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ORIGINAL ARTICLE *Fertility control*

A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls

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STUDY QUESTION: Is there any difference in the clinical performance of the 3-year one-rod etonogestrel (ENG)- and the 5-year two-rod levonorgestrel (LNG)-releasing contraceptive implants during 3 years of insertion, and between implant and intrauterine device (IUD) contraception, in particular complaints possibly related to hormonal contraceptives?

SUMMARY ANSWER: The cumulative contraceptive effectiveness after 3 years and method continuation through 2.5 years were not significantly different between ENG and LNG implants, but both outcomes were significantly worse in the non-randomized age-matched group of IUD users than in the combined implant group.

WHAT IS KNOWN ALREADY: ENG- and LNG-releasing implants are safe and highly efficacious contraceptives with pregnancy rates reported to be 0.0–0.5 per 100 women-years (W-Y). No head-to-head comparative study of the two implants has been undertaken, and little information is available on comparisons of complaints of side effects of implant and copper IUD users.

STUDY DESIGN, SIZE, DURATION: This was an open parallel group RCT with 1:1 allocation ratio of the ENG and the LNG implants with non-randomized control group of women choosing TCu380A IUD to address lack of reliable data on common side effects typically attributed to the use of progestogen-only contraceptives. After device(s) placement, follow-ups were at 2 weeks, 3 and 6 months, and semi-annually thereafter for 3 years or until pregnancy, removal or expulsion of the implant/IUD occurred.

PARTICIPANTS, SETTING, METHODS: The study took place in family planning clinics in Brazil, Chile, Dominican Republic, Hungary, Thailand, Turkey and Zimbabwe. Women seeking long-term contraception were enlisted after an eligibility check and informed consent, and 2982 women were enrolled: 1003, 1005 and 974 in the ENG-implant, LNG-implant and IUD groups, respectively; 995, 997 and 971, respectively, were included in the *per protocol* analysis reported here.

MAIN RESULTS AND THE ROLE OF CHANCE: ENG and LNG implants each had the same 3-year cumulative pregnancy rate of 0.4 per 100 W-Y [95% confidence interval (CI) 0.1–1.4]. A weight of ≥70 kg at admission was unrelated to pregnancy. Method continuation rates for ENG and LNG implants at 2.5 years were 69.8 (95% CI 66.8–72.6) and 71.8 per 100 W-Y (68.8–74.5), and at 3 years 12.1 (95% CI 5.2–22.0) and

[†] The list of WHO study group participants is given in the Appendix.

52.0 per 100 W-Y (95% CI 41.8–61.2), respectively. Bleeding disturbances, the most frequent reason for method discontinuation, were significantly more common in the ENG group [16.7 (95% CI 14.4–19.3)] than in the LNG group [12.5 (95% CI 10.5–14.9)] (P 0.019). The 3-year cumulative loss to follow-up was lower in the ENG- than in the LNG-implant group, 8.1 (95% CI 6.4–10.2) and 14.4 per 100 W-Y (95% CI 12.1–17.1), respectively. The median duration of implant removal was 50 s shorter among women with ENG than among women with LNG implant ($P < 0.0001$). In the observational comparison between IUD and implant users, the 3-year relative risk for pregnancy in IUD group compared with the combined implant group was 5.7 per 100 W-Y (95% CI 4.4–7.3) ($P = 0.0003$). The 3-year expulsion rate of the IUD was 17.8 per 100 W-Y (95% CI 14.5–21.9), while the discontinuation rate for bleeding disturbances was 8.5 (95% CI 6.7–10.9). Frequency of complaints of headache and dizziness was not significantly different between implant and IUD users ($P = 0.16$ and 0.77, respectively), acne and bleeding irregularities were more frequent among implant users ($P < 0.0001$), while heavy bleeding and lower abdominal pain occurred more often among IUD than implant users ($P < 0.0001$).

LIMITATIONS, REASONS FOR CAUTION: Few women were ≤19 years old or nulligravida, the proportion of implant users ≥70 kg was <20% and <8% were obese.

WIDER IMPLICATIONS OF THE FINDINGS: Findings of the study can inform policy makers and clinicians about choice of implant, but also about TCu380A IUD in relation to implants.

STUDY FUNDING/COMPETING INTEREST(S): UNDP/UNFPA/WHO/UNICEF/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization (WHO). This report contains the views of an international expert group and does not necessarily represent the decisions or the stated policy of the WHO.

TRIAL REGISTRATION: ISRCTN33378571 registered on 22 March 2004. The first participant was enrolled on 12 May 2003.

Key words: contraception / implants / implanon / Jadelle / etonogestrel / levonorgestrel / TCu380A IUD / randomized clinical trial

Introduction

Contraceptive implants together with the levonorgestrel (LNG)- and copper-bearing intrauterine devices (IUDs) are long-acting reversible contraceptives (LARC) that give high contraceptive effectiveness without requiring attention, coitus related or otherwise, by the users (Grimes, 2009). A recent study (Winner *et al.*, 2012) showed that these methods were more effective in preventing unintended pregnancies than contraceptive pills, patch and rings, with cumulative pregnancy rates up to 3 years of 0.9 per 100 women-years (W-Y); in comparison, contraceptive pills, patch and ring had pregnancy rates >20 times that of the LARC methods. The high effectiveness of LARC was equal at different women's ages, whereas younger women using pills, patch or ring had significant more frequent contraceptive failures than older women (Winner *et al.*, 2012).

The contraceptive implants available include the one-rod 3-year etonogestrel (ENG) implant (Implanon®), the two-rod 5-year LNG (Jadelle®) implant and another 4-year two-rod LNG-releasing implant manufactured in China (Sino-implant II). For the implants, annual pregnancy rates are reported being between 0.0 and 0.5 per 100 W-Y (Glasier, 2002; Bahamondes *et al.*, 2014).

