

Research Article

Clinical Performance and Levonorgestrel Levels of Sinoplant and Indoplant after Five Years of Continuous Use

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Abstract

Objectives: To compared serum LNG concentrations, contraceptive effectiveness, safety, and acceptability between Sinoplant and Indoplant over five years of continuous use to explore their potential for extended use.

Methods: This prospective cohort study was a two-year extension of a three-year multicenter randomized clinical trial conducted at family planning clinics in Yogyakarta and Surabaya, Indonesia. Of the initial 540 participants, 58 voluntarily consented to participate in the extension study. Serum LNG concentrations were measured at 36, 48, and 60 months. Nonparametric tests were used because of the skewed distribution of the data.

Results: Fifty-five participants completed the 60-month follow-up. At month 60, all participants (100%) had negative urine pregnancy test results. Median serum LNG concentrations at months 36, 48, and 60 were 361.95, 555.00, and 400.00 pg/mL, respectively, in the Sinoplant group and 254.52, 210.00, and 230.00 pg/mL, respectively, in the Indoplant group. Significant within-group variation over time was observed only in the Sinoplant group ($p = 0.006$). No significant between-group differences were observed in overall adverse events or acceptability.

Conclusion: Both implants maintained median serum LNG concentrations above the minimum contraceptive threshold of 180 pg/mL and demonstrated preliminary evidence of continued contraceptive effectiveness through five years of continuous use. However, the small sample size of the extension study and potential selection bias limit the generalizability of these findings. Larger prospective studies are needed before changes to policies regarding extended implant use can be recommended.

Keywords: five years of continuous use; Indoplant; levonorgestrel; Sinoplant; two-rod implant.

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INTRODUCTION

Subdermal progestin-releasing implants are highly effective Long-Acting Reversible Contraceptives (LARCs) that gradually release the active hormone into the systemic circulation. Levonorgestrel (LNG)-releasing implants prevent pregnancy primarily by suppressing ovulation, thickening cervical mucus to inhibit sperm penetration, and inducing endometrial changes that reduce the likelihood of implantation. Depending on the implant type, contraceptive implants are approved for three to five years of use.

In Indonesia, however, current Ministry of Health regulations recommend a three-year duration of use for subdermal contraceptive implants.^{1,2} Although most implants currently available in Indonesia are approved for three years of use, evidence from other countries has demonstrated continued contraceptive effectiveness of some implants for up to five years. Recent evidence has also suggested that certain subdermal implants may remain effective for even longer periods.²

Jadelle, a two-rod LNG-releasing implant originally developed in China, has been extensively studied for extended use. After

insertion, serum LNG concentrations reach peak levels within 24–72 hours, followed by a rapid decline during the first week, a moderate decline during the first month, and a gradual decrease thereafter. Several studies have demonstrated the safety and contraceptive effectiveness of Jadelle for up to five years of continuous use.¹ In Indonesia, Sinoplant and generic Indoplant, both two-rod LNG-releasing implants approved for three years of use, have demonstrated favorable safety, contraceptive effectiveness, and acceptability profiles. However, evidence regarding their pharmacokinetic profiles and clinical performance beyond the approved three-year duration remains limited.

The two rods of Sinoplant and Indoplant each contain 75 mg of LNG, similar to Jadelle. However, the presence of the same active ingredient does not necessarily imply identical pharmacokinetic or clinical performance profiles. Pharmacokinetic evidence suggests that a minimum serum LNG concentration of approximately 180 pg/mL may be required to maintain contraceptive effectiveness. Therefore, evaluating whether serum LNG concentrations remain above this threshold during extended use is clinically relevant.

Given the current three-year duration of approved implant use in Indonesia and the evidence supporting extended use of comparable two-rod LNG implants, further evaluation of Sinoplant and Indoplant is warranted. This study therefore aimed to compare the clinical performance and serum LNG concentrations of Sinoplant and Indoplant over five years of continuous use in Indonesian women. The findings may provide local evidence to inform future evaluation of extended implant use within Indonesia's national family planning program.

