GYNECOLOGY

# Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration—approved duration

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**BACKGROUND:** The subdermal contraceptive implant and the 52-mg levonorgestrel intrauterine device are currently Food and Drug Administration approved for 3 and 5 years of use, respectively. Limited available data suggested both of these methods are effective beyond that time. Demonstration of prolonged effectiveness will improve the cost-effectiveness of the device, and potentially patient continuation and satisfaction.

**OBJECTIVE:** We sought to evaluate the effectiveness of the contraceptive implant and the 52-mg hormonal intrauterine device in women using the method for 2 years beyond the current Food and Drug Administration—approved duration.

**STUDY DESIGN:** We initiated this ongoing prospective cohort study in January 2012. We are enrolling women using the contraceptive implant or 52-mg levonorgestrel intrauterine device for a minimum of 3 and 5 years, respectively (started intrauterine device in ≥2007 or implant in ≥2009). Demographic and reproductive health histories, as well as objective body mass index, were collected. Implant users were offered periodic venipuncture for analysis of serum etonogestrel levels. The primary outcome, unintended pregnancy rate, was calculated per 100 woman-years. We analyzed baseline demographic characteristics using $\chi^2$ test and Fisher exact test, and compared serum etonogestrel levels stratified by body mass index using the Kruskal-Wallis test.

**RESULTS:** Implant users (n = 291) have contributed 444.0 woman-years of follow-up. There have been no documented pregnancies in implant users during the 2 years of postexpiration follow-up. Calculated failure rates in the fourth and fifth years for the implant are calculated as 0 (1-sided 97.5% confidence interval, 0—1.48) per 100 woman-years at 4 years and 0 (1-sided 97.5% confidence interval, 0—2.65) per 100 woman-years at 5 years. Among 496 levonorgestrel intrauterine device users, 696.9 woman-years of follow-up have been completed. Two pregnancies have been reported. The failure rate in the sixth year of use of the levonorgestrel intrauterine device is calculated as 0.25 (95% confidence interval, 0.04—1.42) per 100 woman-years; failure rate during the seventh year is 0.43 (95% confidence interval, 0.08—2.39) per 100 woman-years. Among implant users with serum etonogestrel results, the median etonogestrel level was 207.7 pg/mL (range 63.8-802.6 pg/mL) at the time of method expiration, 166.1 pg/mL (range 67.9 25.0—470.5 pg/mL) at the end of the fourth year, and 153.0 pg/mL (range 72.1-538.8 pg/mL) at the end of the fifth year. Median etonogestrel levels were compared by body mass index at each time point and a statistical difference was noted at the end of 4 years of use with overweight women having the highest serum etonogestrel (195.9; range 25.0-450.5 pg/mL) when compared to normal (178.9; range 87.0-463.7 pg/mL) and obese (137.9; range 66.0-470.5 pg/mL) women ($P = .04$).

**CONCLUSION:** This study indicates that the contraceptive implant and 52-mg hormonal intrauterine device continue to be highly effective for at least 2 additional years of use. Serum etonogestrel evaluation demonstrates median levels remain above the ovulation threshold of 90 pg/mL for women in all body mass index classes.

**Key words:** effectiveness, Food and Drug Administration—approved duration, implant, intrauterine device, prolonged use

## Introduction

Long-acting reversible contraception continues to gain popularity and recent estimates suggest that as many as 12% of US women actively contracepting are using an intrauterine device (IUD) or implant.[1] Improving access to these methods is an important strategy to increasing uptake. Many access barriers still exist for women both domestically and internationally. One way to improve long-acting reversible contraception utilization is to demonstrate safety, efficacy, and cost-effectiveness for time periods beyond the current US Food and Drug Administration (FDA) duration of use. Evidence exists to support the prolonged use of the etonogestrel (ENG) implant and the 52-mg levonorgestrel (LNG) IUD for at least 1 year beyond FDA-approved duration.[2-5] The World Health Organization (WHO) study group on the subdermal implant recently published findings in which there were no documented pregnancies in women using the ENG implant during years 4 and 5.[6] We found scant data in the medical literature for contraceptive effectiveness >6 years for the LNG IUD.

We previously published data from the Effectiveness of Prolonged Use of IUD/Implant for Contraception (EPIC) study in which 1 year of additional use was evaluated.[2] In this current report, we present an analysis of the effectiveness of the subdermal implant and LNG IUD after an additional year of follow-up (2 years beyond FDA-approved duration). We also present comparison data of serum ENG levels by body mass index (BMI) at each additional year of implant use.

