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Sino-implant (II) - a levonorgestrel-releasing two-rod implant: systematic review of the randomized controlled trials

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Abstract

Background—Sino-implant (II) is a subdermal contraceptive implant manufactured in China. This two-rod levonorgestrel-releasing implant has the same amount of active ingredient (150 mg levonorgestrel) and mechanism of action as the widely available contraceptive implant Jadelle. We examined randomized controlled trials of Sino-implant (II) for effectiveness and side effects.

Study design—We searched electronic databases for studies of Sino-implant (II), and then restricted our review to randomized controlled trials. The primary outcome of this review was pregnancy.

Results—Four randomized trials with a total of 15,943 women assigned to Sino-implant (II) had first-year probabilities of pregnancy ranging from 0.0% to 0.1%. Cumulative probabilities of pregnancy during the four years of the product's approved duration of use were 0.9% and 1.06% in the two trials that presented date for four-year use. Five-year cumulative probabilities of pregnancy ranged from 0.7% to 2.1%. In one trial, the cumulative probability of pregnancy more than doubled during the fifth year (from 0.9% to 2.1%), which may be why the implant is approved for four years of use in China. Five-year cumulative probabilities of discontinuation due to menstrual problems ranged from 12.5% to 15.5% for Sino-implant (II).

Conclusions—Sino-implant (II) is one of the most effective contraceptives available today. These available clinical data, combined with independent laboratory testing, and the knowledge that 7 million women have used this method since 1994, support the safety and effectiveness of Sino-implant (II). The lower cost of Sino-implant (II) compared with other subdermal implants could improve access to implants in resource-constrained settings.

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Staff members from Family Health International contributed to this work. H. Meng searched WEIPU, reviewed the initial results, and summarized the abstracts in English. C. Manion searched MEDLINE, POPLINE, EMBASE, and LILACS.

Keywords

levonorgestrel-releasing implant; Norplant; Sino-implant (II); Jadelle; systematic review

1. Introduction

Contraceptive implants were introduced more than 25 years ago with the promise of offering women a highly effective and "forgettable" [1] contraceptive method requiring a minimal amount of effort from the user and provider once inserted. The relatively high initial cost of implants has limited their widespread use in resource-constrained settings [2]. The recent decrease of the public-sector unit cost for Jadelle and Implanon to approximately US$23 and US$20, respectively [3], has resulted in increased distribution. In the past three years, procurements by international donor agencies have more than tripled (221,570 units in 2006 to 788,329 in 2008) [3]. The lower cost Sino-implant (II) (i.e., approximately US$8) should be more widely available in the next few years as an increasing number of national drug regulatory authorities are expected to approve the product, helping to meet the worldwide demand that is currently depleting implant stocks.

Sino-implant (II) is a two-rod contraceptive implant with the same amount of active ingredient as Jadelle (75 mg levonorgestrel per rod; 150 mg total). The main difference between Sino-implant (II) and Jadelle is the current indicated duration of product use (i.e., four years vs. five years, respectively). The manufacturing technology was acquired by Shanghai Dahua Pharmaceutical Co, Ltd. (Dahua) in 1991 and the product specifications have since remained unchanged. Dahua received regulatory approval in China in 1994 and Indonesia in 2002, and has sold over 7 million units to date. Sino-implant (II), including a disposable trocar with a CE Mark (Steiner, submitted), costs about 60% less than Jadelle [3].

With one exception [4], the clinical trials evaluating Sino-implant (II) have been published in Chinese, preventing the data from being readily accessible to English-language readers. This systematic review examines these clinical studies of Sino-implant (II), including those in Chinese, for effectiveness and side effects.

2. Methods

We searched for all published and unpublished studies of Sino-implant (II) with pregnancy as an outcome. Comparative and non-comparative studies were gathered, although we then focused on randomized controlled trials (RCT). We did not use any language restriction. Trials had to have at least one year of Sino-implant (II) use and to have reported our primary outcome of pregnancy. Secondary outcomes evaluated were discontinuation rates due to menstrual-related side effects and total continuation rates.