The two-rod LNG- and the ENG-releasing implants first received drug regulatory approvals in 1996 and 1998, respectively; however, no comparative trial evaluating the two implants has been done (Meirik *et al.*, 2003). Consequently, the UNDP/UNFPA/WHO/UNICEF/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP/WHO) initiated a multicentre RCT of the two implants with a non-randomized control group of users of the TCu380A IUD. The latter group was added to obtain comparative data on incidence of non-serious side effects typically attributed to the use of progestogen-only contraceptives (Brache *et al.*, 2002). Results regarding the methodology of the trial and data on insertion of implants and IUDs, and 6 weeks post-insertion follow-up have been published (Meirik *et al.*, 2013). This article reports results for 3-year follow-up and focusses on contraceptive efficacy, reasons for method discontinuation and continuation rates, side effects of the three methods and data from implant removals.

Materials and Methods

This was an open label parallel RCT with 1:1 allocation ratio of the ENG-releasing implant (Implanon®, Merck & Co., Inc., Whitehouse Station, NJ, USA) and the LNG-releasing implant (Jadelle®, Bayer Healthcare, Berlin, Germany), and a non-randomized age-matched group of women choosing TCu380A IUD (Pregna®, Pregna International, Mumbai, India). The study was approved by the Scientific and Ethical Review Group at HRP/WHO, WHO Secretariat Committee on Research Involving Human Subjects and by the Ethics Committee of all participating centres. The methods of the study have been reported elsewhere (Meirik *et al.*, 2013). Briefly, the study took place in family planning clinics in Campinas, Brazil; Santiago, Chile; Santo Domingo, Dominican Republic; Szeged, Hungary; Bangkok, Thailand; Ankara (three sub-centres), Turkey; and Harare, Zimbabwe. Women seeking LARC methods 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 be 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 an informed consent form before entering the study. Follow-up was for 3 years or until accidental pregnancy, removal or expulsion of the implant/IUD, whatever occurred first. About midway through the study, it was decided to extend the follow-up including the use of the ENG implant to 5 years. Results of the extended follow-up will be reported separately.

Randomization

The randomization sequence for implant users was computer generated at HRP/WHO with variable block size of six or eight and stratified by centre.

For potential implant users, the centres received a list of centre-specific unique subject numbers and a set of opaque sealed envelopes also with subject numbers. At admission, women received a subject number, and immediately before implant insertion, the envelope with the subject number was opened and a slip informed about implant allocation. Women in the IUD group were matched by age (in 5-year bands) to every second woman allocated to an implant.

Participating women

The inclusion criteria were as follows: non-pregnant clinically healthy women aged ≥18 and <45 years, with regular menstrual cycles, ≥6 weeks postpartum, able to keep a menstrual diary and 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 Ed. (WHO, 2000). Implant and IUD insertions were performed within the first 5 days of menstrual cycle by trained healthcare professionals (HCPs): physicians, nurses or midwives. Follow-up visits were scheduled 2 weeks and 3 months after insertion and every 6 months thereafter.

Outcomes

The study focusses on contraceptive efficacy, discontinuation of use and safety of the methods. Diagnosis of pregnancy was based on clinical signs and symptoms, urine pregnancy tests and ultrasound examinations. Reasons for removal of the implant/IUD were medical (expulsion, bleeding problems and other medical reasons) and personal (wish for pregnancy, moving out of reach and other personal reasons). At each follow-up visit, women were specifically asked if they had any complaints of headache, dizziness, acne, their own perception of vaginal bleeding patterns and lower abdominal pain, followed by questions about their health condition in general. Pelvic inflammatory disease (PID) was defined as having complaints of lower abdominal pain; receiving a diagnosis according to ICD 10 codes N70, N71, N73, N74.3 or N74.4; and systemic treatment with antibiotics; whenever judged necessary, information about potential PID and other conditions was obtained from other health facilities the woman had consulted. Duration of implant removal was the time (minutes, seconds) it took from when the scalpel touched the skin until a compress was placed on the site of the removal.

Sample size

A sample of 2000 women randomized to the ENG or LNG implants (1000 in each arm), with 1000 women in the TCu380A IUD group, was aimed at based on the following assumptions: 40% of implant or IUD users would discontinue the use of the method, losses to follow-up would be 5% and discontinuations and losses would be evenly distributed over the 3 years. With 80% of power and 5% significance level in two-sided tests, the chosen sample would allow detection of a 1.6 per 100 W-Y difference in the cumulative 3-year pregnancy rate, assuming a cumulative rate of 0.5 per 100 W-Y; a 7% difference in the 3-year cumulative discontinuation rate, assuming that the rate of stopping implant use altogether would be 40%; and a 6–8% difference in the 3-year cumulative rate of perceived side effects, assuming that the rate would be between 25 and 35%.

Data management and statistical analysis

Data were managed in HRP/WHO, Geneva, Switzerland through August 2006 and from September 2010 and onwards. From September 2006 through August 2010, the *Centro Rosarino de Estudios Perinatales* (CREP), Rosario, Argentina, managed the data. Participating centres sent originals of 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 done by personnel from Family Health International, Research Triangle Park, NC, USA and HRP/WHO project manager. The data were analysed in HRP/WHO in *per protocol* manner using SAS/STAT version 9.2 (SAS, 2011). The survival plots were generated using R software, Version 2.14.2 (R Development Core Team, 2012).

Only women without any protocol violations as detected by the time of analysis were included in the data analysis. Comparisons between the groups were made using the Pearson χ^2 test (two sided) for categorical outcome variables. Risk ratios (RRs) with 95% confidence interval (CI) were computed for binary repeated outcomes using the generalized estimating equation (GEE) log-binomial model. 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. For the present report, we used the K–M estimates for women who discontinued the method up to 38 months after insertion. All women who came in the window 34–38 months and who did not remove the implant/device were censored at this visit.

The log-rank test, stratified for centre, was used to assess differences at the end of first, second and third years. Depending on the outcome variable, the data are presented as mean ± standard deviation (SD), survival rates, cumulative hazard rate (HR) and relative risk (RR) with 95% CI. Significance was established at $P < 0.05$. To do a comparison of continuation rates of the groups that was independent of the scheduled 3-year removal of ENG implants, sensitivity analyses estimated the continuation rates at 2.5 years (30 months) of use and at 34 months. In another sensitivity analyses, the analytical approach of intention to treat (ITT) was applied, where all participants were analysed according to the group of device allocation.

