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Effectiveness, safety and acceptability of Sino-implant (II) during the first year of use: results from Kenya and Pakistan☆,☆☆,★

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Abstract

Background: Sino-implant (II) is a two-rod subcutaneous contraceptive implant used up to 4 years, containing 150 mg of levonorgestrel. We conducted two observational studies of Sino-implant (II) to evaluate its performance in routine service delivery settings.
Methods: We enrolled 1326 women age 18–44 who had Sino-implant (II) inserted at clinics in Pakistan and Kenya. Women were followed-up using either an active or passive follow-up scheme in each study. Study outcomes were: one-year cumulative pregnancy and discontinuation rates; rates of insertion and removal complications; adverse event and side effect rates; reasons for discontinuation; and implant acceptability and satisfaction with clinic services.
Results: A total of 754 women returned for at least one follow-up visit. The overall Pearl pregnancy rate was 0.4 per 100 woman-years [95% confidence interval (CI) 0.1, 0.9] resulting from 1 confirmed post-insertion pregnancy in Kenya and 4 in Pakistan. Country-specific Pearl rates were 0.2 (95% CI 0.0, 0.9) in Kenya and 0.6 (95% CI 0.2, 1.6) in Pakistan. The total cumulative 12-month probability of removal was 7.6% (95% CI 6.1, 9.1), with country-specific removal probabilities of 3.7% in Kenya (95% CI 2.1, 5.3) and 10.8% in Pakistan (95% CI 8.5, 13.2). Four serious adverse events occurred in Kenya and none occurred in Pakistan; one SAE (an ectopic pregnancy) was possibly related to Sino-implant (II). Most women in both countries said they would recommend the implant to others.
Conclusion: The results from these studies reveal high effectiveness and favorable safety and acceptability during the first year of use of Sino-implant.
Implication: The favorable Sino-implant (II) findings from Kenya and Pakistan provide further evidence from disparate regions that Sino-implant (II) is safe, effective and acceptable during routine service delivery.

Keywords: Acceptability; Safety; Effectiveness; Implant

1. Introduction

Sino-implant (II) is a two-rod subcutaneous contraceptive implant used for up to 4 years, containing 150 mg of levonorgestrel and manufactured by Shanghai Dahua Pharmaceutical. It is currently registered in 25 countries with registration efforts underway in several others. The implant is sold under several trade names including Zarin, Femplant, Trust and Simplant.

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A systematic review of four randomized trials of Sino-implant (II), all conducted in China, showed first-year pregnancy probabilities ranged between 0 and 0.1% and 4-year cumulative pregnancy probabilities were 1% [1]. These findings were followed by a recent study conducted in Madagascar which had a one-year pregnancy rate of 0 and a cumulative one-year discontinuation probability of 7.6% [2], providing further evidence of the method's effectiveness, safety and acceptability outside Asia. In tandem with the study in Madagascar, we conducted two observational studies of Sino-implant (II) in Kenya and Pakistan to generate more data on the clinical performance of the method outside of China as well as in various service delivery settings.

2. Materials and methods

2.1. Study design

We conducted two prospective observational studies under separate but similar protocols between July 2011 and February 2013 in Kenya and Pakistan, countries where Sino-implant (II) has been registered since 2008 and 2010, respectively. One study was conducted at three public clinics on the periphery of Nairobi, Kenya; the other study was conducted in clinics in two provinces of Pakistan (Sindh and Punjab) including six government clinics from the Population Welfare Department in Sindh and 13 Marie Stopes Society (MSS) clinics in both provinces. The protocols were approved by the FHI 360 Protection of Human Subjects Committee and the respective in-country IRBs: that of the Kenya Medical Research Institute and the National Bioethics Committee in Pakistan.

The goal of these studies was to evaluate effectiveness, safety and acceptability of Sino-implant (II) during the first year of use. Study outcomes were one-year cumulative pregnancy and discontinuation rates; rates of insertion and removal complications; side effects; serious adverse events; reasons for discontinuation; implant acceptability and satisfaction with clinic services.