We searched for studies of Sino-implant (II) in the following databases: WEIPU (Chinese journals), MEDLINE via PubMed, POPLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL). Search details are available upon request. Search strategies included terms such as (norplant OR jadelle OR sino-implant OR "Sino implant" OR "Chinese implant" OR domestic implant) AND (contracept*). We also examined the reference lists of relevant articles. In addition, we contacted experts in the field for information about any published or unpublished trials not discovered in our search.

We assessed for inclusion all titles and abstracts identified during the literature searches. For the English language searches, one author (LML) reviewed the results to identify reports for inclusion or exclusion. A second author (DAG) examined the reports identified for appropriate categorization. Discrepancies were resolved by discussion. For the Chinese

database, a research assistant reviewed the searches and identified potential studies from the abstracts. The research assistant, bilingual in Chinese and English, summarized the studies in English. The first two authors reviewed the English summaries and identified the reports to be translated. One paper that met the search criteria was published in English [4] while the remainder were translated by a third-party translation company. One author (LML) abstracted the data presented in the published papers and entered the information into tables. Another author (DAG) conducted a second data abstraction and verified correct data entry. Any discrepancies were resolved by discussion or by a third author (MJS). Studies were examined for methodological quality, according to recommended principles [5]. Factors considered were study design, loss to follow-up, and early discontinuation. We also examined the methods used for assessing the outcomes. Due to language limitations and the age of some reports, we did not attempt to contact authors for missing data or further design details.

Life-table probabilities are presented as reported in the articles. These include probabilities of discontinuation due to pregnancy and due to menstrual problems. Reported p values are included.

3. Results

We found 14 published papers of 15 studies (one report summarized two studies) that reported pregnancies for Sino-implant (II) [4, 6-18]. Ten studies were non-randomized and were thus excluded from this systematic review of RCTs. Four papers included five trials that were described as RCTs [4, 6-8]. Details of study design of these RCTs were limited. Double-blinding would not have been possible due to implants having either two rods or six capsules. Implant comparisons included Norplant and similar six-capsule implants made in China, referred to in the reports as No. I, type I, or CLa. These ‘China 6-capsule’ implants are no longer commercially available. These papers referred to randomization, but did not provide information on how the randomization sequence was generated or on allocation concealment (Table 1). These were all multi-site studies ranging from 10 [6] to 100 centers [4] enrolling participants between 1993 and 1995. One of these four papers also included a Phase I trial with three arms of 100 women each [7]; only one pregnancy was reported for Sino-implant (II) over five years and we excluded this small Phase I trial from the further detailed analysis.

The four large trials had 32,613 participants including 15,943 users of Sino-implant (II) (Table 2). No study had information on how pregnancies were assessed. One used menstrual diaries to capture bleeding data [7]. Follow-up was reportedly 92% to 99%. One trial had two years of follow-up [4], while the others each had five years [6-8].

First-year pregnancy probabilities for Sino-implant (II) ranged from 0.0 to 0.1 per 100 women among the three trials that reported data for the first year (Table 2). Cumulative probabilities of pregnancy during the four years of the product's approved duration of use were 0.9% and 1.06% for the two trials presenting data at this interval. Five-year cumulative probabilities of pregnancy ranged from 0.7% to 2.1% among the three trials presenting data for Year 5. In two trials, the probability of pregnancy for Sino-implant (II) was significantly higher than the comparison China 6-capsule implant at Year 5 [7, 8], but the absolute differences were relatively small. The largest difference was between 2.1% for Sino-implant (II) and 0.2% for China 6-capsule ($p<0.005$) [7]. The second trial had five-year cumulative probabilities of 1.57% and 0.26%, respectively ($p<0.001$) [8]. The third trial presenting data at Year 5 compared Sino-implant (II) to the China 6-capsule implant as well as Norplant and no significant differences were observed ($p>0.05$) [6].