METHODS

This prospective cohort study was conducted as a two-year extension of a three-year double-blind, multicenter randomized controlled trial (RCT) comparing Sinoplant and generic Indoplant contraceptive implants.³ The parent trial was originally designed with a three-year follow-up period, and participants provided informed consent for that study duration. After completion of the initial three-year follow-up, participants were re-contacted and invited to participate in an additional two-year extension study. Of the original 540 participants, 58 voluntarily consented

to continue implant use for an additional two years. The extension study was conducted at family planning clinics in Yogyakarta and Surabaya, Indonesia. Because participation in the extension study was voluntary, only a subset of the original trial population continued to the five-year follow-up, resulting in substantial attrition and potential selection bias.

Eligible participants were healthy, fertile women aged 23–38 years who had completed three years of continuous use of the allocated study implant, were sexually active, provided written informed consent after receiving an explanation of the study purpose, risks, and benefits, and agreed to attend scheduled follow-up visits. Women were excluded if they had absolute contraindications to hormonal contraception, including thrombophlebitis, thromboembolism, hypertension, cerebrovascular accident, liver disease, known or suspected breast or genital cancer, or suspected estrogen-dependent neoplasia; anemia; pregnancy; obesity (Broca index >60%); ongoing hormonal treatment with estrogen, progesterone, or thyroid hormones; a history of or current pelvic inflammatory disease; complete amenorrhea for more than one year while using an implant or other hormonal contraceptives; use of medications that could affect hormonal pharmacodynamics or treatment for chronic diseases such as tuberculosis, systemic lupus erythematosus, or chronic liver disease; a family history of any type of cancer; abnormal or undiagnosed genital bleeding; current or recent use of liver enzyme-inducing drugs, including barbiturates, phenytoin, carbamazepine, or rifampicin; severe hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg); severe hirsutism; participation in another clinical study within the preceding three months; or a baseline serum LNG concentration <180 pg/mL.

Both Sinoplant and Indoplant are two-rod silastic contraceptive implants, with each rod containing 75 mg of levonorgestrel (LNG). Sinoplant is manufactured by Catur Dakwah Crane Farmasi Ltd., whereas Indoplant is manufactured by Triyasa Nagamas Farma Industri Ltd. The implants were inserted subdermally into the inner aspect of the upper arm of the nondominant arm, approximately 6–8 cm above the elbow, under local anesthesia using aseptic procedures.

The study outcomes included serum LNG concentrations, contraceptive effectiveness, safety, and acceptability during five years

of continuous implant use. Serum LNG concentrations were measured at 36, 48, and 60 months. Clinical assessments included pregnancy occurrence, body weight, upper arm circumference, systolic and diastolic blood pressure, menstrual patterns, frequency of sexual intercourse, and complaints related to implant use. Demographic characteristics, educational level, occupation, obstetric history, previous contraceptive use, and menstrual characteristics were obtained from the parent trial records. For longitudinal analyses, body weight, upper arm circumference, blood pressure, and serum LNG concentration measured at the 36-month visit were considered baseline values. At the 60-month follow-up, changes in body weight and blood pressure, menstrual patterns, pregnancy occurrence, and reported complaints were evaluated.

Continuous variables were presented as mean $\pm$ standard deviation (SD) or median (minimum–maximum), according to the data distribution. Categorical variables were presented as frequencies and percentages. Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables and the chi-square test, likelihood-ratio test, or Fisher's exact test for categorical variables, as appropriate. Changes in body weight and blood pressure between the 36- and 60-month assessments were analyzed using the appropriate paired statistical test according to data distribution. Changes in serum LNG concentrations across the 36-, 48-, and 60-month follow-up visits within each implant group were analyzed using the Friedman test. A two-sided p -value <0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

This study was approved by the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital (Ref: KE/FK/0478/EC/2021); the Research Ethics Committee for Family Planning and Family Development of the National Population and Family Planning Agency (BKKBN), Indonesia (Ref: 1624/LB.02/H42021); and the Food and Drug Monitoring Agency (BPOM), Indonesia (Refs: R-RG.01.06.32.321.04.21.226 and

B-RG.01.06.32.323.09.21.479). All participants provided written informed consent before enrollment in the extension study.

