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The safety of Sino-implant (II) for women with medical conditions or other characteristics: a systematic review☆,☆☆

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Abstract

Objectives: This study aims to systematically review evidence published on the safety of Sino-implant (II) [SI (II)] among women with medical conditions or characteristics identified by the World Health Organization for eligibility for contraceptive use.

Study design: We searched PubMed, WEIPU, CNKI and Wanfang to identify all relevant evidence published in peer-reviewed journals from 1991 through 2014 regarding the safety of SI (II). We considered studies among women with medical conditions or other characteristics, such as age and parity, as direct evidence and studies among healthy women or a general population of women as indirect evidence.

Results: We identified 108 articles of which 9 met our inclusion criteria. Among women with medical conditions, no evidence was identified for the outcomes of interest, including serious adverse events or outcomes related to medical conditions. Among healthy women, evidence regarding efficacy of SI (II) for women weighing ≥70 kg was conflicting; one study showed an increased pregnancy rate and another showed no relationship. Women with menorrhagia did not experience worsened symptoms and may benefit from SI (II) use. Healthy women using SI (II) were no more likely than users of other methods to gain weight, develop elevated blood pressure, have abnormal liver or bone density tests or develop ovarian cysts or uterine myomas.

Conclusions: Evidence among healthy women suggests SI (II) is safe and had health outcomes similar to those of other levonorgestrel implants. Studies were limited and conflicting regarding efficacy for women ≥70 kg. All included studies were conducted in China, limiting generalizability.

Keywords

Sino-implant II; Contraceptive implant; Levonorgestrel implant; Contraceptive safety

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the World Health Organization or US Centers for Disease Control and Prevention.

☆☆Use of trade names and commercial sources is for identification only and does not imply endorsement by the US Department of Health and Human Services.

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1. Introduction

Contraceptive implants are highly effective long-acting reversible contraceptives that are safe for most women [1] and are in general highly acceptable to those who use them [2]. Sino-implant (II) [SI (II)] is a 2-rod subdermal contraceptive implant that contains the progestin levonorgestrel (LNG) (75 mg per rod, 150 mg total) [3]. SI (II) has been shown to produce a mean serum concentration of LNG of 0.59 ng/mL in the first month, declining to 0.28 ng/mL by the 12th month after insertion [4], and 0.21 ng/mL by the fifth year after insertion [5]. Therefore, it may be expected to have similar characteristics to both the 6-rod LNG-containing implant (Norplant®, consisting of 6 silicon capsules, each containing 36 mg of LNG; no longer in production) and the 2-rod LNG-containing implant (Jadelle®, consisting of 2 silicon rods, each containing 75 mg of LNG)[1]. It may also have similarities to another progestin-only implant containing etonogestrel (Implanon® and Nexplanon ®, consisting of 1 polymer rod containing 68 mg etonogestrel) [6]. In addition to being used in contraceptive implants, LNG, also known as D-(l)-norgestrel or D-norgestrel [7], is one of the most common progestins used in combined oral contraceptives. LNG causes changes in the cervical mucus that prevent penetration by sperm and also inhibits ovulation and leads to altered endometrial development and ovulatory dysfunction in most women [8,9].

SI (II) is manufactured by Shanghai Dahua Pharmaceutical Co, Ltd. (Shanghai, China), is approved for 4 years of use and is currently registered in over 20 countries [10]. SI (II) has been used by millions of women worldwide, primarily in China and Indonesia but also in several African settings [3].

A systematic review of randomized controlled trials to assess the efficacy of SI (II) found that, in four randomized clinical trials (RCTs) with a total of over 15,000 women assigned to the method, pregnancy rates in the first year of use ranged from 0% to 0.1%, and cumulative pregnancy rates through year 4 ranged from 0.9% to 1.06% [3]. These pregnancy rates are similar to those reported for other LNG implants [2] and the etonogestrel implant [11].