Results

Enrolments occurred from 12 May 2004 to 31 January 2008. A total of 2008 women accepted to be randomized to use of ENG or LNG implant, and 974 women chose TCu380A IUD and agreed participation in the study (Fig. 1). Altogether, 995, 997 and 971 women starting use of the ENG implant, LNG implant and IUD, respectively, are included in the current *per protocol* analysis.

Details about the number of women enrolled in each centre as well as the main demographic and reproductive characteristics in the three groups were published previously (Meirik *et al.*, 2013). In brief, the mean (±SD) age of the participants was 27.7 ± 6.2, 28.1 ± 6.4 and 28.7 ± 6.6 years, for the ENG-implant, LNG-implant and IUD groups, respectively. Women ≤35 years old represented 84.5% of the entire sample. Mean (±SD) weight at admission was 60.5 ± 10.9, 60.8 ± 10.8 and 64.6 ± 12.9 kg, for the ENG-implant, LNG-implant and IUD groups, respectively. Less than 20% of both groups of implant users weighed >70 kg, whereas 30.3% of women choosing the IUD weighed >70 kg at admission. More than 80% of the women were married or cohabiting, and only less than 5% were nulligravidas. Among those with at least one pregnancy, >95% reported that the last pregnancy ended in a live birth. More than 95% reported ever previous contraceptive use, and near 70% had used hormonal contraceptives. Almost 15% of the implant users had previously used implants, while one-third of IUD users had used copper IUDs before. The main characteristics of the three groups were similar with the only exception being that the number of nulligravidas was slightly lower in the IUD group.

ENG versus LNG implant

The 3-year cumulative pregnancy rate was 0.4 per 100 W-Y (95% CI 0.1–1.4) for each group of ENG- and LNG-implant users (Table I and

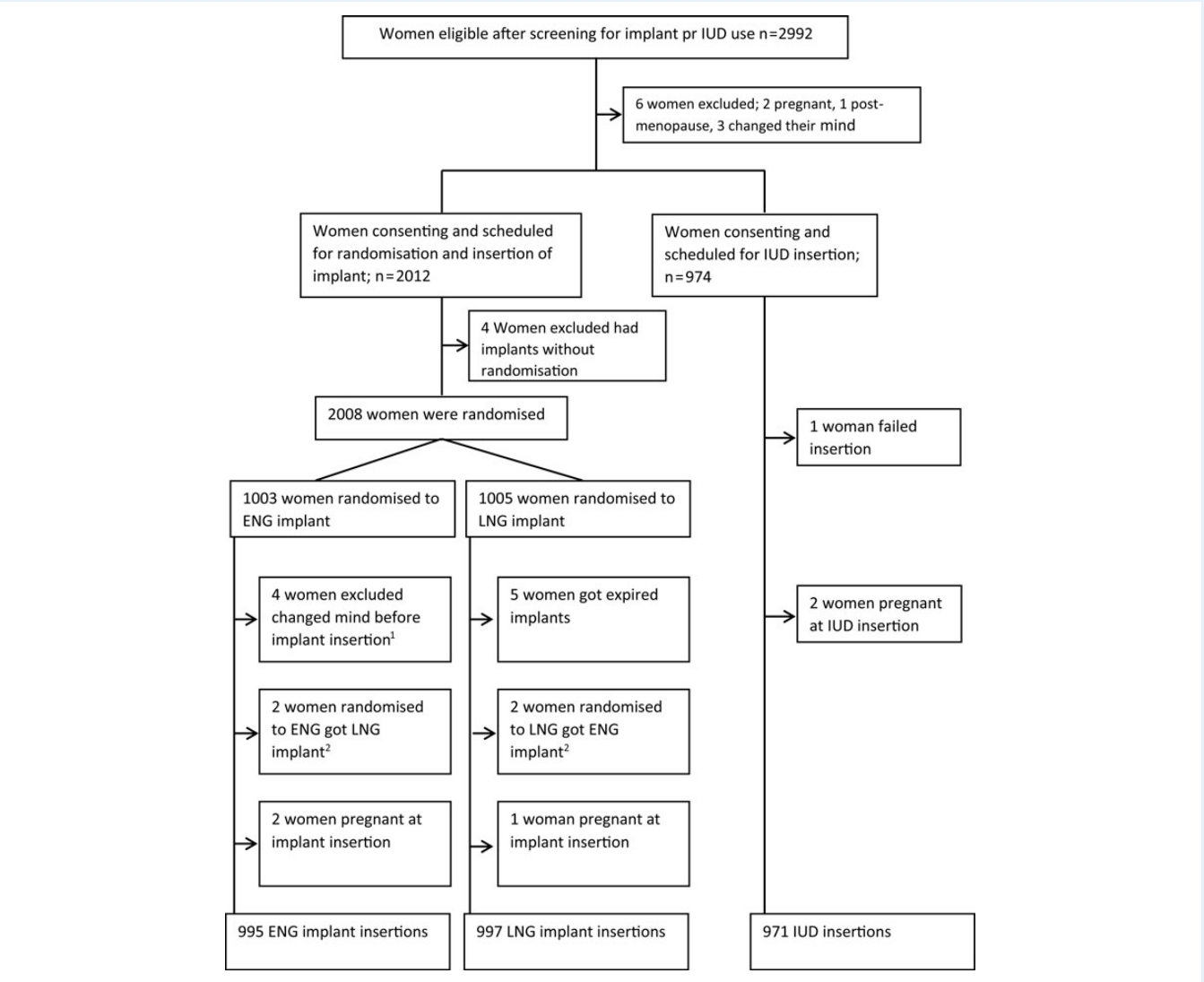

Figure 1 Flowchart of women screened for eligibility and admitted for use of implant or IUD, women randomized to type of contraceptive implant and reasons for non-inclusion in analysis. [1]Four women changed their mind about implant use after randomization and before implant insertion. [2]By mistake, the type of implants was swapped. ENG, etonogestrel; LNG, levonorgestrel; IUD, intrauterine device.