## Materials and Methods

The EPIC study was launched at Washington University in St Louis in 2012. The study began as a prospective cohort

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study of the LNG IUD and implant. However, the study now has several components: (1) a randomized trial of continued use of the implant beyond the FDA-approved duration compared to a new implant; (2) observational study of both the LNG IUD and implant; and (3) the "removal study" that follows women prospectively who have their implant or LNG IUD removed, but do not desire conception. This article will focus on the results of the observational cohort study through 2 additional years of implant and LNG IUD use beyond the FDA-approved duration. The study protocol was approved by the Institutional Review Board at Washington University in St Louis prior to participant recruitment.

Enrollment for the EPIC study began in January 2012 and is currently ongoing. We analyzed data from participants enrolled from January 2012 through July 2016. Women who initiated use of their implant as early as 2009 and their LNG IUD in 2007 and beyond were eligible to participate in this observational study. Women eligible for the EPIC study are between the ages of 18-45 years, English- or Spanish-speaking, sexually active with a male partner, not interested in conception in the next 12 months, and willing to continue use of their subdermal implant or LNG IUD for a minimum of an additional 1 year. Desire to avoid pregnancy for at least 12 months was included to ensure the study was meeting its objective of determining effectiveness of the methods beyond their current FDA-approved duration. Participants had to present within 3 months of the current FDA-approved duration of use (eg, for implant: 33-39 months of use; 57-63 months of use for LNG IUD). Among the cohort, 87.4% of participants (N = 688) were enrolled as former participants of the Contraceptive CHOICE Project, a prospective cohort study of 9256 participants using a range of contraceptive methods. Of the entire EPIC cohort, 12.6% were recruited from outside clinics. Date of method expiration is validated for 100% of the CHOICE participants and a subset of those enrolled from outside facilities using medical chart review for >90% of the cohort.

At study enrollment participants provide written informed consent and complete a staff-administered reproductive health survey that includes questions regarding demographic characteristics including socioeconomic status. Participants were considered low socioeconomic status if they reported any of the following: receiving food stamp, supplemental nutrition, welfare, or unemployment benefits, or if they reported having trouble paying for transportation, housing, medical care, or food. We also collected data regarding intercourse frequency, additional contraceptive method use, menstrual cycle regularity, partner characteristics, and presence of comorbidities that may affect fertility. Participants also underwent objective measurement of height and weight. BMI was calculated as weight (kg) divided by height ($m^2$). Participants were classified into 1 of 3 BMI categories as defined by the WHO, combining the underweight and normal-weight categories.[7] Normal-weight women were defined as those with a BMI <25.0, overweight as 25.0-29.9, and obese as ≥30.0.

Telephone follow-up surveys are completed every 6 months for 36 months or until the participant requests device removal. Once enrollment is complete, all follow-up can be completed by telephone, unless a participant requests a clinic visit. All participants are encouraged to call the study staff and arrange a clinic visit with any concern for pregnancy. Follow-up surveys assess for current method use, use of additional contraceptive methods, frequency of intercourse, and any pregnancies experienced. If a participant reports a pregnancy that was not evaluated with the study team, medical record review documenting confirmation of the pregnancy and the pregnancy outcome are undertaken. For implant users, in addition to the enrollment visit, venipuncture is offered annually (at the anniversary of the implant insertion), at the time of method removal, or if a pregnancy is experienced during implant use. Participants are compensated with a $40 gift card at enrollment, $20 for completion of each survey, and for each venipuncture. At the time of venipuncture, 7 mL of whole blood are collected and allowed to sit upright for clot formation for 1-2 hours. Samples are then centrifuged for 10 minutes at 4°C at 3000 rpm. Serum is aliquoted off and stored in a laboratory freezer at −80°C. Samples are then sent to the Columbia University Medical Center Core Laboratory for ENG analysis where liquid chromatography tandem mass spectrometry is performed by the Biomarkers Core Laboratory of the Irving Institute of Clinical and Translational Research at Columbia University Medical Center (New York, NY).[8] Participants are informed that the results from their ENG assay will not impact their eligibility for study continuation or their clinical care. Participants are asked to inform study staff at any time they suspect they may be pregnant or if they desire method removal. Method removal is provided without charge at any time to all participants.