We conducted a systematic review of published evidence on the safety of SI (II) for women of reproductive age according to the medical conditions and characteristics identified by World Health Organization (WHO) for eligibility for contraceptive use in preparation for a technical meeting to update WHO's Medical Eligibility Criteria for Contraceptive Use (MEC) [1] and to consider the addition of SI (II) to the methods included in the MEC. This review focuses on two main questions. First, for women with medical conditions or other characteristics, do SI (II) users have an increased risk for adverse events compared with nonusers? Second, because we anticipated finding few studies to answer this question, we also sought to draw upon the large body of evidence on the safety of other LNG implants to determine whether SI (II) demonstrates that it is similar with respect to safety to other contraceptive implants. If so, users of the method can follow the MEC guidance already available for implants.

[1]Note that brand names will be used for clarity for the duration of this review; their use does not imply endorsement.

2. Methods

This review was prepared using PRISMA guidelines for the conduct of systematic reviews [12]. We searched PubMed for references in peer-reviewed journals in any language relating to SI (II) from 1991 (5 years before the product was approved for general use in China) through December 2014. Because most of the studies on SI (II) have been conducted in China and published in the Chinese medical literature, we also searched WEIPU, CNKI and Wanfang, indexes for Chinese medical journals. In PubMed, we used the terms “sino implant OR sino-implant OR sinoplant” AND “contracept*”. In WEIPU, we used similar search terms in standard Chinese. We also contacted the authors of a previous review of RCTs assessing the efficacy of SI (II) [3] and cross-referenced the articles we identified with the list of articles considered for that review and hand-searched the reference lists of identified articles.

2.1. Study selection

For this review, studies of any design were included. The title and abstract from each article identified were reviewed to determine whether an article satisfied the review inclusion criteria. English language results were screened by one author (SJP) and a native speaker screened Chinese language results. We sought articles to answer our primary question: among women with medical conditions, such as hypertension or menorrhagia, or other specific characteristics, such as age and parity, do those who use SI (II) have an increased risk for adverse events (e.g. worsened menorrhagia or worsened hypertension) compared with those who do not use SI (II)? Studies that answered this question were considered direct evidence. The ideal comparison group would be women using no contraception or nonhormonal contraception. We were also interested in whether SI (II) has a similar safety profile to other contraceptive implants; therefore, we included studies that examined users of other implants as the comparison group. Although Norplant® is no longer available on the market because there is a large body of evidence on its safety [13], we considered comparisons with this method to be informative. If studies show that SI (II) and Norplant® have similar safety profiles in comparative studies, we may be able to extrapolate to make conclusions about the safety of SI (II).

We excluded articles referring only to implants other than the SI (II), including articles only studying SI (I), Jadelle® and Norplant®. Because this article focuses on safety, we also included only comparative studies to examine whether rates of adverse events were different in SI (II) users than in nonusers. Finally, we excluded publications that reported on a subset of data that was published elsewhere as a larger analysis if that larger analysis was included in the review.

Because we anticipated that we might find limited or no direct evidence, we also sought studies with indirect evidence that answered a secondary question: among healthy women or among a general population of women of reproductive age, do those who use SI (II) have an increased risk for serious adverse events or other relevant outcomes compared with those who do not use SI (II)? As with those studies providing direct evidence, the comparison group could include users of nonhormonal contraceptive methods, other hormonal methods or other implants. For the indirect evidence, in addition to serious adverse events, we also

included studies that examined outcomes that might be relevant to medical conditions, such as information on weight, blood pressure or vaginal bleeding changes after initiation of the method, as well as variations in efficacy related to weight; however, such studies were only included if they directly measured these outcomes and included a comparison group and were excluded if only self-reported symptoms were included.

2.2. Study quality assessment and data synthesis

Evidence from each study included for the review was summarized on a standard abstract form developed for the systematic review process. All Chinese language studies were translated to English. Studies were abstracted by one author (SJP) and verified by a second author (PSS). We did not abstract data on overall contraceptive efficacy (i.e. other than efficacy in relation to body weight) or discontinuation due to side effects such as menstrual problems as a previous systematic review of randomized trials has already established the effectiveness and acceptability of the method, as compared with other LNG implants [3].

