

Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant

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STUDY QUESTION: Is it possible to extend the use of the 3-year one-rod etonogestrel (ENG)-releasing subdermal contraceptive implant to 5 years?

SUMMARY ANSWER: The extended use of the one-rod ENG-releasing subdermal contraceptive implant showed 100% efficacy in years 4 and 5.

WHAT IS KNOWN ALREADY: The initial regulated trials on the ENG-releasing subdermal contraceptive implant conducted in the 1990s were designed to measure cumulative 3-year efficacy. The ENG-implant has both well established safety and efficacy for up to 3 years. Pharmacokinetic data on ENG show high levels at 3 years and some previous clinical research confirms efficacy beyond the current approved duration of 3 years. Today, many women, because the labeled duration has been reached, have the ENG implant removed at 3 years, increasing costs, inconvenience and risks.

STUDY DESIGN SIZE, DURATION: For the first 3 years, this study was an open-label, multi-centre randomized trial comparing the 3-year ENG implant to the 5-year levonorgestrel (LNG)-releasing implant. After 3 years, a subset of 390 ENG participants, consented to extended use. We compared efficacy, side effects and removal procedures of both implants. We used Kaplan–Meier (K–M) analysis. We included an observational cohort of copper intrauterine device (IUD) users as non-users of hormonal contraceptive method for comparative purposes.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study took place in family planning clinics in seven countries worldwide. Women were enlisted after an eligibility check and informed consent, and 1328 women were enrolled: 390, 522 and 416 in the ENG-implant, LNG-implant and IUD groups, respectively.

MAIN RESULTS AND THE ROLE OF CHANCE: Over 200 women used the ENG implant for at least 5 years. No pregnancies occurred during the additional 2 years of follow up in the ENG or LNG implant group. The overall 5-year K–M cumulative pregnancy rates for ENG- and LNG- implants were 0.6 per 100 women-years (W–Y) [95% confidence interval (CI): 0.2–1.8] and 0.8 per 100 W–Y [95% CI: 0.2–2.3], respectively. Complaints of bleeding changes were similar; however, ENG-users were more likely than LNG-users to experience heavy bleeding ($p < 0.05$). The median duration of the implant removal procedure was 64 seconds shorter for the one-rod ENG-implant

†Members of the study group are listed in the Appendix.

(inter-quartile range (IQR) = 30.5, 117.5) compared to the two-rod LNG product (IQR = 77.0, 180.0). The 2-year rate for pregnancy in the IUD group compared with the two implant groups combined was 4.1 per 100 W-Y [95% CI: 2.5–6.5].

LIMITATIONS, REASONS FOR CAUTION: Few women were ≤ 19 years old or nulligravida. Although there was no weight limit for enrolment in the study, the number of women ≥ 70 kg were few.

WIDER IMPLICATIONS OF THE FINDINGS: The results from this study corroborate previous evidence showing high contraceptive efficacy through 4 years for the ENG-implant. Data through 5 years are a novel contribution and further proof of the product's capability to provide safe and effective contraception that rivals the current 5-year LNG-subdermal implant. The findings provide valuable information for policy makers, family planning programmers and clinicians that the ENG-releasing subdermal implant is still highly effective up to 5 years after insertion. Compared to previous efforts, our study population was geographically diverse and our study had the highest number of participants completing at least 5 years of use.

TRIAL REGISTRATION: The trial was registered as ISRCTN33378571.

STUDY FUNDING/COMPETING INTEREST(S): The contraceptive devices and funds for conduct of the study were provided by the United Nations Development Programme/United Nations Population Fund/World Health Organization (WHO)/UNICEF/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), WHO. This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the WHO. All stated authors have no conflict of interest, except Dr Hubacher who reported grants from United States Agency for International Development, during the conduct of the study; other from Advisory Boards (Teva, Bayer, OCON), outside the submitted work.

Key words: subdermal contraceptive implants / etonogestrel / levonorgestrel / extended use / intrauterine device

Introduction

The etonogestrel (ENG)-releasing subdermal contraceptive implant was developed in the 1980s and the first regulatory trials were conducted in the 1990s. Scientists involved in the early development of the product suspected that high contraceptive efficacy would extend beyond 3 years; however, the industry-sponsored trials were not designed to go past 3 years. Thus, the product was approved worldwide with a 3-year indication.