Fig. 2). Among 196 LNG users weighing ≥70 kg at admission, one pregnancy occurred (0.8 per 100 W-Y) (95% CI 1–5.3) and none among 184 ENG users. At the time of the conception of the three pregnancies in LNG-implant users, all three women weighed ≥70 kg, whereas the three conceptions among the ENG-implant users occurred at weight <70 kg. One of the three pregnancies in LNG-implant users was ectopic and none among ENG-implant users.

Bleeding disturbances were the most frequent reason for discontinuation of use in both groups of implant users, reaching 3-year cumulative rates of 16.7 per 100 W-Y (95% CI 14.4–19.3) and 12.5 per 100 W-Y (95% CI 10.5–14.9) for ENG and LNG implants, respectively (Table I) ($P = 0.019$). One expulsion occurred about 6 months after insertion in the LNG-implant group. At 1 and 2 years, there were no differences in continuation rates for the two implants (Table I and Fig. 3). In the sensitivity 1 and 2 analysis at 2.5 years (30 months), rates were also similar, 69.8 per 100 W-Y (95% CI 66.8–72.6) and 71.8 per 100 W-Y (95% CI 68.8–74.5) for ENG and LNG implants, respectively, and at 34 months (Fig. 3). As expected, the method continuation rate by the end of 3 years (38 months) was higher in the LNG-implant group [52.0 per 100 W-Y (95% CI 41.8–61.2)] compared with ENG group [12.1 per 100 W-Y (95% CI 5.2–22.0)]. For the calculation of the continuation rates in this 3-year study (see Materials and Methods section), women attending the 3 years (34–38 months) follow-up visit and consenting to be further followed up were censored by the date of their clinic visit. Six hundred and sixteen women in the ENG-implant group, 595 in the LNG-implant group and 450 in the IUD group attended the 3-year (34–38 months) follow-up visit; of these women, 235 ENG-implant users, 57 LNG-implant users and 41 IUD users discontinued use of their implant/IUD. Among the 235 of ENG-implant users having the implant removed during the 3-year visit, 101 (42%) accepted the offer to have a new implant inserted. After

Table I **Cumulative numbers and rates per 100 with 95% confidence limits (CL) of reason for stopping implant use in first through third years after initiation of use, and overall method discontinuation and losses to follow-up by the type of implant.**

Variable	First year		Second year		Third year[1]	
	ENG implant	LNG implant	ENG implant	LNG implant	ENG implant	LNG implant
No. of women starting interval	995	997	857	843	717	721
Pregnancy, all	1; 0.1 (0.0–0.8)	0; 0.0	1; 0.1 (0.0–0.8)	0; 0.0	3; 0.4 (0.1–1.4)	3; 0.4 (0.1–1.4)
Medical reason for stopping implant use						
Medical reason, all	68; 7.1 (5.6–8.9)	64; 6.7 (5.3–8.5)	140; 15.2 (13.0–17.6)	110; 12.0 (10.0–14.3)	172; 19.1 (16.7–21.8)	138; 15.5 (13.3–18.1)
Bleeding problems, all	57; 6.0 (4.6–7.7)	48; 5.1 (3.9–6.7)	122; 13.4 (11.3–15.8)	87; 9.7 (7.9–11.8)	148; 16.7 (14.4–19.3)	109; 12.5 (10.5–14.9)
Other medical	11; 1.2 (0.6–2.1)	15; 1.6 (1.0–2.6)	18; 2.0 (1.3–3.2)	22; 2.4 (1.6–3.7)	24; 2.9 (1.9–4.3)	28; 3.3 (2.3–4.8)
Personal reasons for stopping implant use						
Personal reasons, all	44; 4.6 (3.5–6.2)	54; 5.8 (4.4–7.5)	98; 10.9 (9.1–13.2)	110; 12.2 (10.3–14.6)	137; 16.0 (13.7–18.6)	142; 16.4 (14.0–19.0)
Planning pregnancy	8; 0.9 (0.4–1.7)	11; 1.2 (0.7–2.2)	29; 3.5 (2.4–5.0)	29; 3.5 (2.4–5.0)	52; 6.7 (5.2–8.8)	42; 5.4 (4.0–7.2)
Other personal reason	35; 3.7 (2.7–5.1)	43; 4.6 (3.4–6.1)	67; 7.5 (5.9–9.4)	76; 8.5 (6.8–10.5)	82; 9.5 (7.7–11.7)	94; 10.9 (9.0–13.2)
Moved out of reach	1; 0.1 (0.0,0.7)	0; 0.0	2; 0.2 (0.1,1.0)	5; 0.6 (0.3,1.4)	3; 0.4 (0.1,1.2)	6; 0.7 (0.3,0.7)
Continuation rates and losses to follow-up						
Overall continuation rate	88.5 (86.3–90.3)	87.9 (85.7–89.8)	75.4 (72.6–78.0)	77.2 (74.4–79.7)	12.1 (5.2–22.0)	52.0 (41.8, 61.2)
Lost to follow-up	24; 2.5 (1.7–3.8)	35; 3.6 (2.6–5.0)	38; 4.3 (3.1–5.8)	53; 5.8 (4.5–7.6)	65; 8.1 (6.4–10.2)	115; 14.4 (12.1–17.1)
Released from follow-up	0; 0.0	0; 0.0	0; 0.0	0; 0.0	0; 0.0	0; 0.0

ENG, etonogestrel; LNG, levonorgestrel.
[1]Third year corresponds to the time period of 25th through 38th months, see text.