The quality of the evidence presented in each individual study was assessed according to the methods of GRADE [14]. Briefly, RCTs were rated as high quality if there were no serious flaws in study quality, including complete reporting of study recruitment methods, adequate randomization procedures and allocation concealment, presence of low and nondifferential loss to follow-up and the use of appropriate analytic methods. RCTs with at least one serious flaw in execution or reporting were rated as intermediate if those flaws were deemed unlikely to bias the results. RCTs with multiple flaws in execution or reporting, in which the flaws were deemed likely to bias the results, were rated as low quality. RCTs with multiple flaws in execution or reporting, with at least one other serious threat to validity, were rated as very low quality. Observational studies were rated as high quality if they had no threats to validity and reported strong associations; as intermediate quality if they reported a strong, consistent association and had no plausible confounders; as low quality if they had no serious flaws in study design but otherwise failed to meet the above criteria; and as very low quality if they had serious flaws in design or execution.

We did not perform metaanalysis for most outcomes due to the heterogeneity of reporting of these outcomes and the small number of studies reporting on each outcome nor did we do so for the outcome of ectopic pregnancy due to the rarity of the outcome.

3. Results

Based upon the search, 107 articles were identified (98 through WEIPU, 9 through PubMed). Of these 107 articles, we reviewed the full text of 20 and found 8 that met our inclusion criteria [15–22]. One additional study was added after hand-searching the reference lists of relevant articles [23], for a total of nine included studies. Eight of these studies were originally published in Chinese and were translated. Among the included articles, six were RCTs, two were prospective observational studies and one was a cross-sectional study. Three studies reported on serious adverse events [18,21,22], while the others reported on outcomes that might be relevant to women with medical conditions (such as changes in blood pressure, menstrual bleeding, hemoglobin or liver function tests). Tables 1 and 2 provide a summary of the objectives, study design, study population, main results,

strengths, weaknesses and quality grade for each of the clinical studies included in this systematic review.

3.1. Direct evidence

We identified no comparative studies that provided direct evidence among women with medical conditions on the association between use of SI (II) and serious adverse events or outcomes relevant to medical conditions.

3.2. Indirect evidence: Serious adverse events

We identified three RCTs that reported on serious adverse effects among healthy women using SI (II) [18,21,22]. One study compared women using SI (II) with those using the 6-rod Chinese-made LNG implant (also known as the CLa implant or Sino-implant (I), hereafter referred to as SI [I]) [21]. In this study, 19,673 parous women aged 17–40 years were randomly allocated to one of these two methods and followed for 24 months. There was one ectopic pregnancy in the SI (I) group compared with three in the SI (II) group (statistics not reported). There were no statistically significant differences between groups in breast, pelvic or cardiovascular abnormalities as assessed by physical examination. Another RCT followed 1000 women randomly allocated to either SI (I) or SI (II) [18] for 5 years. There was one ectopic pregnancy in the SI (I) group and there were no ectopic pregnancies in the SI (II) group. A third RCT enrolled 1001 women to use SI (I), 1000 to use SI (II) and 998 to use Norplant® and followed them for 5 years [22]. No ectopic pregnancies occurred in any of the three groups, and there were no differences between groups in the frequency of removal for any medical reasons, including mammary hyperplasia, cardiovascular disease, cancer, uterine tumors, ovarian cysts or pulmonary cardiomyopathy.

3.3. Indirect evidence: Outcomes relevant to women with medical conditions

We identified seven studies that reported on healthy women using SI (II) that provided indirect evidence on outcomes considered relevant to women with medical conditions [15–20,22,23]. Five of these had information either about method effectiveness related to weight at study initiation [16,22] or weight change while using SI (II) compared with another method [15,18,19]; two, about changes in blood pressure while using SI (II) compared with another method [15,18]; two, about changes in hemoglobin, platelets or mean blood loss [18,23]; one, about bone mineral density and markers associated with bone mineral density [17]; one, about hepatic and renal function tests [22]; and one, about benign ovarian cysts or uterine leiomyomas [20].