Menstrual disorders represented the major side effects for these implants. Cumulative five-year probabilities of discontinuation due to menstrual problems for Sino-implant (II) ranged from 12.5 to 15.5 per 100 women (Table 3). For the other implants, five-year probabilities were 14.6 for Norplant and 13.2 to 19.97 for the China 6-capsule per 100 women. Two trials reported Sino-implant (II) to have significantly lower probabilities than the comparison implants [4, 8], while the other two trials showed the study groups to be similar [6, 7].

Cumulative five-year probabilities of continuation ranged from 68 to 82 per 100 women for Sino-implant (II) in the three trials presenting data at Year 5 and were similar to those for other implants. The five-year probabilities were 74% to 84% for the China 6-capsule and 75% for Norplant. The large two-year trial comparing Sino-implant (II) to the China 6-capsule showed almost no difference between the two (90% and 89%, respectively).

4. Discussion

Sino-implant (II) is one of the most effective contraceptive methods available, with pregnancy rates similar to other contraceptive implants (i.e., Jadelle, Implanon and Norplant). These other implants, along with IUDs, female sterilization and vasectomy, are considered “very effective” (i.e., the highest category of effectiveness) with annual pregnancy rates between 0.0% and 0.9% [19]. Methods like oral contraceptive pills and depot medroxyprogesterone acetate, which are user-dependent, are considered “effective” with annual pregnancy rates from 1% to 9% [19]. Four randomized trials with a total of 15,943 women assigned to Sino-implant (II) had first-year probabilities of pregnancy ranging from 0.0% to 0.1%. The five-year cumulative probabilities of pregnancy from these trials ranged from 0.7% to 2.1%. In some of these large trials, Sino-implant (II) had significantly higher pregnancy rates or significantly lower bleeding rates than the comparison group, but these small differences are unlikely to be clinically important (i.e., the trials were so large as to be able to detect as statistically significant differences that are clinically meaningless). Consistent with the low pregnancy rates in these four randomized trials, the observational studies we examined with a total of 6,564 participants had low rates as well. Of the six non-randomized studies of Sino-implant (II) that reported probabilities of pregnancy (as opposed to simple counts of pregnancies), the probabilities in five studies ranged from 0.0% (Year 6) to 0.64% (Year 7) [10, 13, 16, 18, 20], while the remaining study was 1.2% at Year 4 [9]. Similarly, a large post-marketing surveillance of 7,977 Norplant users conducted in eight countries, including 3,023 Chinese participants, had a 5-year cumulative probability of pregnancy of 1.5% [21].

A chief limitation of the four randomized trials reviewed was the limited description of research methods. Even the most recent randomized trial published in 2004 [6] did not meet the standards of the CONSORT guidelines [22], a common problem in leading Chinese medical journals [23]. Poor implementation of appropriate randomization in Chinese trials is well documented [24]. However, with so few pregnancies across study arms and such high follow-up rates, bias introduced by potentially flawed randomization is unlikely to have accounted for the low pregnancy rates for Sino-implant (II). We also have confirmation that at least two studies [4, 9] adapted a WHO sponsored post-marketing surveillance protocol [19], and three of the four randomized trials [4, 6, 7] included centers or investigators that participated in this WHO trial (Personal communications - H Meng with Dr. Du and Dr. Fang; February 17, 2009). Although this technical assistance from WHO does not guarantee improvements in study design and implementation, this type of collaboration has resulted in gradual improvements [25].

Major strengths of the evidence reviewed include: 1) large number of studies; 2) multi-site studies with up to 100 sites per trial; 3) large study sizes; 4) consistent results across studies;

and 5) low loss to follow-up. Scientific fraud influencing the results is unlikely because it would have had to be systematic involving hundreds of investigators, many of whom were involved in WHO-sponsored research. Despite concerns regarding design, implementation, and reporting, the large body of clinical evidence consistently indicates that Sino-implant (II) is highly effective.