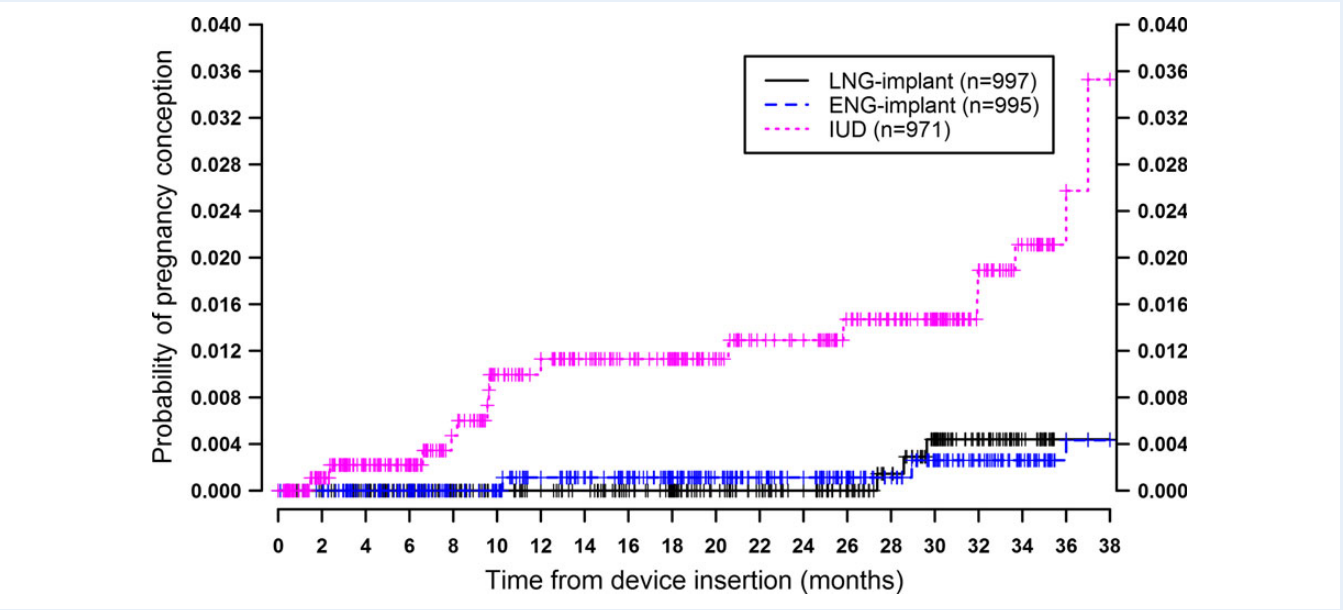

Figure 2 Survival curves with pregnancy occurrence from device insertion up to 3 years of follow-up.

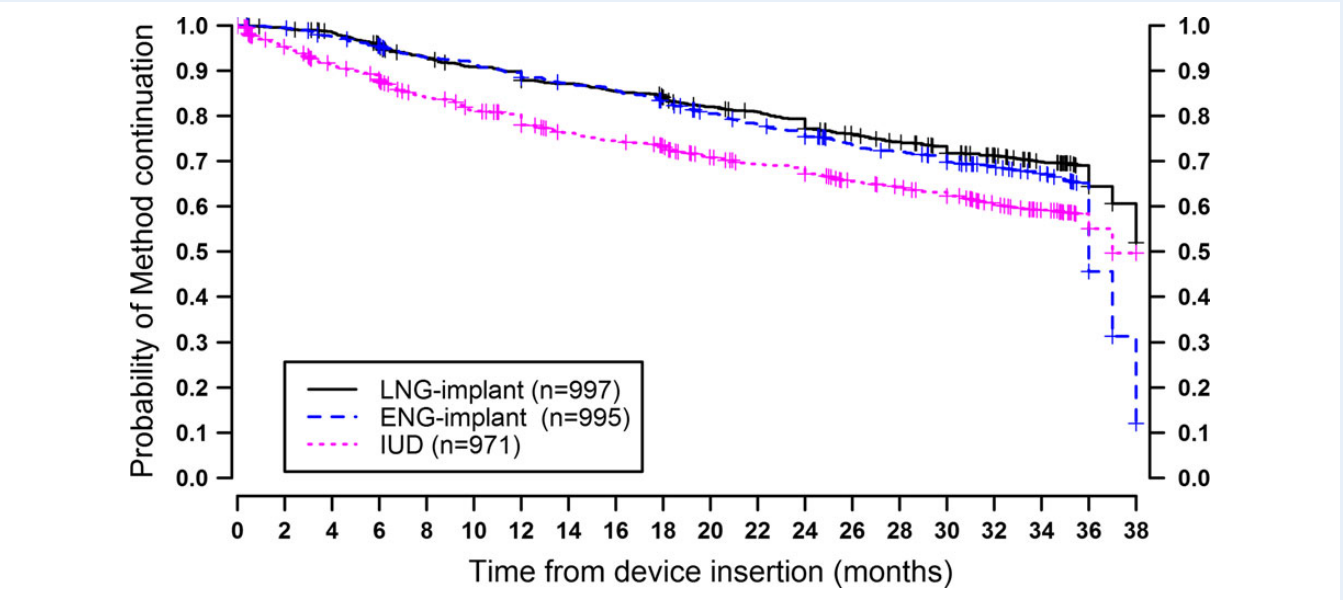

Figure 3 Continuation rates from device insertion up to 3 years of follow-up.

having been informed about off-label continued use of the ENG implant, 381 women consented either in writing (365 women) or verbally (16 women) to continue the use of it and be followed up further.

Losses to follow-up were similar albeit somewhat lower in the ENG- than in the LNG-implant group; by the end of 3 years, it was 8.1 per 100 W-Y (95% CI 6.4–10.2) and 14.4 per 100 W-Y (95% CI 12.1–17.1), respectively (Table I).

The frequency of symptoms and signs reported in the course of the study by ENG- or LNG-implant users is shown in Table II together with diagnoses of PID. Apart from more reports from ENG-implant users about amenorrhoea, there were no significant differences recorded between the two implant groups. The median time for removal of the implant was shorter in the ENG group than in the LNG-implant group ($P < 0.0001$) (Table III) and was reported as easy by HCPs in a greater proportion among ENG users when compared with the LNG group ($P < 0.0001$). In seven LNG- and in two ENG-implant removals, breakage of one of the rods occurred during removal ($P < 0.031$), although removal was complete. One woman needed a sedation to remove the implant

Table II Numbers and GEE estimates of occurrence of symptoms, signs and conditions during use of ENG and LNG implants, and ratio of estimate with 95% CL.