The existing data suggested that an ENG concentration >90 pg/ml is necessary to effectively prevent ovulation (Diaz et al., 1991). In normal-weight women (i.e. BMI = 18.5–24.9 kg/m²), the average ENG concentrations at 2 and 3 years post-insertion are 194 and 156 pg/ml, respectively. The ENG subdermal contraceptive implant is a device consisting of 68 mg of ENG as the active ingredient with an average release rate of 60–70 μ g/day in weeks 5–6, decreasing to ~35–45 μ g/day by the end of the first year, 30–40 μ g/day by year 2, and then to 25–30 μ g/day at the end of the third year (Implanon, 2016). The bioavailability remains constant and close to 100%, and the elimination half-life of the parent compound is around 25 h (Huber and Wenzl, 1998). Pharmacokinetic (PK) analysis showed at the end of the life-span of the ENG implant (i.e. 3 years) the serum levels are above the threshold for effective contraception (Wenzl et al., 1998; Zheng et al., 1999).

Although the ENG-implant is approved for use up to 3 years, some reports demonstrate effectiveness beyond that. Two studies did not report any pregnancies through the fourth year of use (Kiriwat et al., 1998; McNicholas et al., 2015). The extended use of the ENG-implant could reduce the frequency of removal/insertion procedures, and consequently improve implant cost-effectiveness, while improving convenience for women.

Subdermal implants have grown in popularity in resource-poor countries over the past decade, particularly in sub-Saharan Africa. In 2005, international donor agencies purchased approximately 84 000 subdermal implants for the region; since then, the annual number of units increased steadily and peaked in 2015 when 7.4 million were purchased (Reproductive Health Supplies Coalition, 2015). Approximately 50% of implants were ENG-products; thus, extended use of the ENG-implant would have tremendous global impact.

This article reports results for extended use up to 5 years after insertion of the ENG-implant and compares the results to the 5-year levonorgestrel (LNG)-releasing implant, with a focus on contraceptive performance, side effects and reasons for method discontinuation. Also, we compare the performance with a non-randomized group of women who received a TCu380A intrauterine device (IUD) as users of a non-hormonal contraceptive method.

Materials and methods

The original 3-year design of this study was a randomized open parallel group trial of the 1-rod ENG (Implanon[®], Merck & Co., Inc., Whitehouse Station, NJ, USA) and the 2-rod LNG subdermal contraceptive implants (Jadelle[®], Bayer Healthcare, Berlin, Germany) with a 1:1 allocation ratio, and a non-randomized control group of women using the TCu380A IUD (Pregna[®], Pregna International, Mumbai, India) (Bahamondes et al., 2015). The trial was registered as ISRCTN33378571. The study was approved by the Scientific and Ethical Review Group at Development and Research Training in Human Reproduction (HRP/the World Health Organization (WHO), WHO Secretariat Committee on Research Involving Human Subjects, and by the Ethical Committees of all participating centres.

The study took place in family planning clinics (centres) in: Campinas, Brazil; Santiago, Chile; Santo Domingo, Dominican Republic; Szeged, Hungary; Bangkok, Thailand; Ankara, Turkey; Harare, Zimbabwe. The

inclusion criteria were: non-pregnant clinically healthy women seeking long-acting reversible contraceptive methods; aged >18 and <45 years; with regular menstrual cycles; ≥ 6 weeks post-partum; able to keep a menstrual diary; willing to return to the clinic for follow-up visits. Exclusion criteria for implant and IUD acceptors were those published by WHO in Medical Eligibility Criteria for Contraceptive Use 2nd Edition (2000). The methods of the study been reported in detail elsewhere (Bahamondes *et al.*, 2015).

Potential participants were informed about the study, including the randomization of implants; that the implants and IUDs and the insertions and removals would be without cost for the women; and that if randomized to ENG-implant there would a free choice of a replacement implant at no cost after removal of the original ENG-implant at 3 years. Eligible women willing to participate signed a written informed consent form before entering the study. Follow-up visits were scheduled for 2 weeks and 3 months after insertion and every 6 months thereafter.