In each study we planned to enroll approximately 600 women aged 18–44 who chose to use Sino-implant (II) and who met clinic eligibility criteria for the method. Prior to study enrollment, participants were provided study details and signed an informed consent, underwent pregnancy screening via a pregnancy checklist, and had implants inserted by trained nurses in Kenya and physicians in Pakistan. Due to budgetary constraints, the studies scheduled active follow-up of half of the participants, while the other half were assigned to a passive surveillance cohort with no scheduled follow-up visits. In Kenya, individual participants were randomly assigned to the active or the passive cohort. In Pakistan, clinics were randomly assigned to conduct active or passive follow-up, stratified by type of clinic (government or MSS) and client volume to achieve rough balance in participant numbers. In both countries, participants in the active cohort were asked to return for 3- and 12-month follow-up visits, while women in the passive cohort were asked to return only if they suspected pregnancy, had medical problems or implant complications, or decided to remove the implant.

2.2. Study settings

Though we did not collect data on religion, the majority of Kenyans near the Nairobi clinics are Christian Kikuyu. Two of the clinics were peri-urban while the third was located in a more rural area. All three clinics offered a choice of free long-acting contraceptive methods including Sino-implant (II), Jadelle and IUCDs.

Nearly all women in Pakistan are Muslim and we presume that our study participants were predominantly Muslim from urban or peri-urban areas. The government clinics involved in this study provided a full range of contraceptive methods gratis. The MSS study clinics provided Sino-implant (II) free to study participants, but charged a nominal fee for other methods.

2.3. Data collection

After obtaining written informed consent, trained study staff comprising nurses, research assistants and counselors confirmed study eligibility, collected demographic information and contraceptive and medical histories, and recorded information about implant insertion based on clinic notes and participant responses. At each follow-up visit, study staff measured weight and blood pressure and collected self-reported information on pregnancy, side effects, continuation status, and acceptability. Nurses removed implants when requested and recorded reasons for removal and removal complications. At 12-month visits or whenever indicated, urine pregnancy tests were performed.

Data were captured on paper forms during in-person visits or telephone interviews. The sites double-entered data in EpiData 3.1.

2.4. Statistical analyses

We estimated that enrolling 300 women in the active cohort for each study, with loss to follow-up at 12 months less than 20% and the true 12-month cumulative probability of pregnancy no more than 1%, would provide 90% chance of ruling out a 4.5% pregnancy probability (i.e. obtaining an upper 95% confidence bound of less than 4.5%) and obtaining an estimated one-year pregnancy probability of less than 2% [1]. We calculated Pearl pregnancy rates (number of confirmed post-insertion pregnancies divided by the total woman-years of observation). We used life table methods to calculate the cumulative probability of implant removal. Women in the active cohort were censored at the time of implant removal or the time of their last clinic visit, whichever was first; women in the passive cohort were censored 12-months post-insertion or earlier if they returned spontaneously to remove an implant. Women who did not have any clinical indication of pregnancy were considered not pregnant through the time of their last clinic visit for the active cohort; or through the 12-month follow-up period if not censored earlier for the passive cohort.

Although only half the women were scheduled for follow-up, a number of women in the passive cohort returned for one or more clinic visits. We present the combined effectiveness, safety and acceptability data for all study participants regardless of cohort. We consider this combined analysis our primary analysis utilizing the most complete set of data. However, we conducted sensitivity analyses to check the robustness of the findings. First, to eliminate any unmeasured source of bias when presenting the combined cohort data, we present the Pearl rate and the removal probability for the active cohorts only. Second, we censored women at the date of pregnancy, implant removal, or last study visit, which would remove person-time from the denominator from unobserved women in the passive cohort.

Many of the questionnaire items were asked at multiple follow-up visits (side effects, acceptability items), so we refer to those responses as "ever" reported.