Symptoms, signs, conditions	ENG implant		LNG implant		RR[2] (95% CI)	*P*-value
	No. with ≥1 complaint[1]	Risk estimate, per 100[2]	No. with ≥1 complaint[1]	Risk estimate per 100[2]		
Headache	593	31.3	574	31.9	1.0 (0.89–1.08)	0.72
Dizziness	443	17.9	432	18.9	0.9 (0.83–1.07)	0.37
Acne	450	17.3	423	18.7	0.9 (0.81–1.05)	0.22
Lower abdominal pain	501	20.2	452	22.1	0.9 (0.81–1.03)	0.14
Amenorrhoea	387	18.7	464	15.2	1.2 (1.08–1.41)	0.001
Irregular bleeding	856	48.7	858	48.3	1.0 (0.95–1.07)	0.76
Heavy bleeding	352	13.0	393	11.6	1.1 (0.97–1.29)	0.11
Prolonged bleeding	559	22.6	568	22.0	1.0 (0.93–1.14)	0.58
PID	12	0.2	12	0.2	1.1 (0.47–2.48)	0.85

[1]The number of women in whom the symptom, sign or condition was reported on at least at one of the follow-up visits.
[2]Binomial GEE model with log and identity links, model with study group only.
ENG: etonogestrel; LNG: levonorgestrel.

Table III Numbers and GEE estimates of occurrence of symptoms, signs and conditions during use of contraceptive implants (ENG and LNG) and TCu380A IUD, and ratios of GEE estimate with 95% CIs of implant versus IUD.

Symptoms, signs, conditions	ENG and LNG implants		TCu380A IUD		RR[2] (95% CI)	*P*-value
	No. with ≥1 complaint[1]	Risk estimate, per 100[2]	No. with ≥1 complaint[1]	Risk estimate, per 100[2]		
Headache	1167	31.6	517	33.6	0.9 (0.88–1.02)	0.16
Dizziness	875	18.4	388	18.7	1.0 (0.88–1.10)	0.77
Acne	873	18.0	313	13.1	1.4 (1.20–1.56)	<0.000
Lower abdominal pain	953	21.2	594	35.8	0.6 (0.54–0.65)	<0.000
Amenorrhoea	851	16.9	84	2.7	6.3 (5.00–8.33)	<0.000
Irregular bleeding	1714	48.5	378	13.66	3.6 (3.23–4.00)	<0.000
Heavy bleeding	745	12.3	484	23.9	0.5 (0.47–0.58)	<0.000
Prolonged bleeding	1127	22.3	417	19.0	1.2 (1.05–1.30)	0.002
PID	24	0.2	26	0.7	0.3 (0.18–0.58)	0.000

[1]The number of women in whom the symptom, sign or condition was reported on at least at one of the follow-up visits.
[2]Binomial GEE model with log and identity links, model with study group only.
ENG: etonogestrel; LNG: levonorgestrel.

due to difficulty in removal. Women's perception of moderate to severe pain at implant removal was low and similar (<3%) among the two groups of users.

Implants versus IUD

The 3-year cumulative pregnancy rate for the TCu380A IUD users of 2.8 per 100 W-Y (95% CI 1.3–6.0) was significantly higher than the combined rate of 0.4 per 100 W-Y (95% CI 0.2–1.0) for users of ENG and LNG implants [relative risk 5.7 (95% CI 4.4–7.3)] ($P = 0.0003$) (Table IV). Ectopic pregnancies occurred in 2 of the 14 pregnancies in the IUD group. While the risk of a diagnosis of PID was similar between ENG- and LNG-implant users, among women using IUD the 3-year cumulative incidence of an episode of at least one diagnosis of PID was 0.69 per 100 W-Y compared with 0.22 per 100 W-Y in implant users ($P < 0.0001$). Among the IUD users, the 3-year cumulative discontinuation rate for bleeding disturbances was significantly lower than among implant users, 8.5 per 100 W-Y (95% CI 6.7–10.9) and 14.6 per 100 W-Y (95% CI 13.1–16.4), respectively ($P < 0.0001$). Cumulative expulsion rates of the copper IUD for the first, second and third years of use were 9.4 per 100 W-Y (95% CI 7.7–11.6), 13.1 per 100 W-Y (95% CI 11.0–15.6) and 17.8 per 100 W-Y (95% CI 14.5–21.9), respectively. Other medical reasons for removal of the IUD or implant were more frequent in the IUD users than in the implant users (Table IV). The 3-year continuation rate in the IUD group was 49.7 per 100 W-Y (95% CI 45.3–54.0) and higher than that of the combined implant group. However, by 2.5 years, the continuation rate for the combined implant group was significantly higher than that of the IUD group, 70.8 per 100 W-Y (95% CI 68.7–72.8) and 62.3 per 100 W-Y (95% CI 59.1–65.4), respectively ($P < 0.0001$). The results of the ITT sensitivity

Table IV **Cumulative numbers and rates per 100 with 95% CL of reason for stopping implant or IUD use in first through third years after initiation of use, and overall method discontinuation and losses to follow-up by implant and IUD.**