RESULTS

A total of 58 participants voluntarily consented to continue implant use for five years. Of these, 49 participants were from Yogyakarta and 9 were from Surabaya. The mean age was 27.66 ± 5.03 years in the Sinoplant group and 28.96 ± 4.36 years in the Indoplant group. In both groups, most participants had a high school education and were housewives. No significant between-group differences were observed in age, education, or occupation ($p > 0.05$). The most commonly used previous contraceptive method was the 3-month injectable contraceptive (52.63% in the Sinoplant group and 45.00% in the Indoplant group). The most common reasons for discontinuing previous contraceptive methods were side effects and other reasons, including the desire to switch methods, menstrual disorders, forgetfulness, concerns about contraceptive failure, and inconvenience (Table 1).

Regarding baseline menstrual characteristics, most participants had not experienced excessive bleeding lasting more than seven days (84.38% and 84.62% in the Sinoplant and Indoplant groups, respectively), bleeding between menstrual periods (90.62% and 92.31%), menstrual intervals longer than 35 days (75.00% and 92.31%), menstrual intervals shorter than 21 days (84.38% and 92.31%), amenorrhea lasting more than three months (76.90% and 88.47%), or menstrual cramps interfering with daily activities and requiring medication (76.90% and 84.62%). Most participants had a menstrual duration of less than eight days (90.62% and 96.15%, respectively). No significant between-group differences were observed in baseline menstrual characteristics (Table 1).

There were no significant between-group differences in baseline health parameters, including height, body weight, upper arm circumference, systolic blood pressure, or diastolic blood pressure ($p > 0.05$) (Table 1).

Table 1. Baseline Characteristics of Participants

Parameter	Sinoplant (n=32)	Indoplant (n=26)	P-value
Demographic characteristics			
Age, years (mean ± SD)	27.66 ± 5.03	28.96 ± 4.36	0.358*
Education, n (%)			
Elementary school	1 (3.13)	0 (0)	0.651***
Junior high school	8 (25.00)	6 (23.08)	
Senior high school	20 (62.50)	16 (61.54)	
University	3 (9.37)	4 (15.38)	
Occupation, n (%)			
Housewife	22 (68.75)	20 (76.92)	0.426***
Employee	5 (15.63)	5 (19.23)	
Self-employed	4 (12.50)	1 (3.85)	
Others	1 (3.12)	0 (0)	
Vital signs			
Height, cm (mean ± SD)	153.78 ± 5.19	152.85 ± 9.69	0.104*
Weight, kg (mean ± SD)	57.59 ± 9.82	56.08 ± 12.20	0.602*****
Upper arm circumference, cm (mean ± SD)	26.34 ± 3.37	27.88 ± 3.67	0.137*
Systolic blood pressure, mmHg (mean ± SD)	112.31 ± 11.04	111.23 ± 13.32	0.307*
Diastolic blood pressure, mmHg (mean ± SD)	75.16 ± 6.90	76.38 ± 6.17	0.525*
Obstetric history and contraceptive use			
Number of children (mean ± SD)	1.88 ± 0.79	1.92 ± 0.74	0.839*
Desire to have another child, n (%)			0.912**
Yes	14 (43.75)	11 (42.30)	
No	18 (56.25)	15 (57.70)	
Sexual intercourse, times/week (mean ± SD)	1.75 ± 0.76	1.77 ± 0.77	0.892*
Previous contraceptive use, n (%)			
Yes	19 (59.38)	20 (76.92)	0.157**
No	13 (40.62)	6 (23.08)	
Type of previous contraception, n (%)			
IUD	1 (5.26)	3 (15.00)	0.034*
1-month injection (combined injectable)	4 (21.05)	0 (0)	
3-month injection (DMPA)	10 (52.63)	9 (45.00)	
Pill	1 (5.26)	3 (15.00)	
Condom	3 (15.80)	2 (10.00)	
Implant	0 (0)	3 (15.00)	
Duration of previous contraceptive use, months, median (min–max)	3 (0–75)	24 (0–60)	0.365*
Reasons for discontinuing previous contraception, n (%)			
Side effects	7 (36.84)	5 (25.00)	0.192***
Health reasons	1 (5.26)	1 (5.00)	
Pregnancy planning	0 (0)	1 (5.00)	
Expensive cost	0 (0)	1 (5.00)	
Expired	0 (0)	3 (15.00)	
Contraceptive failure	1 (5.26)	0 (0)	
Others	10 (52.64)	9 (45.00)	
Menstrual characteristic			
Menarche age, years, median (min–max)	13 (10–17)	13 (12–16)	0.484*
Menstrual cycle length, days, median (min–max)	28 (21–50)	30 (14–30)	0.631*
Menstrual duration, days, median (min–max)	7 (4–8)	7 (4–7)	0.360*
Number of pads on the heaviest menstrual day, median (min–max)	3 (1–5)	3 (2–5)	0.743*
Ever experienced excessive bleeding (>7 days), n (%)			
Yes	5 (15.62)	4 (15.38)	1.000*****
No	27 (84.38)	22 (84.62)	