3.3.1. Effect of body weight on contraceptive effectiveness—Two studies analyzed efficacy rates based on the weight of the woman at study initiation; neither provided separate estimates by implant type, although the majority of pregnancies in both studies occurred among women using SI (II). One study was an RCT that randomized 7941 parous women aged 17–40 years to either SI (I) or SI (II) and followed them for 5 years [16]. There were a total of 69 pregnancies (of which the majority, 86%, were among users of SI [II]). Among those who became pregnant, women who weighed ≥70 kg at baseline had three times the pregnancy rate of those who weighed b60 kg (statistical analysis not reported); this was based on four pregnancies in the group of women weighing ≥70 kg. The

authors reported that there was no relation between the amount of time the implant was used and the risk of pregnancy among those who weighed ≥70 kg (statistics not reported). Another RCT (also mentioned above) with 2999 women who used either SI (I) or SI (II) reported that there was no relation between weight and pregnancy. This was based upon eight pregnancies that occurred (of which the majority, 63%, occurred in the SI (II) group; statistical analyses not reported) [22].

3.3.2. Weight change—Four studies (three RCTs and one cohort study) reported on weight change among users of SI (II) compared with users of other progestin-only methods [15,18,19] or nonhormonal or no method [20]. One RCT included 2297 users of either SI (I) or SI (II) and found that mean weight increased in both groups over the 5 years of the study, but the difference between groups was not statistically significant [18]. Another RCT included 300 women using SI (I), SI (II) or Norplant®. Mean weight increased in all groups but there was no significant difference between groups [19]. This study reported on the subgroup of women weighing ≥70 kg at study initiation and found that weight change over 2 years ranged from a decrease of 10 kg to an increase of 4 kg but did not compare the weight change in this group to that among women who weighed less than 70 kg at study initiation. A third RCT including 1846 women using either SI (I) or SI (II) found that both groups gained a modest amount of weight over 2 years (b1 kg; between-group comparative statistics not reported) [15]. A cohort study that included 315 users of SI (II) and 302 women using either no method or no hormonal method found no difference in weight between groups at study initiation [20]. Over the 3 years of observation, both groups gained a modest amount of weight; however, nonusers gained significantly more weight than users of SI (II) (mean gain 2.7 vs. 1.3 kg, pb.05).

3.3.3. Mean menstrual blood loss, hemoglobin—One RCT reported on both menstrual blood loss and change in hemoglobin [23]; another provided information on change in hemoglobin and platelets [18]. One of these RCTs included 89 women (mostly with normal levels of menstrual blood loss, although a subset met criteria for menorrhagia) who were randomly assigned to SI (I), SI (II) or Norplant® and followed for 1 year [23]. SI (II) users had significantly decreased mean blood loss compared with baseline at cycle 3 but no significant difference at cycle 6 or 12. Norplant® and SI (II) users had significantly decreased mean blood loss at cycle 12 compared with baseline; however, there was no statistically significant difference between study groups at any time point. In the subgroup of women with menorrhagia (mean menstrual blood loss≥80 mL, n=9), mean blood loss decreased from 112.8 to 60.5 mL by cycle 12 (pb.05); estimates were not provided separately by implant group. Mean hemoglobin levels increased in all groups in the study, including among those using SI (II), in whom mean hemoglobin increased from 111.1 g/L to 137.6 g/L at 1 year (pb.001). Mean hemoglobin levels also increased in the subgroup of women with menorrhagia, from a mean of 109.2 g/L to 133.4 g/L (mean hemoglobin at cycle 12 not significantly different among those with menorrhagia compared with those without menorrhagia; estimates not reported stratified by method). In another RCT including 2297 participants, a subset of 300 [allocated to SI (I), SI (II) or Norplant®] had their hemoglobin checked before and after placement (time interval not reported) and no significant differences were found between groups [18].

3.3.4. Bone mineral density—One cross-sectional study assessed bone mineral density and serum markers associated with bone formation [17]. In this study, 166 women who had used SI (I), SI (II) or Norplant® for at least 3 years were compared with women who had used no hormonal contraceptive for at least 1 year. No differences were found among the groups in terms of bone mineral density, serum calcium, phosphorus, alkaline phosphatase, osteocalcin or estrogen. Additionally although the hydroxyproline/creatinine and calcium/creatinine ratios (indicative of bone formation) were higher in Norplant® users than nonusers (pb.01), no such difference was found among SI (II) users. There was no effect of age on osteocalcin levels among women using SI (II), although osteocalcin levels were lower both in women aged 35–39 and ≥40 years using Norplant®.