Variable	First year		Second year		Third year[1]	
	Implants	TCu380A IUD	Implants	TCu380A IUD	Implants	TCu380A IUD
No. of women starting interval	1992	971	1700	698	1438	571
Pregnancy	1; 0.1 (0.0–0.4)	9; 1.1 (0.6–2.2)	1 ;0.1 (0.0–0.4)	10; 1.3 (0.7–2.4)	6; 0.4 (0.2–1.0)	14; 2.8 (1.3–6.0)
Medical reasons for stopping implant use						
Medical reasons, all	132; 6.9 (5.8–8.1)	140; 15.2 (13.0–17.7)	250; 13.6 (12.1–15.2)	191; 21.6 (19.0–24.5)	310; 17.3 (15.6–19.2)	228; 28.8 (25.2–32.8)
Device expulsion	1; 0.1 (0.0–0.8)	85; 9.4 (7.7–11.6)	1; 0.1 (0.0–0.8)	112; 13.1 (11.0–15.6)	1; 0.1 (0.0–0.8)	128; 17.8 (14.5–21.9)
Bleeding problems, all	105; 5.5 (4.6–6.7)	33; 3.8 (2.7–5.3)	209; 11.5 (10.2–13.1)	49; 6.1 (4.7–8.1)	257; 14.6 (13.1–16.4)	62; 8.5 (6.7–10.9)
Other medical	26; 1.4 (0.9–2.0)	22; 2.6 (1.7–3.9)	40; 2.2 (1.6–3.0)	30; 3.8 (2.6–5.4)	52; 3.1 (2.4–4.0)	38; 5.2 (3.8–7.1)
Personal reasons for stopping method use						
Personal reasons, all	98; 5.2 (4.3–6.3)	57; 6.9 (5.3–8.8)	208; 11.6 (10.2–13.2)	100; 13.0 (10.8–15.6)	279; 16.2 (14.5–18.0)	129; 17.7 (15.1–20.8)
Planning pregnancy	19; 1.0 (0.7–1.6)	20; 2.5 (1.6–3.9)	58; 3.5 (2.7–4.5)	41; 5.7 (4.2–7.7)	94; 6.1 (5.0–7.4)	53; 7.8 (6.0–10.2)
Other Personal	78; 4.1 (3.3–5.1)	36; 4.3 (3.1–5.9)	143; 8.0 (6.8–9.4)	57; 7.5 (5.8–9.6)	176; 10.2 (8.9–11.8)	74; 10.5 (8.4–13.0)
Moved out of reach	1; 0.1 (0.0–0.4)	1; 0.1 (0.0–0.8)	7; 0.4 (0.2–0.9)	2; 0.3 (0.1–0.8)	9; 0.6 (0.3–1.1)	2; 0.3 (0.1–0.8)
Continuation and losses to follow-up						
Continuation rate	88.2 (86.7–89.5)	78.0 (75.3–80.6)	76.3 (74.3–78.1)	67.2 (64.1–70.2)	30.3 (23.1–37.9)	49.7 (45.3–54.0)
Lost to follow-up	59; 3.1 (2.4, 4.0)	61; 7.0 (5.5–8.9)	91; 5.1 (4.1, 6.2)	88; 10.9 (8.9–13.3)	180; 11.3 (9.8, 13.0)	142; 19.9 (17.1–23.1)
Released from follow-up	0; 0.0	1; 0.1 (0.0–1.0)	0; 0.0	2; 0.3 (0.1–1.2)	0; 0.0	3; 0.5 (0.1–1.2)

[1]Third year corresponds to the time period of 25th through 38th months, see text.
IUD: intrauterine device.

Table V Difficulties and complications at implant removal and pain as perceived by women at, by type of implant.

Observations at removal	ENG implant[2] No. of removals 546	LNG implant[3] No. of removals 340	*P*-value
Duration of removals (seconds)			
Median	68	120	<0.00001
Interquartile range	39–120	69–195	
Range	4–903	4–1200	
Mean (SD)	94 (98)	161 (156)	
Missing values	27	29	
Reported ease of removal			
Easy, *n* (%)	492 (94%)	254 (81%)	<0.0001
Slightly difficult, *n* (%)	22 (4%)	47 (15%)	
Difficult, *n* (%)	8 (2%)	12 (4%)	
Missing values	24	27	
Complication at removal[1]			
No	520 (99.6%)	306 (97.8%)	0.031
Yes	2 (0.4%)	7 (2.2%)	
Missing values			
Women's perception of pain at removal			
None	444 (86%)	252 (81%)	0.068
Mild	65 (13%)	49 (16%)	
Moderate	8 (2%)	6 (2%)	
Severe	0	3 (1%)	
Missing values	29	30	

ENG, etonogestrel; LNG, levonorgestrel.
[1]Of 334 ENG-implant and 292 LNG-implant removals by end of third year, 24 and 24, respectively, had missing values.
[2]Complications at ENG-implant removals: implant broken (2).
[3]Complications at LNG-implant removals: implant broken (7) and sedation (1).

analysis gave results that were almost identical to that of the *per protocol* analysis, albeit that in the ITT analysis, the pregnancy rates in the ENG- and LNG-implant groups were 0.5 W-Y (95% CI 0.2–1.4) and 0.6 W-Y (95% CI 0.3–1.5), respectively.

Among complaints and symptoms reported by women in response to a question about health problems in general, lower abdominal pain and 'heavy bleeding' were more frequently reported among IUD users than among implant users (Table V), while implant users more often reported acne, amenorrhoea, irregular bleeding and prolonged bleeding. Headache and dizziness were the most frequently reported complaints, not being significantly different between the IUD and implant groups. The risk of PID among implant users was about a third of that of IUD users, and the RR was 0.3 per 100 W-Y (95% CI 0.2–0.6). The method continuation rate by group is shown in Fig. 3.

Regarding severe adverse events, there were 12 women who died: 7 from complications due to HIV infection, 1 each due to lung, cervical and breast cancers, 1 due to viral meningitis and 1 from road accident. Detailed information on reported serious adverse events is available in Supplementary data, Annex I.

Discussion

Main findings in this 3-year study of contraceptive implants and copper IUDs are that the one-rod ENG and two-rod LNG implants both had very high and undistinguishable contraceptive efficacy. The continuation rates for the two implants were similar up to 2.5 years (30 months). Also, up to 2.5 years, the continuation rate for the two implants combined was higher than that of the TCu380A IUD. Bleeding disturbances were the most frequent reason for stopping the use of both implants and the TCu380A IUD, which is in line with previous reports on contraceptive implants and IUDs (Zheng *et al.*, 1999; Power *et al.*, 2007; O'Brien *et al.*, 2008). ENG-implant users quoted bleeding disturbances as reason for removing the implant significantly more often compared with LNG-implant users; however, this difference did not lead to any difference of the overall 2.5-year continuation rate of the two implants. The result of the ITT sensitivity analysis showed marginally higher pregnancy rates for the two implants than what was the results of the *per protocol* analysis. The reason for the difference is that women who were found to be pregnant at implant insertion were included as method failures in the ITT analysis.