Bleeding between menstrual periods, n (%)			
Yes	3 (9.38)	2 (7.69)	1.000****
No	29 (90.62)	24 (92.31)	
Ever experienced a menstrual interval >35 days, n (%)			
Yes	8 (25.00)	2 (7.69)	0.160****
No	24 (75.00)	24 (92.31)	
Ever experienced a menstrual interval <21 days, n (%)			
Yes	5 (15.62)	2 (7.69)	0.442****
No	27 (84.38)	24 (92.31)	
Ever missed menstruation for >3 months, n (%)			
Yes	6 (23.10)	3 (11.53)	0.495****
No	26 (76.90)	23 (88.47)	
Menstrual cramps interfering with activities and requiring medication, n (%)			
Yes	6 (23.10)	4 (15.38)	1.000****
No	26 (76.90)	22 (84.62)	
Past menstrual duration, n (%)			
<8 days	29 (90.62)	25 (96.15)	0.620**
≥8 days	3 (9.38)	1 (3.85)	
Total	32	26	58

Notes: Mann–Whitney U test; ** Chi-square test; *** Likelihood-ratio test; **** Fisher's exact test; ***** Independent-samples t-test.

At the 60-month follow-up, three of the 58 enrolled participants discontinued the study. The reasons for discontinuation were a desire to switch contraceptive methods ($n = 1$) and withdrawal of consent ($n = 2$). Thus, 55 participants completed the five-year follow-up, comprising 32 participants in the Sinoplant group and 23 in the Indoplant group.

At 60 months, all 55 participants who completed the follow-up had negative urine pregnancy test results, and no pregnancies were reported during the five-year follow-up period. Within the Sinoplant group, one participant reported intermenstrual bleeding lasting five days, with an average of one pad per day. No significant between-group differences were observed in vital signs, menstrual patterns, sexual intercourse frequency, or reported complaints at the 60-month follow-up (Table 2).

Body weight changes were assessed by comparing measurements at 36 and 60 months. A significant within-group difference in body weight was observed in the Sinoplant group ($p = 0.039$), whereas no significant change was observed in the Indoplant group ($p = 0.337$). However, the between-group difference in weight change was not statistically significant ($p = 0.638$) (Table 3).

No significant between-group differences were observed in changes in systolic or diastolic blood pressure ($p = 0.328$ and $p = 0.406$, respectively). Within-group analysis showed no significant change in systolic blood pressure between 36

and 60 months in either the Sinoplant group ($p = 0.258$) or the Indoplant group ($p = 0.936$). For diastolic blood pressure, no significant change was observed in the Sinoplant group ($p = 0.165$), whereas a significant increase was observed in the Indoplant group ($p = 0.023$) (Table 3).