Based on review of data on PK and efficacy of the ENG-implant beyond 3 years (Huber and Wenzl, 1998; Kiriwat *et al.*, 1998), about midway through the study it was decided to extend the follow-up from 3 to 5 years, including use of the ENG-implant to 5 years. The study extension was approved by the WHO Ethics committee and at each centre by local or national Ethics Committees, or both. All centres except the centre in Hungary, agreed to take part in the extended follow-up.

At the 36-month visit or earlier, all study participants were invited to participate in the study extension for an additional 2 years. Women with the ENG-subdermal implant were informed that the use of the implant after 3 years was experimental; written informed consent was obtained from those accepting extended use. Women with the LNG-subdermal implant or IUD also provided informed consent for extended participation. Women not accepting extended use of ENG-implant were offered, free of charge, a second implant or other contraceptive method of their own choice. All participants in the extended follow-up continued with follow-up visits every 6 months.

At each follow-up visit women were asked about vaginal bleeding patterns, lower abdominal pain, and general questions about their health condition. Also, they were specifically asked if they had any complaints of headache, dizziness and acne. Any suspicion of pregnancy led to urine pregnancy testing.

Reasons for removal of the implant/IUD were categorized as either medical (pregnancy, expulsion, bleeding problems and other medical reasons) or personal (wish for pregnancy, moving to out of reach location and other personal reasons).

The main outcome of the extended study was to obtain the 4- and 5-year annual and cumulative rates of effectiveness, continuation rate and side effects for both contraceptive implant systems. We also measured duration of subdermal implant removal, defined as the time between incision with the scalpel and bandage/compress placement after the procedure.

Data management and statistical analysis

Data were managed in HRP/WHO, Geneva, Switzerland through August 2006 and from September 2010 onwards. From September 2006 through August 2010 the *Centro Rosarino de Estudios Perinatales* (CREP), Rosario, Argentina managed the data. Participating centres sent originals of the completed case report forms to HRP/WHO and CREP at regular intervals. Regular on-site monitoring of the participating centres according to Good Clinical Practice Guidelines started in 2006 and was performed by personnel from Family Health International, Research Triangle Park, NC, USA and the HRP/WHO project manager. The data were analyzed in HRP/WHO in a per protocol manner using SAS/STAT version 9.2 (SAS, 2011). The survival plots were generated using R software, Version 2.14.2

(R Core Team, 2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

In the previous report, we estimated 3-year cumulative contraceptive efficacy rates using all participants' data because everyone initially consented to a 3-year follow-up period. In this new analysis for 5-year contraceptive efficacy, we used data from the subset that, first, consented to extended observation in years 4 and 5 or second, experienced product failure (pregnancy with the product *in situ*) in the first 3 years. To construct fair-comparison cohorts and to minimize potential bias, we specifically excluded data from participants who were censored with the products *in situ* or who had the products removed prior to 3 years for reasons other than method failure; this decision slightly over-estimates the method failure rates since the accumulated person-months of observation for excluded data are not represented in the denominator of the calculations. This is the most conservative approach (worst case scenario) for estimating cumulative pregnancy rates, given the unusual circumstances involving the re-consent process for extended duration.

Comparisons between groups were made using the Pearson χ^2 test (two-sided) for categorical outcome variables. Risk ratios (RR) with 95% confidence interval (CI) were computed for binary repeated outcomes using the generalized estimating equation (GEE) log-binomial model. The Kaplan–Meier (K–M) method was used to estimate the overall method continuation rates, and the cumulative risk of discontinuation, by reason. Time from insertion was computed in months. Depending on the outcome variable, the data are presented as mean \pm SD, survival rates, cumulative hazard rate (HR), RR with 95% CI. Significance was established at $P < 0.05$.

Results

LNG- and ENG-users were similar on all socio-demographic characteristics. IUD users were older and had more children than subdermal implant users (Table I). Obesity (defined as a BMI; $\text{kg}/\text{m}^2 \geq 30$) was similar in the two subdermal implant groups (about 6.5%).

