects with breast neoplasms. None of the subjects experienced deep vein thrombosis or myocardial infarction.

A total of 330 of 942 subjects (35.0%) discontinued implant use prematurely for a variety of reasons. Of these,

TABLE 1

Demographic and other subject characteristics (all-subjects-treated group).

Characteristic	All studies (n = 942)
Age, yrs (mean ± SD)	27.7 ± 5.4
Age group	n %
18–20	86 9.1
21–25	278 29.5
26–30	291 30.9
31–35	195 20.7
36–40	92 9.8
> 40	0 0
Height, cm (mean ± SD)	161 ± 7.5
Weight, kg (mean ± SD)	59.7 ± 9.7
Body mass index (BMI) kg/m^2 (mean ± SD)	23 ± 3.2
BMI group	n %
≤20	158 16.8
>20–22	240 25.5
>22–24	242 25.7
>24–26	140 14.9
>26	162 17.2
Obstetric and contraceptive history	n %
No. of previous pregnancies	
0	184 19.5
1	221 23.5
2	274 29.1
3	135 14.3
>3	128 13.6
No. of deliveries	
0	284 30.1
1	261 27.7
2	260 27.6
3	101 10.7
>3	33 3.5
Last contraceptive method[a]	
None	96 10.2
Oral	229 24.3
Injectables	2 0.2
IUD	97 10.3
Foam, condoms, diaphragm, spermicide	368 39.1
Others[b]	57 6.1
Usual duration of bleeding (days)	
(Mean ± SD)	4.6 ± 1.3
(Median)	5
(Min–Max)	1–9

Note: IUD = intrauterine device.

[a] Subjects who recorded more than one contraceptive method are counted more than once.

[b] Includes implants.

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128 subjects (13.6%) discontinued due to AEs, 105 (11.1%) discontinued owing to bleeding irregularities, 76 (8.1%) withdrew for other reasons, and 21 (2.2%) were lost to follow-up (Fig. 1 and Table 3). Besides bleeding irregularities, AEs that caused greater than 1% of subjects to discontinue from the study included emotional lability (2.3%), weight increase (2.3%), headache (1.6%), acne (1.3%), and depression (1.0%). Regional differences were observed in the incidence of discontinuations due to AEs. Specific AEs that were reported as the reason for discontinuation more frequently in U.S. sites (n = 330) compared with non-U.S. sites (n = 612) included emotional lability (6.1% vs. 0.3%), depression (2.4% vs. 0.2%), nervousness (0.9% vs. 0.2%), weight increase (3.3% vs. 1.8%), abnormal sexual function (1.2% vs. 0%), and insertion site pain (0.9% vs. 0.0%).

Most discontinuations for a reason other than bleeding (85 of 128 [66%]) occurred during the first year of treatment (Fig. 2). Of a total of 105 subjects who discontinued as a result of bleeding irregularities, 67 subjects (63.8%) discontinued in the first year of treatment.

Implant Site Condition, Insertion and Removal Complications

A minority of subjects reported implant site abnormalities during any of their assessments. The most frequently occurring implant site complication was pain, occurring in 27 out of 942 subjects (2.9%) at any visit. At the last assessment, pain was reported by 5 out of 942 subjects (0.5%). In the entire clinical study program, a total of 9 out of 941 ENG implant–treated subjects (1.0%) had complications at implant insertion, and 15 out of 900 of ENG implant–treated subjects (1.7%) had complications at implant removal. Insertion complications included: implant retained in needle of the applicator, slight bleeding, hematoma formation, and difficult insertion. Removal complications included: breaking the implant, inability to palpate the implant before removal, removal difficulty due to deep insertion, implant fixed by fibrous tissue, implant too flexible for easy removal, implant adherent to underlying tissue, and difficulty locating the implant.

Bleeding Pattern Analyses

Because bleeding irregularities are common and expected in contraceptive users they are analyzed separately from other adverse events using the RP approach recommended by WHO.