Serum LNG concentrations were measured at 36, 48, and 60 months. Because of the high variability in serum LNG concentrations, the data were summarized using both mean $\pm$ SD and median (min–max) values (Figure 1). The mean serum LNG concentrations at 36 months were 448.04 ± 449.21 pg/mL in the Sinoplant group and 299.67 ± 117.58 pg/mL in the Indoplant group. At 48 months, the corresponding mean concentrations were 467.24 ± 199.83 pg/mL and 378.96 ± 326.20 pg/mL, respectively. At 60 months, the mean concentrations were 397.40 ± 209.16 pg/mL in the Sinoplant group and 392.71 ± 333.68 pg/mL in the Indoplant group.

At 36 months, the median serum LNG concentration was significantly higher in the Sinoplant group than in the Indoplant group (361.95 vs. 254.52 pg/mL; $p = 0.015$). A similar between-group difference was observed at 48 months (555.00 vs. 210.00 pg/mL; $p = 0.010$). At 60 months, the median LNG concentrations were 400.00 pg/mL in the Sinoplant group and 230.00 pg/mL in the Indoplant group, with no statistically significant between-group difference ($p = 0.179$). Within-group analysis showed significant variation in serum LNG concentrations over time in the Sinoplant group ($p = 0.006$),

whereas no significant variation was observed in the Indoplant group ($p = 0.923$) (Table 4).

At 60 months, the median serum LNG concentrations in both groups remained

above the predefined 180 pg/mL threshold. Although individual LNG concentrations varied considerably, no pregnancies were reported among participants who completed the five-year follow-up.

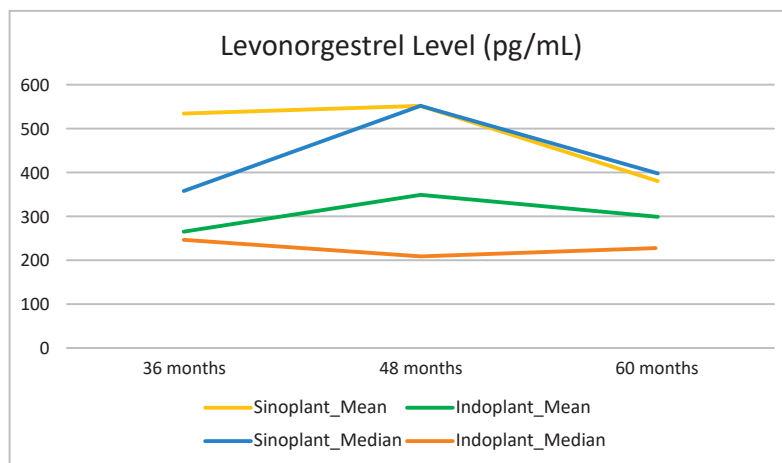
Table 2. Clinical Findings and Acceptability at 60 Months

Parameter	Sinoplant (n=32)	Indoplant (n=23)	P-value
Vital signs			
Weight, kg (mean $\pm$ SD)	60.73 $\pm$ 9.84	58.24 $\pm$ 12.12	0.404*
Upper arm circumference, cm (mean $\pm$ SD)	27.09 $\pm$ 3.60	27.22 $\pm$ 4.03	0.905*
Systolic blood pressure, mmHg, median (min–max)	117 (86–141)	110 (96–130)	0.091**
Diastolic blood pressure, mmHg (mean $\pm$ SD)	72.88 $\pm$ 8.62	72.52 $\pm$ 8.51	0.881*
Menstrual pattern at 60 months			
Had menstruation after implant insertion, n (%)			
Yes	31 (96.88)	23 (100)	1.000***
No	1 (3.12)	0 (0)	
Number of pads used during menstruation, n (%)			
≤ 3 pads/day	29 (93.54)	19 (82.60)	0.384***
> 3 pads/day	2 (6.46)	4 (17.40)	
Bleeding outside menstruation, n (%)			
Yes	1 (3.12)	0 (0)	1.000***
No	31 (96.88)	23 (100)	
Duration of bleeding outside menstruation, days, mean (n=1)	5.00		
Amount of bleeding outside menstruation, pads/day, mean (n=1)	1.00		
Number of sexual intercourse episodes, times/week (mean $\pm$ SD)	1.94 $\pm$ 0.72	1.83 $\pm$ 0.65	0.573**
Complaints after 60 months			
Any complaint, n (%)			
Yes	4 (12.50)	1 (4.35)	0.387***
No	28 (87.50)	22 (95.65)	
Dizziness/headache, n (%)			
Yes	0 (0)	1 (4.35)	0.418***
No	32 (100)	22 (95.65)	
Nausea/vomiting, n (%)			
Yes			
No	32 (100)	23 (100)	
Facial spots/acne, n (%)			
Yes			
No	32 (100)	23 (100)	
Weight change, n (%)			
Yes	2 (6.25)	1 (4.35)	1.000***
No	30 (93.75)	22 (95.65)	
Decreased sexual desire, n (%)			
Yes	1 (3.12)	1 (4.35)	
No	31 (96.88)	22 (95.65)	
Changes in menstrual pattern, n (%)			
Yes			
No	32 (100)	23 (100)	
Spotting, n (%)			
Yes	2 (6.25)	0 (0)	0.504***
No	30 (93.75)	23 (100)	
Visual disturbance, n (%)			
Yes			
No	32 (100)	23 (100)	
Total	32	23	55