A total of 1538 women had the device *in situ* by 36.5 month post-insertion of which 1328 were eligible and consented for extended follow-up: 390 ENG- users, 522 LNG-users, and 416 IUD-users (Fig. 1). The K–M loss to follow-up rate (95% CI), at 24 months, among those who started the post 3-year follow-up was 1.9 (0.2, 4.1), 0.8 (0.3, 2.2) and 1.1 (0.4, 2.9) for ENG-, LNG- and IUD-users respectively. Only 1–2% of participants were lost to follow-up in the extended 2-year period. A total of 204 ENG-subdermal implant users reached the 5-year mark with the product *in situ*.

In the extended period while the products were *in situ*, no subdermal implant users became pregnant among 7060 and 10 883 woman months of observation for the ENG and LNG subdermal implant group, respectively (Table II). After 5 years, the cumulative pregnancy rates among ENG- and LNG-users were statistically equivalent: [0.6 (95% CI = 0.2–1.8)] and [0.8 (95% CI = 0.2–2.3)], respectively.

Because the approved duration of ENG- implant is 2 years shorter than the LNG-implant, higher proportions of women on the ENG-implant sought device removal compared to LNG-users in the extended period (Table II). From the time of insertion, ENG-users accumulated over 22 000 months of use. Personal reasons were the most frequent reason for discontinuation in both groups of implant users in the fourth and fifth years of use (Table III).

In the extended period, ENG- and LNG-users had similar rates of side effects (Table IV). The only significant difference was the report of subjectively heavy menstrual bleeding (HMB): ENG-users had

Table 1 Background characteristics of extended observation cohorts at the time of contraceptive implant insertion.

	LNG implant n (%) 522	ENG implant n (%) 390	Copper IUD n (%) 416
Age, years			
Mean (SD)	28.6 (6.4)	27.8 (6.1)	29.5 (6.7)
[Min, Max]	[18.0, 44.0]	[18.0, 43.0]	[18.0, 44.0]
Median (IQR)	28.0 (23.0, 33.0)	27.0 (23.0, 32.0)	29.0 (24.0, 35.0)
Age, category*			
< 20	29 (5.6)	28 (7.2)	17 (4.1)
21–35	402 (77.0)	308 (79.0)	313 (75.2)
>35	91 (17.4)	54 (13.6)	86 (20.7)
Highest education*			
Never attended	6 (1.1)	2 (0.5)	4 (1.0)
Primary	115 (22.0)	71 (18.2)	110 (26.4)
Secondary	302 (57.9)	241 (61.8)	202 (48.6)
Technical/Vocational	37 (7.1)	35 (9.0)	27 (6.5)
University	62 (11.9)	41 (10.5)	73 (17.5)
Marital status			
Married or cohabiting	462 (88.9)	333 (85.4)	373 (89.7)
Regular partner, not cohabiting	33 (6.4)	38 (9.7)	33 (7.9)
Currently no regular partner	25 (4.8)	19 (4.9)	10 (2.4)
Total number of pregnancies*			
Nulligravida	22 (4.2)	16 (4.1)	4 (1.0)
1–2	330 (63.2)	255 (65.4)	265 (63.7)
≥3	170 (32.6)	119 (30.5)	147 (35.3)
Previous use of hormonal contraceptive methods (%)*	392 (75.1)	307 (78.7)	288 (69.2)
Previous use of subdermal implants (%)*	104 (20.6)	77 (20.4)	34 (8.4)
BMI (kg/m ²)			
Mean (SD)	23.9 (3.9)	23.7 (3.8)	25.8 (4.8)
Median (IQR)	23.6 (21.1, 26.0)	23.2 (20.7, 25.8)	25.2 (22.3, 28.2)
BMI category*			
Underweight: < 18.5	37 (7.1)	26 (6.7)	7 (1.7)
Normal weight: 18.5–24.9	300 (57.5)	235 (60.3)	192 (46.2)
Overweight: 25.0–29.9	151 (28.9)	104 (26.7)	141 (33.9)
Obese: ≥30.00	34 (6.5)	25 (6.4)	76 (18.3)

*Pearson χ^2 test. $P < 0.05$ for 3-cohort comparisons.