Our primary outcome is unintended pregnancy during prolonged use. Pregnancy rates are presented in woman-years of follow-up. Participants contributed to this analysis beginning at method expiration (end date of FDA-approved duration) until the last contact date, through 30 months post-expiration. Secondary outcomes include quantification of serum ENG levels at various time points during prolonged use of the implant and comparison of ENG levels across BMI classes. For ENG level assessment, we defined "year 3" to be any sample drawn from expiration through 6 months of additional use (3.5 years), a "year 4" sample to have been collected from 3.5 through 4.5 years of use, and a "year 5" sample to have been collected from 4.5 through 5.5 years of use. Our cohort retention rate is 97.9% at 12 months and 94.8% at 24 months.

All statistical analyses were performed using SAS Software (v.9.4.; SAS Institute, Cary, NC). Significance levels ($\alpha$) were set at 0.05. Demographic characteristics of all participants are presented as means, SD, and percentages. Unintended pregnancy rate was calculated using number of unintended pregnancies divided by total woman-years of follow-up and

95% confidence interval (CI) was calculated. Since there were 0 pregnancies documented in the implant group during the follow-up period, a 1-sided 97.5% CI was calculated. The $\chi^2$ test and Fisher exact test were performed to examine the subjects' characteristics differences across the 3 BMI groups. ENG levels were not normally distributed; thus, the Kruskal-Wallis test was used to compare the median ENG levels across the 3 BMI categories at 3, 4, and 5 years of implant use.

## Results

At the time of analysis, 291 implant users were enrolled in the EPIC study, contributing 444.0 woman-years of time to this analysis. Of these users, 223 (77%) used their method for >12 additional months and 102 (35%) for >24 additional months. The mean duration of prolonged implant use is 18.9 additional months (range 0-44.1 months). This cohort includes 496 LNG IUD users contributing 696.9 woman-years of time to this analysis. Of these users, 347 (70%) used their method for >12 additional months and 160 (32%) for >24 additional months. The mean duration of prolonged IUD use is 19.3 additional months (range 0.2-41.1 months).

Overall, the mean age of the entire study population (IUD and implant) was 29.9 years. Black women accounted for 58.5% (N = 459) of the cohort with 35.7% (N = 280) subjects reporting white race. The majority of the study population (96.7%, N = 760) were non-Hispanic. Less than half of the subjects were categorized as low socioeconomic status (46.7%, N = 367) and 49.9% (N = 392) were single or never married. Comparison of the characteristics of the study population by method type are shown in Table 1. Compared to IUD users, implant users are younger, less educated, and more likely to be single and to report lower socioeconomic status. Participant BMIs ranged from 16.5-62.7. In our cohort, 25% (N = 58) were of normal weight, 22% (N = 55) were overweight, and 53% (N = 127) were obese or morbidly obese. Patients with higher BMIs in our population were more likely to be older ($P = .02$), to have

**TABLE 1**
**Baseline demographic and reproductive characteristics of implant and levonorgestrel intrauterine device users**

| Characteristic, n (%) | Implant, n = 291 | IUD, n = 496 | *P* |
|---|---|---|---|
| Age, y | | | <.001 |
| 18-22 | 90 (30.9) | 7 (1.4) | |
| 23-29 | 138 (47.4) | 186 (37.5) | |
| 30-34 | 33 (11.3) | 140 (28.2) | |
| 35-45 | 30 (10.3) | 163 (32.9) | |
| Race[a] | | | <.001 |
| Black | 205 (70.4) | 254 (51.4) | |
| White | 63 (21.6) | 217 (43.9) | |
| Other | 23 (7.9) | 23 (4.7) | |
| Ethnicity[b] | | | .16 |
| Hispanic | 13 (4.5) | 13 (2.6) | |
| Non-Hispanic | 278 (95.5) | 482 (97.2) | |
| Education | | | <.001 |
| ≤High school | 99 (34.0) | 92 (18.5) | |
| Some college or vocational school | 154 (52.9) | 184 (37.1) | |
| ≥College | 38 (13.1) | 220 (44.4) | |
| Medical insurance status[b] | | | <.001 |
| None | 103 (35.5) | 132 (26.6) | |
| Medicare/Medicaid | 63 (21.7) | 77 (15.5) | |
| Private | 124 (42.8) | 287 (57.9) | |
| Low socioeconomic status[b,c] | | | <.001 |
| Yes | 172 (59.1) | 195 (39.4) | |
| No | 119 (40.9) | 300 (60.6) | |
| Marital status[b] | | | <.001 |
| Single or never married | 189 (64.9) | 203 (41.0) | |
| Married or cohabitating | 96 (33.0) | 254 (51.3) | |
| Separated/divorced/widowed | 6 (2.1) | 38 (7.7) | |
| Gravidity[d] | | | .16 |
| 0 | 83 (28.7) | 144 (29.6) | |
| 1-2 | 128 (44.3) | 185 (38.0) | |
| ≥3 | 78 (27.0) | 158 (32.4) | |
| BMI[a] | | | .07 |
| <25 | 73 (25.1) | 162 (32.8) | |
| 25-30 | 67 (23.0) | 106 (21.5) | |
| ≥30 | 151 (51.9) | 226 (45.7) | |