3. Results

We enrolled 1326 women (Fig. 1) between the two studies, with 602 in Kenya (300 active cohort; 302 passive cohort) and 724 in Pakistan (392 active cohort; 332 passive cohort). The mean age of enrolled women was 28 in both studies (Table 1). The mean weight of study participants was 62 kg in Kenya and 54 kg in Pakistan. All enrolled women in Pakistan and most in Kenya were married. Ninety-one percent of women in Pakistan and 41% in Kenya were

Enrolled: N

	Pakistan	Kenya	Total
Active	392	300	692
Passive	332	302	634
Total	724	602	1,326

Returned for 1+ follow-up visit: N

	Pakistan	Kenya	Total
Active	392	297	689
Passive	51	14	65
Total	443	311	754

	Pakistan	Kenya	Total
End of study status[1]: N (%)			
Pregnant [2,3]	4 (1.0)	1 (0.3)	5 (0.7)
Implant removal [2]	74 (17.6)	22 (7.1)	96 (13.4)
Early study discontinuation for non-removal reason	0 (0.0)	1 (0.3)	1 (0.1)
Completed 12 months of follow-up, continuing implant [3]	333 (79.3)	253 (82.1)	586 (80.5)
Lost to follow-up [4]	9 (2.1)	31 (10.1)	40 (5.5)
Total	420	308	728

[1] *No end of study status assigned to women in the passive cohort unless they were pregnant or had implant removal.*
[2] *In Kenya, 23 women had implant removed. One participant was also pregnant at removal; pregnancy is considered her final status. In Pakistan, 77 women had implants removed. Three of these participants were also pregnant; pregnancy is considered their final status.*
[3] *This includes women in both active and passive cohorts.*
[4] *Only women in the active cohort could be lost to follow-up.*

Fig. 1. Participant Flow Diagram.

Table 1
Select sociodemographic, obstetric and contraceptive characteristics of participants

	Pakistan (N=724)	Kenya (N=602)	Total (N=1326)
	n (%)	n (%)	n (%)
Age (years)			
18–24	133 (18.4)	201 (33.4)	334 (25.2)
25–29	261 (36.0)	177 (29.4)	438 (33.0)
30–34	217 (30.0)	135 (22.4)	352 (26.5)
>34	113 (15.6)	89 (14.8)	202 (15.3)
Mean (SD)	28.6 (4.8)	28.0 (5.8)	28.3 (5.3)
Median (range)	28 (18 to 41)	27 (18 to 44)	28 (18 to 44)
Marital status			
Single	0 (0.0)	40 (6.6)	40 (3.0)
Married/living in couple	724 (100)	531 (88.2)	1255 (94.6)
Widowed/divorced/separated	0 (0.0)	31 (5.1)	31 (2.4)
Education level			
Did not complete primary	318 (43.9)	47 (7.8)	365 (27.5)
Completed primary	172 (23.8)	357 (59.3)	529 (39.9)
Completed secondary/vocational/technical/higher	234 (32.3)	198 (32.9)	432 (32.6)
Occupation			
Unemployed/housewife	656 (90.6)	247 (41.0)	903 (68.1)
Employed outside the home	68 (9.5)	355 (59.0)	423 (31.9)
Gravidity			
Mean (SD)	4.3 (2.3)	2.5 (1.3)	3.5 (2.1)
Median (range)	4 (1 to 20)	2 (0 to 8)	3 (0 to 20)
Parity			
Mean (SD)	3.7 (2.0)	2.4 (1.2)	3.1 (1.8)
Median (range)	3 (0 to 20)	2 (1 to 8)	3 (0 to 20)
Contraceptive method prior to study			
None	445 (61.5)	112 (18.6)	557 (42.0)
Oral	43 (5.9)	228 (37.9)	271 (20.4)
Condom	108 (14.9)	14 (2.3)	122 (9.2)
Injectable	79 (10.9)	151 (25.1)	230 (17.3)
IUCD	23 (3.2)	2 (0.3)	25 (1.9)
Implant	0 (0.0)	20 (3.3)	20 (1.5)
Other	26 (3.6)	75 (12.5)	101 (7.6)

unemployed/housewives. One third of women in both countries had completed secondary school or higher.