Independent-samples t-test; ** Mann–Whitney U test; *** Fisher's exact test.

Table 3. Changes in Weight and Blood Pressure from 36 to 60 Months

Parameter	Sinoplant: 36 months	Sinoplant 60 months	<i>P-value*</i>	Indoplant 36 months	Indoplant: 60 months	<i>P-value*</i>
Weight, kg, median (min–max)	59 (41–82)	60.5 (41–84)	0.039	58 (35–81)	60 (35–80)	0.337
Weight change, kg (mean $\pm$ SD)		–3.14 $\pm$ 8.22			–1.15 $\pm$ 5.63	
between-group <i>p-value</i> [‡]				0.638		
Systolic blood pressure, mmHg, median (min–max)	110 (90–140)	117 (86–141)	0.258	110 (100–156)	110 (96–130)	0.936
Systolic blood pressure change, mmHg (mean $\pm$ SD)		–2.87 $\pm$ 14.80			0.87 $\pm$ 13.15	
between-group <i>p-value</i> [‡]				0.328		
Diastolic blood pressure, mmHg (mean $\pm$ SD)	75.16 $\pm$ 6.90	72.87 $\pm$ 8.62	0.165	77.22 $\pm$ 6.08	72.52 $\pm$ 8.51	0.023
Diastolic blood pressure change, mmHg, median (min–max)		0 (–21–21)			5 (–17–25)	
Between-group <i>p-value</i> [‡]				0.406		
Diastolic blood pressure, mmHg (mean $\pm$ SD)	75.16 $\pm$ 6.90	72.87 $\pm$ 8.62	0.165	77.22 $\pm$ 6.08	72.52 $\pm$ 8.51	0.023
Diastolic blood pressure change, mmHg, median (min–max)		0 (–21–21)			5 (–17–25)	
between-group <i>p-value</i> [‡]				0.406		

**Figure 1.** LNG level at 36 months, 48 months and 60 months**Table 4.** Serum Levonorgestrel Levels at 36, 48, and 60 Months of Continuous Implant Use

Duration (month)	Sinoplant, median (min–max), pg/mL	Indoplant, median (min–max), pg/mL	between-group <i>P-value*</i>
36	361.95 (245–2,650)	254.52 (110–425)	0.015
48	555.00 (235–900)	210.00 (118–830)	0.010
60	400.00 (170–790)	230.00 (87–640)	0.179
within-group <i>P-value</i> [†]	0.006	0.923	

Note: *Mann–Whitney U test; [†]Friedman test.

DISCUSSION

Three main mechanisms contribute to the contraceptive efficacy of subdermal implants: suppression of ovulation, thickening of cervical mucus, and induction of endometrial atrophy.^{4,5} Globally, two primary types of subdermal implants are available, containing either levonorgestrel (LNG) or etonogestrel (ENG). The minimum serum concentrations required to effectively prevent ovulation have been reported to be approximately 180 pg/mL for LNG and 90 pg/mL for ENG.^{2,6-8} This study compared serum LNG concentrations, safety, contraceptive effectiveness, and acceptability of Sinoplant and Indoplant implants over five years of continuous use.