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Table 1

Summary of study characteristics

Study	Study design	Study initiation	Study N	Implant(s)	Follow-up (years)	Methodological quality issues
Fan et al. [6]	Randomized trial	Recruited: 1993	2,999	Sino-implant (II) vs China 6-capsule vs Norplant	5	'Randomized prospective' study. No information on sequence generation or allocation concealment. Follow-up was >99%.
Fang et al. [4]	Randomized trial	Recruited: Nov 93 to Jan 95	19,673	Sino-implant (II) vs China 6-capsule	2	Participants were 'randomly allocated.' No information on sequence generation or allocation concealment. Follow-up was 94%.
Qi et al. [7]	Randomized trials (Phase I and II)	Dec 1993 to Jan 1995	2,300	Sino-implant (II) vs China 6-capsule vs Norplant (Phase I only)	5	Participants 'randomly enrolled.' No information on sequence generation or allocation concealment. Follow-up >99%. Two cases excluded for non-compliance.
Xing et al. [8]	Randomized trial	Nov 1993 to Jan 1995	7,941	Sino-implant (II) vs China 6-capsule	5	Eligible persons 'randomized into groups of the study.' No information on sequence generation or allocation concealment. Follow-up was 92%.

Table 2

Cumulative probability of discontinuation due to pregnancy (per 100 women)

Study	Implant	Study N	Body weight (kg)[a]	Age (years)[a]	Year 1	Year 2	Year 3	Year 4	Year 5	Reported P value
Fan et al. [6]	Sino-implant (II)	1000	55.7 + 7.5	31.1 + 4.6	0	---	0	---	0.7	>0.05[b]
	China 6-capsule	1001	55.5 + 7.3	31.4 + 4.3	0.1	---	0.1	---	0.4	
	Norplant	998	55.4 + 7.4	31.4 + 4.4	0	---	0	---	0	
Fang et al. [4]	Sino-implant (II)	9934	54	Range: 17 to 40 (68%: 25 to 34)	---	0.28				<0.001
	China 6-capsule	9739			---	0.05				
Qi et al. [7]; phase II	Sino-implant (II)	1000	55.67 + 6.90	32.1 + 4.7	0.10	0.20	0.30	0.90	2.10	<0.005[c]
	China 6-capsule	1000	55.33 + 7.21	32.1 + 4.8	0	0.10	0.10	0.20	0.20	
Xing et al. [8]	Sino-implant (II)	4009	54.03	Range: 17 to 40 (72%: 25 to 34)	0.08	0.23	0.23	1.06	1.57	<0.001[d]
	China 6-capsule	3932			0.03	0.05	0.05	0.23	0.26	

[a] Mean or mean + SD, unless otherwise specified.

[b] Between groups at Year 5; details not provided.

[c] At Years 4 and 5.

[d] Test performed on Pearl index at Year 5 but life-table probabilities presented in table.

Table 3

Cumulative probability of discontinuation due to menstrual problems (per 100 women)

Study	Implant	Study N	Year 1	Year 2	Year 3	Year 4	Year 5	Reported p value
Fan et al. [6]	Sino-implant (II)	1,000	2.7	---	10.0	---	12.5	>0.05[b]
	China 6-capsule	1,001	3.1	---	12.0		16.4	
	Norplant	998	2.9	---	10.9	---	14.6	
Fang et al. [4]	Sino-implant (II)	9,934	---	7.84				<0.01
	China 6-capsule	9,739	---	8.96				
Qi et al. [7]; phase II[a]	Sino-implant (II)	1,000	2.80	6.51	8.11	10.41	12.91	>0.05[c]
	China 6-capsule	1,000	2.40	6.61	8.72	11.52	13.23	
Xing et al. [8]	Sino-implant (II)	4,009	---	---	---	---	15.48	<0.001
	China 6-capsule	3,932	---		---	---	19.97	

[a]Provided menstrual cards to record bleeding problems.

[b]Between groups at Year 5; details not provided.

[c]At Year 5.