Among the Kenyan cohort, oral contraceptive pills were the most common family planning method recently used at enrollment (38%) followed by injectables (25%). In Pakistan, most (62%) women reported currently using no contraceptive method at baseline (Table 1). In Kenya, the median number of previous pregnancies and births were both 2, while the number was higher in Pakistan with a median gravidity of 4 and median parity of 3.

Reports of satisfaction with clinic services and the implant insertion procedures were very high in both studies with nearly all women reporting an overall satisfactory experience at enrollment. One insertion complication was reported in Kenya and 7 were reported in Pakistan, mostly involving pain during the procedure.

3.1. Primary analysis

Between the active and passive cohorts, 754 women returned for at least one follow-up visit (311 in Kenya and 443 in Pakistan; Fig. 1). Of women in the active cohorts, 31/300 in Kenya (10%) and 9/392 in Pakistan (2%) were lost to follow-up. The overall Pearl rate was 0.4 per 100 woman-years (95% confidence interval [CI] 0.1, 0.9) resulting from 1 post-insertion pregnancy in Kenya and 4 in Pakistan. Country-specific Pearl rates were 0.2 (95% CI 0.0, 0.9) in Kenya and 0.6 (95% CI 0.2, 1.6) in Pakistan. No serious adverse events (SAEs) occurred in Pakistan and 4 occurred in Kenya; one of these SAEs (an ectopic pregnancy) was possibly related to Sino-implant (II).

Twenty-three Kenyan women and 77 Pakistani women had implants removed, making the total 12-month cumulative probability of removal 7.6% (95% CI 6.1, 9.1), with country-specific removal probabilities of 3.7% in Kenya (95% CI 2.1, 5.3) and 10.8% in Pakistan (95% CI 8.5, 13.2). Two removal complications (pain) were reported, both in Pakistan. Most of the women who removed implants did so for vaginal bleeding abnormalities and a variety of other medical and personal reasons (Table 2). The most common side effect reported in both countries was headache (6.1% in Kenya and 36.6% in Pakistan; Table 2). Other side effects included mood changes (1.0% in Kenya and 18.1% in

Table 2
Side effects and removal reasons reported during follow-up

	Pakistan	Kenya	Total
	n (%)	n (%)	n (%)
Ever noticed physical or mental health changes since implant insertion[a,b]			
None[c]	-	250 (80.4)	250 (33.2)
Headaches	162 (36.6)	19 (6.1)	181 (24.0)
Weight gain	52 (11.7)	12 (3.9)	64 (8.5)
Weight loss	2 (0.5)	12 (3.9)	14 (1.9)
Hair loss[c]	34 (7.7)	-	34 (4.5)
Acne	16 (3.6)	3 (1.0)	19 (2.5)
Mood changes	80 (18.1)	3 (1.0)	83 (11.0)
Arm pain or numbness	12 (2.7)	5 (1.6)	17 (2.3)
Other	89 (20.1)	16 (5.1)	105 (13.9)
Total women with 1 or more follow-up visits	443	311	754
Why did you have implant removed[a,d]			
Irregular, prolonged or heavy bleeding	27 (35.1)	5 (21.7)	32 (32.0)
Became pregnant[e]	3 (3.9)	3 (13.0)	6 (6.0)
Spontaneous expulsion	2 (2.6)	3 (13.0)	5 (5.0)
Other medical reason	28 (36.4)	8 (34.8)	36 (36.0)
Family opposition	10 (13.0)	2 (8.7)	12 (12.0)
Wanted to get pregnant	8 (10.4)	4 (17.4)	12 (12.0)
Other personal reasons	1 (1.3)	2 (8.7)	3 (3.0)
Total women with implant removal	77	23	100

[a] More than one response possible.
[b] The denominator includes all women who returned for at least 1 follow-up visit.
[c] "None" was not a response choice in Pakistan. "Hair loss" was not a response choice in Kenya.
[d] The denominator includes all women who reported implant removal during follow-up.
[e] In Kenya, two women who had implants removed were pregnant before implant insertion. Therefore, these two women are not included in the pregnancy analysis.