There was a total of 4,431 evaluable RPs during RPs 2–8. The total group experienced an average 17.5 bleeding-spotting days per 90-day RP, fewer than half of which (7.5 days) were described as bleeding days. Bleeding pattern indexes also show that infrequent bleeding was common, comprising 33.3% of RPs overall. Amenorrhea ranked second, comprising 21.4% of RPs. Of all the bleeding episodes recorded, 16.9% of the RPs were characterized by prolonged bleeding. Frequent bleeding comprised 6.1% of RPs. No particular pattern characterized ENG implant use.

TABLE 2

Cumulative Pearl Indices for exposure to the etonogestrel implant including six pregnancies with estimated conception date ≤14 days after implant removal (efficacy dataset).

Parameter	Through year 1 (days 1–365)	Through year 2 (days 1–730)	Through year 3 (days 1–1095)
All subjects (n = 923)			
Cumulative number of pregnancies	2	4	6
Exposure, woman-years	833.5	1491.8	1755.8
28-day cycle equivalents	10866	19447	22888
Pearl Index	0.24	0.27	0.34
95% CI	0.03–0.87	0.07–0.69	0.13–0.74
Subjects ≤35 years old at entry (n = 833)			
Cumulative no. of pregnancies	2	4	6
Exposure, woman-years	753.0	1348.8	1584.0
28-day cycle equivalents	9816	17582	20648
Pearl Index	0.27	0.30	0.38
95% CI	0.03–0.96	0.08–0.76	0.14–0.82

Note: CI = confidence interval.

Darney. ENG implant clinical experience. Fertil Steril 2008.

The proportion of ENG implant–treated subjects who discontinued primarily owing to bleeding irregularities varied among the study site locations. The rate of discontinuation due to bleeding irregularities or amenorrhea in the U.S. and Europe was 14.4%, whereas in Southeast Asia, Chile, and Russia it was 3.7%. Amenorrhea rarely constituted a reason to discontinue ENG implant use, regardless of geographic region.

TABLE 3

Number (%) of subjects (≥1% by system-organ class in all studies) who discontinued due to adverse events (all-subjects-treated group).[a]

System-organ class and WHO preferred term	All studies (n = 942) n	(%)
Psychiatric disorders	36	3.8
Emotional lability	22	2.3
Depression	9	1.0
Metabolic and nutritional disorders	25	2.7
Weight increase	22	2.3
Skin and appendages disorders	20	2.1
Acne	12	1.3
Central and peripheral nervous system disorders	20	2.1
Headache	15	1.6
Reproductive disorders, female	14	1.5
Sexual function abnormal	4	0.4
Breast pain	3	0.3

Note: WHO = World Health Organization.

[a] Adverse events other than bleeding irregularities.

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Figure 3 shows bleeding parameters for RPs 1–8 (1–720 days) for all of the study participants. The greatest mean number of bleeding-spotting days was observed during RP 1 because the ENG implant was inserted during spontaneous menstruation. The number of bleeding-spotting days decreased between RPs 2 and 3 and remained stable thereafter. This decrease may have resulted from patients discontinuing as a result of a bleeding irregularity, leaving for analysis those less likely to experience bleeding. The number of bleeding-only days and bleeding-spotting episodes remained stable throughout the duration of the studies.

Bleeding Irregularities in Comparative Studies With the LNG Implant

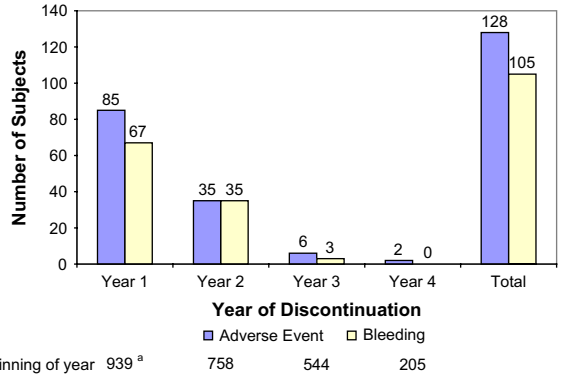
Table 4 presents comparative data for bleeding parameters and bleeding pattern indexes from randomized comparative trials of the ENG implant and the LNG implant. The mean number of bleeding-spotting days, bleeding-only days, and bleeding-spotting episodes per 90-day RP was significantly lower in ENG implant–treated subjects compared with LNG implant–treated subjects. On the other hand, with the exception of amenorrhea, mean bleeding pattern indexes were generally similar between the two groups. The incidence of amenorrhea was significantly higher in the ENG implant group compared with the LNG implant group ($P<.0001$).