*BMI*, body mass index; *IUD*, intrauterine device.

[a] Data missing for 2 participants; [b] Data missing for 1 participant; [c] Low socioeconomic status defined as any participant reporting difficulty paying for basic needs such as food, shelter, or childcare or receiving public assistance; [d] Data missing for 11 participants.

*McNicholas et al. Prolonged use of IUD and implant. Am J Obstet Gynecol 2017.*

**TABLE 2**
**Demographic characteristics by body mass index of implant users contributing etonogestrel levels**

| Characteristic, n (%) | BMI <25, n = 58 | 25-30, n = 55 | ≥30, n = 127 | *P* |
|---|---|---|---|---|
| Age, y | | | | .02 |
| 18-22 | 23 (39.7) | 23 (41.8) | 26 (20.5) | |
| 23-29 | 26 (44.8) | 26 (47.3) | 65 (51.2) | |
| 30-34 | 5 (8.6) | 4 (7.3) | 22 (17.3) | |
| 35-45 | 4 (6.9) | 2 (3.6) | 14 (11.0) | |
| Race | | | | .10 |
| Black | 36 (62.1) | 38 (69.1) | 100 (78.7) | |
| White | 18 (31.0) | 11 (20.0) | 19 (15.0) | |
| Other | 4 (6.9) | 6 (10.9) | 8 (6.3) | |
| Ethnicity | | | | .05 |
| Hispanic | 1 (1.7) | 6 (10.9) | 4 (3.1) | |
| Non-Hispanic | 57 (98.3) | 49 (89.1) | 123 (96.9) | |
| Education | | | | .45 |
| ≤High school | 14 (24.1) | 19 (34.5) | 47 (37.0) | |
| Some college or vocational school | 35 (60.3) | 30 (54.5) | 68 (53.5) | |
| ≥College | 9 (15.5) | 6 (10.9) | 12 (9.4) | |
| Medical insurance status | | | | .40 |
| None | 18 (31.0) | 18 (34.6) | 47 (38.8) | |
| Medicare/Medicaid | 8 (13.8) | 12 (23.1) | 25 (20.7) | |
| Private | 32 (55.1) | 22 (42.3) | 49 (40.5) | |
| Low socioeconomic status[a] | | | | .002 |
| Yes | 23 (39.7) | 35 (63.6) | 84 (66.1) | |
| No | 35 (60.3) | 20 (36.4) | 43 (33.9) | |
| Marital status | | | | .73 |
| Single or never married | 40 (69.0) | 40 (72.7) | 85 (66.9) | |
| Married or cohabitating | 16 (27.6) | 15 (27.3) | 40 (31.5) | |
| Separated/divorced/widowed | 2 (3.4) | 0 (0.0) | 2 (1.6) | |
| Gravidity[b] | | | | .005 |
| 0 | 24 (41.4) | 20 (37.0) | 24 (18.9) | |
| 1-2 | 25 (43.1) | 21 (38.9) | 59 (46.5) | |
| ≥3 | 9 (15.5) | 13 (24.1) | 44 (34.6) | |

*BMI*, body mass index.