Note: Levonorgestrel (LNG) implant and etonogestrel (ENG) implant users statistically equivalent on all measures. IUD, intrauterine device; IQR, inter-quartile range.

significantly higher rates (95% CI = 1.01, 1.73) yet the absolute level was still low (only 12%).

Implant removal information for the full 5 years of the study was available for 332 and 444 ENG- and LNG-users, respectively (Table V). The median time required for the removal procedure was 1 min for the ENG- and 2 min for the LNG-implant. For about 2 and 9% of ENG- and LNG-implants, respectively, removals were deemed slightly difficult or difficult.

Discussion

This study examined contraceptive efficacy of the ENG-subdermal implant beyond its approved duration of 3 years and up to 5 years. Of

the 390 participants who wanted to continue use of the product, none became pregnant in the fourth and fifth years under observation. Although attrition reduced the amount of efficacy data, over 200 women used the product for at least 5 years.

Others are also examining extended use of the ENG-implant. In the US-based contraceptive CHOICE study, investigators have data on 123 women completing 4 years of use and 34 users completing 5 years of use; zero pregnancies have occurred after 229 W-Y of extended use (McNicholas et al., 2015). Median levels of ENG in serum were 188 and 177 pg/ml at 3 and 3 years, respectively. The investigators are expecting to enroll a total of 550 ENG-implant users and currently have 287 (personal communication, Dr. Colleen McNicholas, November 12, 2015). A study of 47 Thai women (Kiriwat et al., 1998)