DISCUSSION

The rate of unintended pregnancies in the U.S. far exceeds that in other developed nations. Of the 6 million pregnancies in the U.S. each year, about 3 million are unintended or

FIGURE 2

Number of subjects discontinuing, by year of discontinuation.



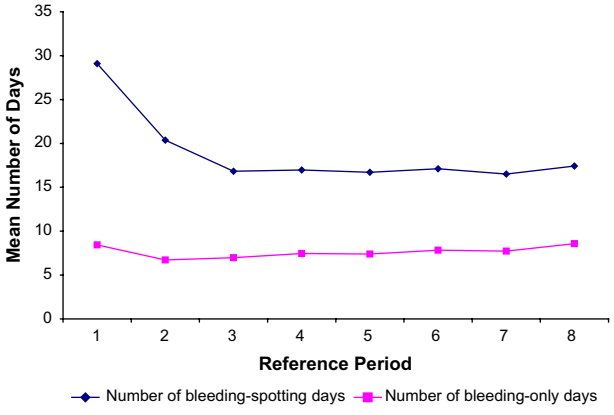
[a]All-Subjects-Treated Group safety dataset (N = 942) excluding 3 subjects without any post-baseline assessments.

Darney. ENG implant clinical experience. Fertil Steril 2008.

unplanned, of which over a million are terminated by elective abortion (5). About 60% of the unplanned pregnancies occur in women using some form of contraception during the month they conceived (6). The high rate of unintended pregnancies is not due to low efficacy of contraceptives, but to the challenges women and couples face in using methods correctly and consistently (5). The more common user-dependent contraceptive methods, such as condoms and combined oral contraceptives, are characterized by considerable differences between "perfect use" efficacy (ranging from <1% to about 6% for these methods) and "typical use" effectiveness (ranging from 4% to about 20%). This gap between perfect- and typical-use efficacy narrows substantially for methods that are not related to coitus and do not require daily administration (7). Longer-acting contraceptives are not distinguished from combined oral contraceptives by improved efficacy, safety, or acceptability, so much as by ease of use adaptable to the different cultural and lifestyle characteristics that make daily adherence difficult (8).

FIGURE 3

Bleeding parameters for the reference period analysis group.



Darney. ENG implant clinical experience. Fertil Steril 2008.

We have presented the results of 11 well controlled, GCP-compliant, clinical studies of the ENG implant. The results from the trials demonstrate that the ENG implant is a highly effective contraceptive for up to 3 years after implantation. No pregnancies were reported while the subjects had the ENG implants in place. A total of six pregnancies were reported in the entire study population during the first 14 days after implant removal. These pregnancies were included in the calculation of the overall pregnancy rate and Pearl Index. Among women ≤35 years of age at entry, this inclusion resulted in a cumulative Pearl Index of 0.38 pregnancies per 100 woman-years of use, which is similar to other long-acting contraceptive methods, including sterilization (9). Because the subjects ranged only from 80% to 130% of ideal body weight, these trials cannot predict efficacy in obese users of Implanon.

The occurrence of six pregnancies during the first 14 days after removal may be explained by the effect of the ENG released by the implant on endogenous FSH and E_2 production. Although the ENG implant inhibits ovulation, substantial ovarian activity is still present. With the ENG implant in place, serum FSH levels are similar to those seen in the normal follicular phase. In addition, serum E_2 levels decrease during the first 4 weeks after ENG implant insertion but begin to rise gradually 6 months after insertion. The presence of preovulatory follicles which secrete normal amounts of E_2 suggests normal FSH bioactivity with the ENG implant in place and that ovarian activity is present. Thus, ovulation is inhibited but synthesis of endogenous E_2 continues. As a consequence, when the ENG implant is removed, a return of ovulation and potential conception can occur within a matter of days to 1 week (data on file, Organon International, Roseland, NJ), explaining the six pregnancies within two weeks of removal.