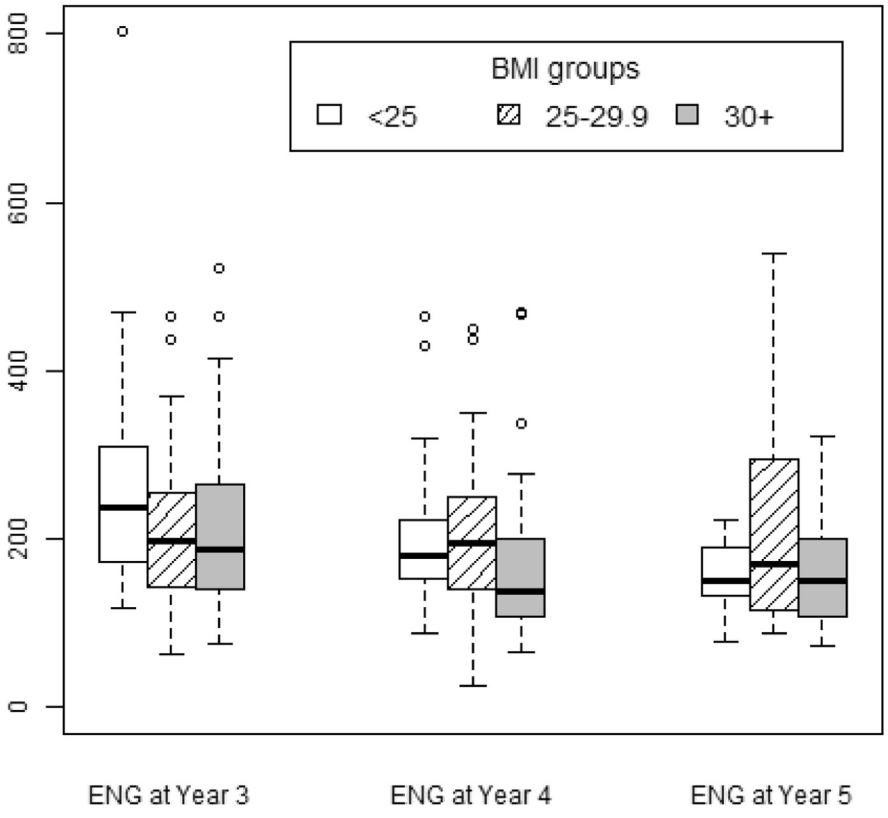
[a] Defined as any participant reporting difficulty paying for basic needs such as food, shelter, or childcare or receiving public assistance; [b] Data missing for 1 participant.

*McNicholas et al. Prolonged use of IUD and implant. Am J Obstet Gynecol 2017.*

higher gravidity ($P < .01$), and to be of lower socioeconomic status ($P < .01$) (Table 2).

The 291 implant users contributed 157 year-3 samples, 143 year-4 samples, and 50 year-5 samples. We examined the association between ENG levels and BMI classes for each year of use. The median ENG level at 3 years of use was 207.7 pg/mL (range 63.8-802.6 pg/mL), 166.1 pg/mL (range 25.0-470.5 pg/mL) at 4 years of use, and 153.0 pg/mL (range 72.1-538.8 pg/mL) at 5 years of use. We found no differences in median serum ENG levels across BMI groups at method expiration ($P = .10$) or at the end of the fifth year of use ($P = .62$). We did find a significant difference in ENG levels by BMI after 4 years of use ($P = .04$); however, the trend was not linear with median levels in the overweight group higher than both the normal-weight and

**FIGURE**
**Serum etonogestrel levels by BMI at 3,4, and 5 years of use**




Median etonogestrel (ENG) levels at years 3, 4, and 5 by body mass index (BMI) categories.

*McNicholas et al. Prolonged use of IUD and implant. Am J Obstet Gynecol 2017.*

obese groups. The median ENG levels for each BMI class at each year of use are shown in the Figure. To date we have documented 2 pregnancies in the LNG IUD group. The failure rate in the sixth year of use (1 year postexpiration) is calculated as 0.25 (95% CI, 0.04−1.42) per 100 woman-years; failure rate during the seventh year (2 years postexpiration) is 0.43 (95% CI, 0.08−2.39) per 100 woman-years. In the cohort of implant users, we have documented 0 pregnancies. We calculate failure rate in the fourth year of use to be 0 (1-sided 97.5% CI, 0−1.48) per 100 woman-years and the rate in the fifth year of use is 0 (1-sided 97.5% CI, 0−2.65) per 100 woman-years.

## Comment

Our findings continue to support effectiveness of the 52-mg LNG IUD and ENG implant in preventing pregnancy for up to 2 additional years beyond their current FDA-approved durations of 3 and 5 years, respectively.