As expected, the removal of the one-rod ENG implant took less time and was perceived as easier by medical staff than the removal of the two-rod LNG implant, although neither the differences of duration of removal nor ease of it appears being of much clinical significance. The reported perception of pain and lack thereof at implant removal was virtually identical, and about 80% of the women in both implant groups reported no pain at removal.

The pattern of complaints and symptoms as reported by implant users compared with IUD users was in many aspects anticipated; IUD users

reported more often lower abdominal pain and heavy menstrual bleeding than implant users, while for acne, amenorrhoea, irregular or prolonged bleeding, it was the opposite. These observations correspond with what previously has been found in observational studies of side effects of users of contraceptive implants and IUDs (Davies *et al.*, 1993; Kiriwat *et al.*, 1998; Sivin *et al.*, 1998, 2010; Funk *et al.*, 2005). Headache and dizziness, however, complaints frequently reported to be associated with hormonal contraception, were not significantly different between the IUD and implant users. PID is a rare condition that can be difficult to diagnose clinically (Meirik, 2007), and it was less often diagnosed in users of implant than in IUD users [relative risk estimate 0.2 (95% CI 0.18–0.58)]. This very low relative risk estimate may reflect reality, but it may also be biased downwards because *a priori* belief among some healthcare providers that the IUD is strongly associated with PID may well have led them to more easily assume a clinical diagnosis of PID in users of IUD than in implant users. Current evidence is that the modern copper IUDs are only weakly associated with PID (Farley *et al.*, 1992; Hubacher *et al.*, 2013).

Strength of this study is the randomization of the two implants being studied, albeit the different characteristics of the two implants precluded a blinded trial. To our knowledge, it is the first head-to-head RCT of the one-rod ENG and the two-rod LNG implants. The ENG implant was previously compared with the six-capsule LNG implant (Norplant®) (Zheng *et al.*, 1999) in a smaller RCT 2-year trial that also confirmed the safety and high contraceptive effectiveness of the implants. Other strengths of the study were that it was multicentre with centres across regions of the world with diverse ethnicities and cultural backgrounds and that it included a comparison group of IUD users. Although the IUD group was not randomized, it was centre- and age-matched, allowing comparison of two principally different, hormonal and non-hormonal, long-term contraceptive methods.

One limitation was that the implant versus IUD comparison was of observational nature and not a RCT comparison that was done between the two types of contraceptive implants. The high expulsion rate observed in the IUD group of users is noteworthy. Information that reached two of the authors indicates that some batches of the TCu380A IUDs provided to the study may have had a too narrow space between the insertion tube and the rod, and, when removing the rod after having placed the IUD, the threads of the IUD could be caught between the rod and the tube and dislocate the IUD to a low position in the uterine cavity (L. Bahamondes and O. Meirik, personal information, 2006). This problem has since long been corrected. Other limitations are that of women admitted, few were below the age of 20 years, nulligravidas, overweight or obese. As reported previously (Meirik *et al.*, 2013), the time period from initiating the study to reporting it was influenced by problems associated with delays of some potential centres in deciding not to participate in the study and with outsourcing of data management. The former eventually led to an increase in the enrolment quota and prolonged the period of enrolment in some participating centres, and the latter to time-consuming cleaning of data.

A comparison of continuation rates between the ENG and the LNG implants through 3 years will inevitably be affected by the shorter approved effective lifespan of 3 years of the ENG implant against 5 years for the LNG implant. In this study, the continuation rate of the ENG implant was compounded by the offer to continue the use of the originally inserted ENG implant through the fourth and fifth years after placement, which many women consented to do after having been informed about this off-label extension of use of it. Hence, an unbiased 3-year continuation rate for the ENG implant could not be calculated from data of this study. The K–M estimate was 12.1 per 100 after censoring women who attended the visit that originally was scheduled for implant removal. However, the continuation rates of the two implants were very similar up through 2.5 years and also up to 34 months, indicating that the overall balance women make of the contraceptive efficacy, convenience of use and side effects was similar for the two implants up to the end of the approved effective lifespan of the ENG implant.

A simplified calculation of proportion of women having ENG implant inserted and *de facto* continued implant contraception beyond 3 years indicates the following: at start of the 34th month after implants insertion, 616 women in the ENG-implant group, for whom information was available, were still using the implant. In the period of 34–38 months after insertion, 235 of the 616 women had their implant removed, and of these, 101 chose to have a new implant inserted. Another 381 ENG-implant users being censored during the 34–38 post-insertion interval chose to continue in the extension of the study and to use the originally inserted implant beyond 3 years. Thus, 3 years after, 995 women had ENG implant inserted and 482 (48.4%) women continued or chose to continue implant contraception. However, the approved shorter lifespan of the ENG implant compared with that of the LNG implant used in this study does negatively affect continuation rates of implant contraception beyond 3 years.

In conclusion, this RCT showed that the ENG and LNG implants have the same contraceptive effectiveness and similar reasons for implant removal for all combined medical reasons in the 3 years after insertion, continuation rates for the two implants were similar up to the middle of the third year of use and had, during this time period, higher continuation rates than the TCu380A IUD. The difference of the median of the duration of removal between the two implants is without clinical significance in the common practice. Comparison of occurrence of side effects reported by implant and IUD users confirmed that some complaints usually attributed to progestogen-only contraceptives were more common among implant users (acne, amenorrhoea, irregular bleeding) than in IUD users. However, complaints of headache and dizziness frequently attributed to hormonal contraceptives were not significantly different. Lower abdominal pain and heavy bleeding were more frequent among IUD users than implant users. The results of the study can help policy makers to decide which type of implant to introduce in the family planning programmes.

Supplementary data

Supplementary data are available at http://molehr.oxfordjournals.org/.

Authors' roles

L.B. and V.B. were PI at Brazil and Dominican Republic, respectively; O.M. was one of the managers of the study at the beginning; M.A., N.A.H. and S.L. were officers at the HRP/WHO.

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Conflict of interest

None declared.

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Appendix

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