More than 3.3 million ENG implants have been distributed since their introduction in more than 30 countries. From introduction in 1998 through March 2007, a total of 1,688 spontaneous pregnancies have been reported, resulting in an overall postmarketing Pearl Index of 0.024 (data on file, Organon International, Roseland, NJ). These postmarketing findings should be interpreted with caution, because they are obtained from spontaneous reports, not controlled studies. Examination of postmarketing data on the ENG implant has shown that most pregnancies can be attributed to the following three causes: 1) insertion of the ENG implant in women who were already pregnant or failure to insert the ENG implant during the recommended time during the cycle (so-called "luteal phase" pregnancies); 2) concomitant use of hepatic enzyme-inducing antiepileptic drugs; and 3) failure to insert the ENG implant at all (10, 11). Introduction in the U.S. includes a comprehensive mandatory training program to familiarize clinicians with the counseling, insertion, and removal procedures for the ENG implant.

TABLE 4

Parameters of bleeding pattern per 90-day reference period during the first 2 years of use (treatment duration ≥720 days).

	Comparative studies		
Parameter	**ENG implant (n = 59)**	**LNG implant (n = 55)**	***P* value**
Mean bleeding parameters			
Number of B-S days	14.2	18.2	.0202
Number of B days	6.3	10.1	.0002
Number of B-S episodes	1.9	2.9	.0001
Bleeding pattern indices (%)			
Amenorrhea	29.5	4.5	<.0001
Infrequent B-S	34.6	33.3	.5274
Frequent B-S	3.9	3.7	.5886
Prolonged B-S	11.3	7.5	.3517

Note: Reference periods 2–8. Mean over all reference periods. Values are number of subjects who had treatment duration ≥720 days and had bleeding-spotting parameters assessed in at least 1 reference period. B = bleeding; B-S = bleeding-spotting; ENG = etonogestrel; LNG = levonorgestrel.

Darney. ENG implant clinical experience. Fertil Steril 2008.

The ENG implant was generally well tolerated when administered as described in the product labeling. Common drug-related AEs associated with the use of the ENG implant, such as headache, weight increase, acne, breast pain, emotional lability, and abdominal pain, are side effects commonly found among users of progestin-only and combined estrogen-progestin contraceptives (4). Acceptability of these symptoms varies widely among women, so that the most frequently reported AEs may not be the same as the AEs most likely to lead to discontinuation. Headache and breast pain appear to be common and more acceptable side effects, but weight increase and emotional lability are less acceptable, making them two of the more common reasons for discontinuation.

The amount of vaginal bleeding associated with the use of the ENG implant was generally modest, but the pattern over the duration of treatment was unpredictable. Discontinuation rates owing to bleeding irregularities were approximately 14% in the U.S. and Europe, but only 4% in Southeast Asia, Chile, and Russia. These local differences in discontinuation cannot be explained by differences in bleeding characteristics, which were similar from place to place, suggesting that cultural and social factors may be involved.

When the ENG implant's bleeding pattern was compared with that of LNG implant–treated subjects in a small cohort of subjects in comparative trials, the number of bleeding days, bleeding and spotting days, or bleeding episodes was significantly lower in ENG implant–treated subjects and the incidence of amenorrhea was higher. The significance of these findings is limited because of the small numbers of subjects in the three comparative studies and because of the longer duration of action of LNG implant and its failure to suppress ovulation during later (>3) years of use, when bleeding becomes more regular (12). The present study findings should help clinicians to counsel patients on bleeding irregularities and other side effects associated with the ENG implant so that women can decide if they want to use this highly effective method (5, 13, 14).

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