Our findings supplement the limited available data on prolonged use including a small Thai study that found 0 pregnancies in 75 women who used the ENG implant for 4 years. With an additional 411.7 woman-years of use for an additional year, we have strengthened the evidence from our initial publication. Likewise, this cohort now includes >250 woman-years of use for 2 additional years, demonstrating continued efficacy, consistent with recent data published by WHO.[6]

Our previously published data from the EPIC study represented the first publication in the medical literature to correlate clinical pregnancy outcomes with pharmacokinetic measures of ENG levels in implant users continuing to use their method beyond the FDA-approved duration. The median ENG levels at each year remained well >90 pg/mL, a previously published threshold for ovulation suppression. However, the absolute threshold of contraceptive effectiveness remains poorly defined and may be <90 pg/mL as secondary mechanisms such as cervical mucus changes may prevent pregnancy should ovulation occur. In the future, we hope to evaluate the rate of decline of serum ENG levels as well as the amount of ENG that remains in the device at the time of removal. We also will assess suppression of ovulation in women continuing their method beyond the FDA-approved duration. These data would help to further define the clinical relevance of implant pharmacokinetics.

Our study also differentiates ENG levels across women of varying BMIs at 3, 4, and 5 years of implant use. Previous pharmacokinetic data suggested that obese women have lower serum ENG levels than their normal-weight counterparts, but clinical data have not shown an increased pregnancy rate in this group.[9,10] Although we found that after 4 years of use, women with the highest BMIs had significantly lower ENG levels than women with lower BMIs, the clinical relevance is questionable given we did not find a linear trend in ENG levels by BMI. Furthermore, we saw no difference in ENG levels across BMI categories at 5 years of implant use, although our numbers are small. More importantly, our data indicate that median ENG levels at 4 and 5 years of use remained >90 pg/mL regardless of BMI class. Thus, we do not believe that women with elevated BMIs are at increased risk of contraceptive failure with extended implant use.

Our study supports prior publications indicating that the 52-mg LNG IUD can be used safely for up to 7 years. Our failure rate of 0.25-0.43 per 100 woman-years is comparable to the published failure rate during its current FDA-approved use period of 5 years, and is clearly superior to a pregnancy risk with use of the oral contraceptive pill, transdermal patch, or vaginal ring. Consistent with our findings, Sivin[3] randomized >2000 women to a LNG-releasing IUD or a copper IUD and followed up participants long-term. No pregnancies occurred with either device in years 6 or

7. The LNG device used in this study released 20 μg/d, but was not identical to the 52-mg LNG IUD used today.

Our study has several strengths. The EPIC study includes a large and diverse cohort of women that represent a spectrum of age, race, and socioeconomic status, supporting its generalizability to a larger population. This additional year of follow-up for implant users, we believe, represents the only published prospective data providing evidence of up to 5 years of efficacy in a US population. As previously mentioned, very recent data in an international population also demonstrated continued effectiveness for 2 additional years of use.[6] Unlike our study, this WHO study randomized women to either the single rod ENG implant or the 2-rod LNG implant. Their population was followed up from the time of implant insertion, where as our cohort enrolled at the time of method expiration. Despite minor differences in methodology, the 2 studies confirm the same finding of continued effectiveness for an additional 2 years of use.

In addition to providing data for the fifth year of implant use, we have strengthened the evidence for 4 years of use with a larger and more robust cohort. Our study also draws on objective sources of data including height and weight measurements used to calculate BMI and a specific serum ENG assay findings for ENG levels. Similarly, the size of our cohort of 52-mg LNG IUD users has increased at 6 and 7 years, further increasing the precision of our estimates and supporting our prior findings and that of Sivin.[3]

One limitation of our study is the relatively small numbers of ENG samples we have at 5 years of implant use. We may not yet have the power to detect small differences among BMI classes at 5 years of use. We are reassured, however, by the median ENG levels that remain well over the 90 pg/mL mark for all BMI categories and that we have had no pregnancies in any group. A final limitation is that we used self-report to document contraceptive failures. While we validated positive reports whenever possible, it is possible that women may underreport unintended pregnancies due to social desirability bias.

In conclusion, our continued follow-up of woman using their contraceptive implants and LNG IUDs after the FDA-approved duration of 3 and 5 years, respectively, strengthened our previous findings that the ENG implant and LNG IUD can be safely used for an additional year, and provides evidence that they can be used for 2 additional years. Our data suggest that the implant and the LNG IUD each maintain their contraceptive effectiveness for at least an additional 2 years. ENG levels are maintained above the contraceptive threshold of 90 pg/mL in all BMI classes at 3, 4, and 5 years. ■

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