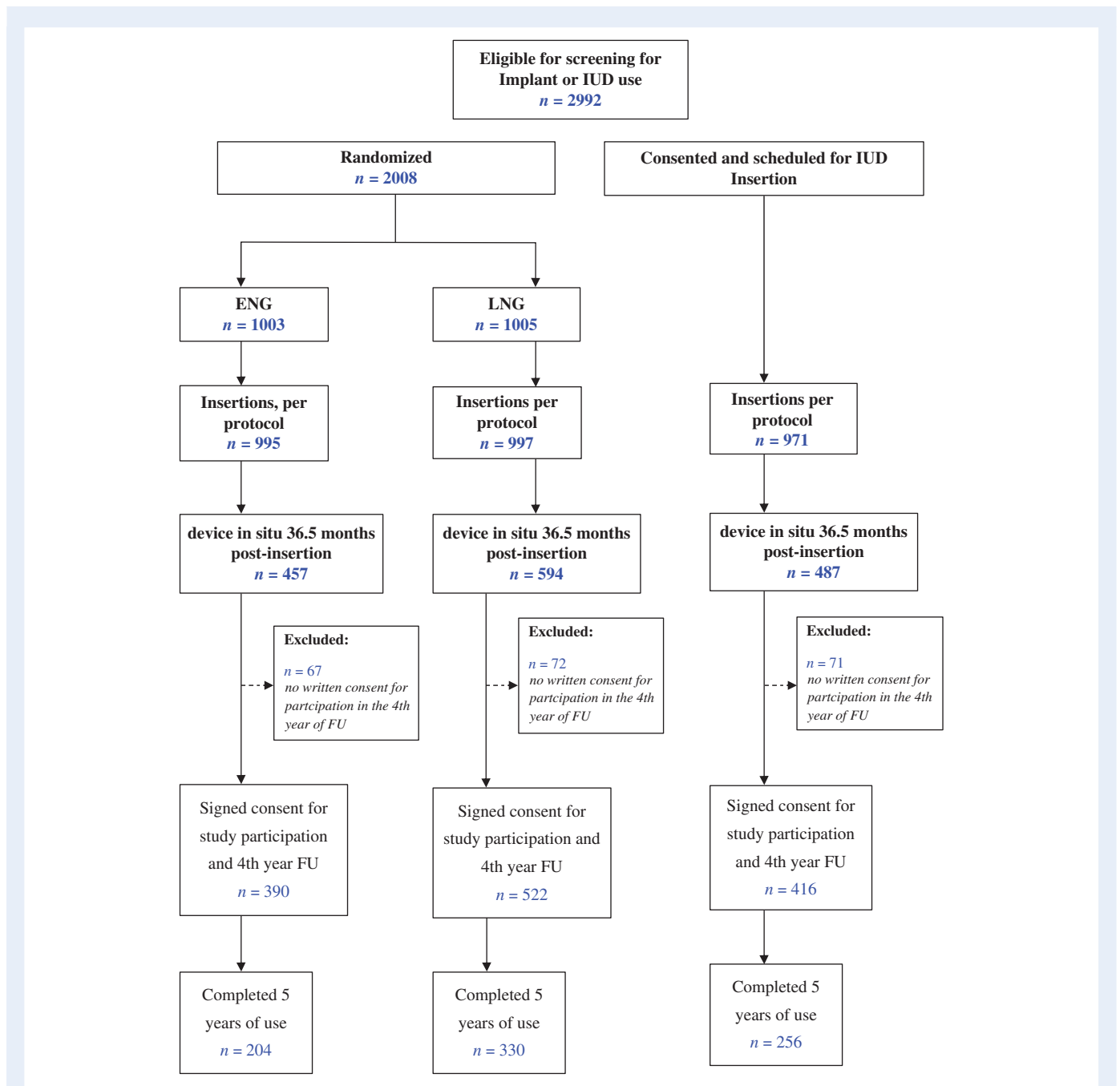


Figure 1 Flowchart of the women screened for eligibility to continue and admitted for use of an implant or IUD beyond 3 years and reason for non-inclusion in analysis. ENG, etonogestrel; LNG, levonorgestrel; IUD, intrauterine device; FU, follow up.

and a study of 151 Chinese women (Zheng *et al.*, 1999) completing 4 years of use did not record any ENG-implant failures. Both the trials in Thailand and China were open, non-comparative and had a smaller sample of participants who completed the trial, however they demonstrated excellent contraceptive efficacy for 4 years of use and ENG was well tolerated.

Progestogen-only injectables, including depot medroxyprogesterone acetate (DMPA; 150 mg administered IM every 3 months), are used worldwide. In 2008, a global expert working group at the WHO reviewed the evidence, and noted that injection of DMPA can be given

up to 4 weeks late without requiring additional contraceptive protection (WHO, 2000). With backing from the WHO, many ministries of health worldwide are saving resources by accepting a 4-month injection window.

Changing the product label to reflect a lengthier duration of use is a worthy goal. However, it is unclear whether the licensed owner of the ENG product supports this type of effort. A regulatory body such as the US Food and Drug Administration requires data on at least 200 subjects using a product for the intended duration; thus on this factor alone, our multi-centre trial satisfies that requirement.

Table II Extended use data and number of events by year and cohort.

	LNG implant	ENG implant	Copper IUD
Number of pregnancies in the first three years *	3	3	14
Extended year 4 data			
Number of women starting	522	390	416
Number of women completing	470	311	373
Woman-months of observation	6254	4606	4995
Number of pregnancies	0	0	1**
Extended year 5 data			
Number of women starting	470	311	373
Number of women completing	330	204	256
Woman-months of observation	4629	2454	3521
Number of pregnancies	0	0	2
Year 1–5 cumulative data			
Total woman-months of observation	30 325	22 044	24 134
Total number of pregnancies for 5 years of observation	3	3	17
Cumulative pregnancy rates** (Kaplan Meier Rates)	0.8 (0.2–2.3)	0.6 (0.2–1.8)	4.1 (2.5–6.5)

*Number of pregnancies reported previously in Bahamondes et al. (2015) in the first 3 years.

**One additional pregnancy that occurred around 36 months was reported above. The Kaplan–Meier (K–M) method was used to estimate the overall cumulative pregnancy rates.

Table III Year 4 and 5 cumulative numbers and rates per 100 women (with 95% confidence interval (CI)) of reason for stopping implant-use.