A previous study conducted in China reported that Sino-implant (II), consisting of two flexible silicone rods containing 75 mg of LNG each, was approved for four years of use. Sino-implant (II) demonstrated high contraceptive effectiveness, with an estimated Pearl Index of less than 1% during the third, fourth, and fifth years of use among Chinese women of reproductive age.⁹ Its predecessor, Jadelle, consists of two rods, each containing 75 mg of LNG in a silicone elastomer matrix, and has received regulatory approval for five years of use. A previous study evaluated Jadelle for up to seven years of continuous use. However, serum LNG concentrations showed that approximately one-third of samples collected during the sixth and seventh years were below 180 pg/mL, suggesting that contraceptive protection beyond five years may be reduced, particularly among women with higher body weight.²

Regarding clinical safety and tolerability, only one participant in the Sinoplant group reported bleeding outside the menstrual period at the 60-month follow-up. The bleeding lasted five days and was reported to be low in volume, at approximately one pad per day. This low frequency of bleeding-related complaints in our cohort contrasts with findings from broader studies. For example, a 2016 study from New Zealand reported that women using Jadelle commonly experienced three disruptive bleeding patterns: irregular bleeding, amenorrhea, and prolonged bleeding. Approximately 18% of women requested early implant removal within the first year, with more than half citing severe dissatisfaction with bleeding irregularities as the primary reason.¹⁰ The relatively low frequency of bleeding complaints observed in the present

study should, however, be interpreted cautiously because of the small and highly selected follow-up population.

Weight changes between the third and fifth years after implant insertion differed between the two groups. The Sinoplant group showed a mean weight change of -3.14 ± 8.22 kg, with a statistically significant within-group difference ($p = 0.039$), whereas no significant change was observed in the Indoplant group ($p = 0.337$). However, the between-group comparison of weight change was not statistically significant ($p = 0.638$). These findings therefore do not provide evidence of a differential effect of the two implant types on body weight. Previous research from Nigeria reported greater weight gain among women using LNG implants than among those using ENG implants after 12 months of use.¹¹ Differences in study duration, population characteristics, and baseline factors may contribute to the variation between these findings.

At the end of the five-year observation period, all 55 participants who completed the follow-up had negative urine pregnancy test results, and no pregnancy was reported. Although these findings indicate excellent contraceptive effectiveness among the participants who completed follow-up, the 100% rate should be interpreted in the context of the small sample size and substantial attrition from the parent study. Previous studies have reported varying pregnancy rates with Jadelle. The Pearl Index increased from 0.2 in the fourth year to 0.9 in the fifth year of use.¹² Conversely, another study reported a Pearl Index of 0.4 during the first three years of Jadelle use, with no pregnancies observed during the final two years.^{13,14} In a study conducted in the United States, 199 women received Jadelle implants across multiple clinical sites and were followed for seven years with serial serum LNG measurements. Five pregnancies occurred during the study period, including two in the fifth year and three in the seventh year. All five women had serum LNG concentrations at or below 180 pg/mL at the time of conception. Moreover, the two pregnancies occurring during the fifth year were preceded by persistently low LNG concentrations during the three preceding assessments.²

Serum LNG concentrations in the present study showed variability over time. In the Sinoplant group, the median concentration increased from 361.95 pg/mL at 36 months to 555.00 pg/mL at 48 months before declining to

400.00 pg/mL at 60 months. In the Indoplant group, the median concentrations were 254.52, 210.00, and 230.00 pg/mL at 36, 48, and 60 months, respectively. The transient increase observed in the Sinoplant group at 48 months should be interpreted cautiously. Although drug release from subdermal silastic delivery systems is generally expected to decline over time, measured serum hormone concentrations may be influenced by interindividual pharmacokinetic variability and analytical variation.¹⁵ Therefore, the observed increase at 48 months does not necessarily indicate an increase in the actual LNG release rate from the implant.