Pakistan), weight gain (3.9% Kenya and 11.7% Pakistan), and hair loss (7.7% Pakistan only).

Bleeding patterns were generally acceptable with 290/311 (93%) Kenyan participants and 325/443 (73%) Pakistani participants ever reporting acceptable bleeding patterns during follow-up. Of the 311 Kenyan women who reported their experience with the implant, 137 (94%) ever reported having a very favorable experience with the implant during follow-up (Table 3). The rate was somewhat lower in Pakistan with 31% of women ever reporting very favorable experience and 75% ever reporting a somewhat favorable experience. In Kenya, 9 out of 10 women ever reported that there was nothing they disliked about the implant, whereas in Pakistan less than half the women reported disliking nothing about the implant. In both studies, the most common dislike ever reported was menstrual changes (18% in Kenya and 67% in Pakistan). In Kenya, almost all women said they would definitely recommend the implant to a friend whereas in Pakistan the number was slightly less with four fifths of women reporting that they would definitely recommend it to a friend.

3.2. Sensitivity analyses

When considering the active cohorts only, four pregnancies occurred in the active cohort, all in Pakistan. The two-country combined Pearl rate for women in the active cohort was 0.6 (95% CI 0.2, 1.6). The country-specific Pearl rates in the active cohorts were as follows: Kenya 0.0 (95% CI 0.0, 1.3) and Pakistan 1.2 (95% CI 0.3, 3.0).

Again considering only women in the active cohorts, 21 of 300 Kenyan women and 49 of 392 Pakistani women had implants removed, making the total 12-month cumulative probability of removal 10.7% (95% CI 8.2, 13.1%), with country-specific removal probabilities of 7.1% in Kenya (95% CI 4.1, 10.2%) and 13.4% in Pakistan (95% CI 9.6, 17.3%).

When we used an alternative analysis approach and removed the contribution of person-time from women in the passive cohort who did not return for any follow up visits, the combined (both countries, both cohorts) Pearl rate was 0.8 (95% CI 0.3, 1.9), about double our primary estimate.

4. Discussion

Until now, the vast majority of data on Sino-implant (II) comes from China [1]. As Sino-implant (II) becomes available in additional countries, gathering broader data on its effectiveness, safety and acceptability is imperative. These studies from Kenya and Pakistan showed that the Sino-implant (II) was safe and effective as delivered through routine health services during the first year of use, with 12-month pregnancy rates below 1% in both countries. Self-reported acceptability as well as continuation rates in both countries were generally high, though notably higher in

Table 3
Self-reported implant acceptability by women who returned for at least 1 follow-up Visit