Variable	Year 4		Year 5	
	LNG implant	ENG implant	LNG implant	ENG implant
No. of women starting interval	522	390	470	311
Pregnancy (all)	0;0.0	0;0.0	0;0.0	0;0.0
Medical reason, all	1.2 (0.5, 2.6)	1.4 (0.6, 3.3)	2.7 (1.6, 4.6)	3.4 (1.9, 6.1)
Bleeding problems	0.8 (0.3, 2.1)	1.4 (0.6, 3.3)	2.3 (1.3, 4.1)	3.4 (1.9, 6.1)
Other medical	0.4 (0.1, 1.6)	0.0	0.4 (0.1, 1.6)	0.0
Personal reasons, all	8.0 (5.9, 10.7)	17.1 (13.7, 21.3)	14.2 (11.4, 17.6)	25.8 (21.7, 30.5)
Planning pregnancy	3.8 (2.4, 5.8)	5.6 (3.7, 8.4)	5.7 (4.0, 8.2)	8.4 (5.9, 11.9)
Other personal reason	3.4 (2.1, 5.3)	8.6 (6.1, 11.9)	6.1 (4.3, 8.6)	12.3 (9.2, 16.2)
No longer willing to continue	0.8 (0.3, 2.2)	2.5 (1.3, 4.7)	2.3 (1.3, 4.1)	5.4 (3.4, 8.5)

Data analysed using Pearson χ^2 test.

In sub-Saharan Africa alone, approximately 3 million women will receive the ENG-implant in 2016 (Reproductive Health Supplies Coalition, 2015). Conservatively, if 30–40% of ENG-implant initiators have the product removed at the 3-year point only because of the labelled duration (Weisberg et al., 2014; Bahamondes et al., 2015), then approximately 900 000 to 1 200 000 users in sub-Saharan Africa may seek removal in 2019 for the labelling limitation. Extending use of the ENG-implant will save resources, including the time of health personnel, and for the users save additional cost and will require fewer removal and insertion procedures.

In the fourth and fifth year of use, side effects from the two implants were similar; the only exception was HMB which was significantly

more common with the ENG-subdermal implant compared to the LNG-subdermal implant, which was equivalent in first 3 years (Bahamondes et al., 2015).

As stated in our previous publication (Bahamondes et al., 2015), the strengths of our study were that, to the best of our knowledge, it is the first head-to-head study comparing the one-rod ENG and the two-rod LNG subdermal implants up to 5 years, conducted across regions of the world with diverse ethnicities and cultural backgrounds and included a comparison group of IUD users. However, one limitation was that although there was no weight limit for enrolment in the study, few obese women (BMI > 30 kg/m²; n = LNG: 34, ENG: 25) were assessed during years 4–5 of ENG-subdermal implant use.

Table IV Numbers and generalized estimating equation estimates of occurrence of symptoms, signs and conditions during extended use of ENG and LNG implants, and ratio of estimate with 95% CI.

Symptom	LNG implant N = 510		ENG implant N = 387		Risk ratio (95% CI)
	Number with symptom	Risk estimate per 100	Number with symptom	Risk estimate per 100	
Headache	280	32.3	198	31.8	0.98 (0.84, 1.14)
Dizziness	182	16.9	130	16.4	0.97 (0.78, 1.20)
Acne	128	11.5	89	10.0	0.87 (0.66, 1.14)
Lower abdominal pain	205	20.3	134	17.9	0.88 (0.72, 1.08)
Amenorrhea	92	7.3	65	7.8	1.07 (0.76, 1.51)
Irregular bleeding	393	47.0	280	46.2	0.98 (0.88, 1.09)
Heavy bleeding	118	9.0	103	12.0	1.32* (1.01, 1.73)
Prolonged bleeding	208	18.0	165	19.5	1.08 (0.90, 1.31)

*Risk ratios (RR) with 95% confidence interval (CI). $P < 0.05$.

Table V Difficulties and time taken for implant removal.

	LNG implant (N = 444)	ENG implant (N = 332)
Duration of removal procedure (seconds)		
Mean (s.d.)	149.2 (114.2)	78.0 (59.7)
Median (quartiles)	124.0 (77.0, 180.0)	60.0 (30.5, 117.5)*
Minimum/maximum (removal time in seconds)	19/1215	6/417
Ease of removal (% distribution (n))		
Easy	90.8 (404)	97.9 (335)*
Slightly difficult	7.2 (32)	1.8 (6)
Difficult	2.0 (9)	0.3 (1)

*Pearson χ^2 test. $P < 0.01$.