Additional biological and analytical factors may contribute to variability in measured circulating LNG concentrations. Quantitative hormone measurements obtained over several years may be affected by differences in assay performance, calibration, reagent batches, and sample handling or storage.¹⁶ Furthermore, circulating LNG concentrations may vary according to individual pharmacokinetic characteristics, including protein binding, metabolism, and clearance. These factors may partly explain the variability observed between participants and across follow-up time points. Importantly, despite the observed variability, the median LNG concentrations in both groups at 60 months remained above the commonly cited 180 pg/mL threshold associated with suppression of ovulation.^{2,6-8}

These pharmacokinetic findings are broadly consistent with clinical evidence from previous studies, which reported cumulative pregnancy probabilities of approximately 0.9–1.06% through four years of implant use.^{13,17} In the present study, the median LNG concentrations at five years were 400 pg/mL in the Sinoplant group and 230 pg/mL in the Indoplant group, with no statistically significant difference between groups ($p = 0.179$). These findings suggest that both implants maintained measurable LNG exposure at five years and were associated with effective contraception among participants who completed follow-up. However, the present study was not designed or powered to establish pharmacokinetic or therapeutic equivalence between the two products.

Previous research comparing the *in vivo* LNG release rates of Sino-implant (II) and Jadelle in the Dominican Republic found that Sino-implant (II) released LNG at significantly lower rates than Jadelle.¹⁸ The LNG release rate of Sino-implant (II) through the third year was reported to be

comparable to that of Jadelle through the fifth year, supporting the three-year duration of action for which Sino-implant (II) was prequalified by the World Health Organization.¹⁸ For Jadelle, the LNG release rate is approximately 100 µg/day one month after insertion and decreases to approximately 40, 30, and 25 µg/day at the end of the first, third, and fifth years, respectively.¹² These differences in release kinetics highlight the importance of interpreting serum LNG concentrations alongside clinical outcomes and the approved duration of use of each implant.

STUDY LIMITATIONS

Several important limitations should be considered when interpreting the findings of this extension study. First, substantial participant attrition occurred between the baseline multicenter randomized controlled trial ($n = 540$) and the five-year follow-up cohort ($n = 58$ enrolled; $n = 55$ completed). This substantial reduction in sample size limited the statistical power to detect small but potentially clinically meaningful differences in pregnancy rates, adverse events, and other safety outcomes between the two implant groups.

Second, participation in the extension phase was voluntary, introducing the possibility of selection bias. Although the original randomized treatment allocation was retained among participants who entered the extension study, the characteristics of participants who remained in the study may differ from those who did not continue follow-up. Therefore, the findings may not be generalizable to the entire population enrolled in the parent trial.

Finally, several potentially relevant factors, including individual metabolic clearance, baseline body mass index, and socioeconomic characteristics, were not comprehensively evaluated or adjusted for in multivariable analyses because of the limited sample size. These factors may have influenced body weight changes, serum LNG concentrations, and other clinical outcomes.

CONCLUSION

This five-year follow-up study provides preliminary clinical and pharmacokinetic evidence that both Sinoplant and Indoplant maintained contraceptive effectiveness and acceptable safety profiles among participants who completed follow-up. At 60 months, no pregnancies were

reported, and median serum LNG concentrations remained above the commonly cited threshold associated with suppression of ovulation. No significant between-group difference in LNG concentration was observed at five years.

However, these findings should be interpreted cautiously because of the small follow-up sample, substantial attrition from the parent randomized trial, and potential selection bias associated with voluntary participation in the extension study. Therefore, the results should not be considered sufficient evidence to support changes in the recommended duration of implant use. Larger, adequately powered prospective studies with longer follow-up are warranted to confirm the long-term contraceptive effectiveness, safety, and pharmacokinetic profiles of Sinoplant and Indoplant before any changes to national family planning recommendations or regulatory guidance are considered.

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CONFLICT of INTEREST

The authors declare that they have no competing financial or personal interests that could inappropriately influence the performance or reporting of this research. The study sponsor, PT. Catur Dakwah Crane Farmasi, provided funding and supplied the Sinoplant implants evaluated in this trial. The sponsor had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the article for publication.

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