	Pakistan (N=443) (%)	Kenya (N=311) (%)	Total (N=754) (%)
Overall experience with implant[a]			
Very favourable	137 (30.9)	292 (93.9)	429 (56.9)
Somewhat favourable	331 (74.7)	32 (10.3)	363 (48.1)
Indifferent	95 (21.4)	1 (0.3)	96 (12.7)
Somewhat unfavourable	20 (4.5)	14 (4.5)	34 (4.5)
Very unfavourable	10 (2.3)	4 (1.3)	14 (1.9)
Disliked about implant[a]			
Menstrual changes	298 (67.3)	55 (17.7)	353 (46.8)
Other side effects	27 (6.1)	14 (4.5)	41 (5.4)
Appearance	3 (0.7)	0 (0.0)	3 (0.4)
Way it feels	46 (10.4)	7 (2.3)	53 (7.0)
Insertion procedure	4 (0.9)	0 (0.0)	4 (0.5)
Nothing	200 (45.1)	281 (90.4)	481 (63.8)
Other	23 (5.2)	12 (3.9)	35 (4.6)
Liked about implant[a]			
Lasts for 4 years	338 (76.3)	144 (46.3)	482 (63.9)
Easy to use	99 (22.3)	203 (65.3)	302 (40.1)
Low risk for pregnancy	49 (11.1)	89 (28.6)	138 (18.3)
Few side effects	25 (5.6)	165 (53.1)	190 (25.2)
Nothing	28 (6.3)	7 (2.3)	35 (4.6)
Other	1 (0.2)	13 (4.2)	14 (1.9)
Would recommend implant method to a friend[a]			
Definitely not	27 (6.1)	1 (0.3)	28 (3.7)
Probably not	19 (4.3)	1 (0.3)	20 (2.7)
Probably yes	174 (39.3)	19 (6.1)	193 (25.6)
Definitely yes	364 (82.2)	300 (96.5)	664 (88.1)

[a] More than one response possible. Responses were captured across visits.

Kenya than Pakistan. However, the one-year continuation rate observed in Pakistan was similar to the one-year Norplant continuation rate in a previous study in Pakistan [3] and also similar to the overall one-year continuation rate found during clinical trials of Jadelle conducted in several countries [4]. Furthermore, data from other hormonal implant studies indicate that women in Pakistan typically have lower 1-year continuation rates than other countries studied [3,5,6].

The sole pregnancy observed in Kenya was ectopic reported 14 months after implant insertion, with an uncertain estimated date of conception. We included four post-insertion pregnancies from Pakistan in our Pearl rate calculations. This group included two pregnancies that may have pre-dated enrollment or occurred as a result of the women not using a back-up contraceptive method immediately after implant insertion, despite having menstruation more than 7 days before insertion.

A major strength of both studies was the very high retention rate for participants in the active follow-up cohorts, yielding substantial person-years of observation. Also, by collecting data from two countries with differing clientele, we captured country-specific response patterns in regards to perceived side effects and acceptability of the method. The higher rates of reported side effects in Pakistan, lower acceptability of bleeding patterns, and higher removal rates there may be influenced by an array of cultural, religious, or economic factors that were not explored in our studies. Prior contraceptive experience may have played a role in women's attitudes towards the implant. In Kenya, a large portion of women who enrolled in the study had recently used a hormonal contraceptive method. In contrast, most women in Pakistan had not been using a hormonal method prior to enrollment, potentially magnifying the impact of bleeding disturbances and other side effects associated with the hormonal contraceptive methods.

Inherent in our studies were two design limitations. First and foremost, only half of study participants were actively followed through 12 months, as women in the passive group only returned at their own prompting. This financially-driven feature had multiple ramifications. We were unable to assign an end-of-study status to most women in the passive cohorts. Since women had other options for care in these areas, and those unhappy with the method could have attended other clinics, we probably missed side effects and removals. Most importantly, we may have missed an unknowable number of pregnancies. Using a more conservative estimate of the follow-up time contributed by women in the passive cohorts, the estimate of the pregnancy rate about doubled. Further restricting the analysis to women in the active follow-up cohort only yielded a Pearl rate that was intermediate. The upper bound of the 95% CIs in our primary and sensitivity

analyses were consistently below 2%. These analyses provide evidence of high effectiveness.

The second main limitation is the one-year follow-up period. Sino-implant (II) is approved for four years of use, and our study outcomes should be measured over that entire interval. Still, the favorable findings from both countries provide further evidence from disparate regions that Sino-implant (II) is safe, effective and acceptable during routine service delivery. Further research studies should incorporate active follow-up of all participants in order to provide more precise and accurate pregnancy and continuation estimates.

Longer follow-up of Sino-implant (II) users should also be done to collect effectiveness, safety and acceptability data over the full 4-year period of use to inform policy makers and providers about the potential programmatic value of Sino Implant (II).

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