In conclusion, this study showed that the ENG- and LNG-subdermal implants have the same contraceptive effectiveness beyond 3 years up to 5 years with no major differences in occurrence of side effects.

Extended duration of the ENG-subdermal implant would have many policy and programmatic benefits. First, it is safer for users; less frequent removal and fewer insertion cycles reduce trauma to the skin and reduce the chances of surgical errors. Furthermore it also saves time and resources for the health system and opens new hours of consultation at services habitually full of women seeking attention. Second, extended use saves resources. For example, if international donor agencies pay US\$ 9 per unit, if the product has two additional years, then the cost per couple-year of protection drops from US\$ 3 to US\$ 1.80. Third, voluntary continued use of a long-acting contraceptive method reduces the chances of unintended pregnancy when users transition to other products.

To the best of our knowledge this is the first study to report on ENG-subdermal implant use up to 5 years. Without securing a change in the product label, the logical next step is that WHO evaluate the available evidence on ENG-subdermal implant safety and efficacy as for DMPA, and make similar recommendations for extended use.

Authors' roles

M.A., N.H. and S.L. were officers at the HRP/WHO. A.A., L.B. and V.B. were PI at Turkey, Brazil and Dominican Republic, respectively. DH is Senior Epidemiologist at FHI360. All authors conceptualized the study. MA wrote the first draft of the article. NH and SL contributed to quantitative data analysis, A.A., L.B., V.B. and D.H. critically reviewed the article. All authors contributed to further drafts. All authors read and approved the final article.

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Conflict of interest

All stated authors have no conflict of interest, except Dr Hubacher who reported grants from United States Agency for International Development, during the conduct of the study; other from Advisory Boards (Teva, Bayer, OCON), outside the submitted work.

Appendix

WHO study group on contraceptive implants for women

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References

- Bahamondes L, Brache V, Meirik O, Ali M, Habib N, Landoulsi S; WHO Study Group on Contraceptive Implants for Women. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. *Hum Reprod* 2015;**30**:2527–2538.
- Diaz S, Pavez M, Moo-Young AJ, Bardin CW, Croxatto HB. Clinical trial with 3-keto-desogestrel subdermal implants. *Contraception* 1991;**44**:393–408.
- Huber J, Wenzl R. Pharmacokinetics of Implanon. An integrated analysis. *Contraception* 1998;**58**:855–905.
- Implanon Prescribing Information. <http://www.implanon-usa.com/en/consumer/main/prescribing-information.xhtml>https://www.merck.com/product/usa/pi_circulars/i/implanon/implanon_pi.pdf (6 May 2016, date last accessed).
- Kiriwat O, Patanayindee A, Koetsawang S, Korver T, Bennink HJ. A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. *Eur J Contracept Reprod Health Care* 1998;**3**:85–91.
- McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration. *Obstet Gynecol* 2015;**125**:599–604.
- Reproductive Health Supplies Coalition RHInterchange Website. http://rhi.rhsupplies.org/rhi/index.do?locale=en_US (6 May 2016, date last accessed).
- Wenzl R, van Beek A, Schnabel P, Huber J. Pharmacokinetics of etonogestrel released from the contraceptive implant Implanon. *Contraception* 1998;**58**:283–288.
- Weisberg E, Bateson D, McGeechan K, Mohapatra L. A three-year comparative study of continuation rates, bleeding patterns and satisfaction in Australian women using a subdermal contraceptive implant or progestogen releasing-intrauterine system. *Eur J Contracept Reprod Health Care* 2014;**19**:5–14.
- World Health Organization. Medical eligibility criteria for contraceptive use. In: *Reproductive Health and Research*, 2nd edn. Geneva: World Health Organization, 2000.
- Zheng SR, Zheng HM, Qian SZ, Sang GW, Kaper RF. A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. *Eur J Contracept Reprod Health Care* 1999;**4**:85–93.