3.3.5. Blood pressure—Two studies were identified that compared blood pressure between users of SI (II) and users of other methods. One is a previously described RCT [18] that compared blood pressure among women randomized to SI (I), SI (II) or Norplant®; the other is a previously described cohort study that compared blood pressure among users of SI (II) and women using no hormonal method [20]. In the RCT, two women who were normotensive at study initiation were reported to have increased blood pressure during the study, although the allocation status of these participants is not specified and it is not clear whether blood pressure was measured on all 2297 women or only a subset of 300 women [18]. In the observational study, which followed 617 users of either SI (II) or no hormonal method, both systolic and diastolic blood pressures were higher in nonusers than SI (II) users after 3 years (pb.05).

3.3.6. Hepatic function—One previously mentioned RCT checked hepatic function tests at 1, 2 and 5 years postinsertion in a subset of the nearly 3000 women randomized to SI (I), SI (II) or Norplant® [22]. Among the 50 cases selected from each group for testing, there were no abnormalities in any of the groups (results not reported).

3.3.7. Benign ovarian cysts and leiomyomas—One cohort study, further described above, assessed the development of ovarian cysts and leiomyomas yearly for 3 years among over 600 women using either SI (II) or using no method or no hormonal method [20]. Women using SI (II) were more likely to develop ovarian cysts evident on ultrasound and were less likely to develop leiomyomas than nonusers of hormonal methods. All the ovarian cysts resolved spontaneously.

4. Discussion

SI (II) is in use in multiple countries, with positive reports of the feasibility and acceptability of its use in routine service delivery in varying locations [24,25]. It uses the same quantity of hormone, 150 mg LNG, as another implant that is already included in the MEC (Jadelle®). SI (II) and other LNG-containing implants are the same with respect to hormone formulation, quality profile [26] and daily release rates [27], {although in vitro tests have shown that SI (II) has less of a “burst effect” than Norplant® [28]}. SI (II) is among the most effective contraceptive methods available, with 5-year cumulative pregnancy rates estimated between 0.7% and 2.1% [3].

Although evidence is available for the efficacy of SI (II), evidence for the safety of the method for women with medical conditions or other characteristics is scarce. We sought to determine if women with medical conditions or other characteristics, such as age and parity, using SI (II) have an increased risk for adverse events compared with those who do not use SI (II) but were unable to identify any studies that addressed our primary question. We did however identify studies that provided indirect evidence by reporting on serious adverse events, weight change among method users, effectiveness related to weight, bone mineral density, menstrual blood loss and hemoglobin changes, lipid and liver profile changes and benign ovarian cysts and uterine tumors among healthy women.

4.1. Serious adverse events

Three studies reported on serious adverse events, such as ectopic pregnancy or method discontinuation due to medical reasons, among healthy women using SI (II) compared with women not using SI (II) [18,21,22]. The results from these three studies, which were all of intermediate quality, reported few adverse events and suggested that SI (II) has a similar safety profile to other LNG-containing implants.

4.2. Other medical conditions

One study found that users of SI (II) gained less weight than users of nonhormonal or no contraceptives [20] and three studies found no significant difference between weight changes of SI (II) users and users of other implants [15,18,19], although users in most studies tended to gain weight over time. There was no evidence of declining effectiveness over time in overweight women [16]. Results on effectiveness for overweight women were equivocal, with one study finding it to be decreased [16] among women weighing ≥70 kg and another finding no relation between weight and effectiveness among the eight pregnancies that occurred [22].

Evidence from one cross-sectional study is reassuring with respect to bone mineral density and surrogate markers of bone turnover and formation [17]. There was no evidence of an effect on hepatic function [22] or blood pressure [18,20]. Although there was an increased likelihood of developing ovarian cysts among users of SI (II), the cysts were asymptomatic and users were less likely to develop uterine fibroids [20].

In addition to the results from the systematic review, we identified several studies that did not meet our inclusion criteria due to lack of a comparison group but may be informative with respect to SI (II) safety among women with other medical conditions or characteristics, such as age and parity. A noncomparative study among healthy women found no change in lipid profiles over time among women using SI (II) [29]; another noncomparative study found no difference in total cholesterol, HDL or LDL [30]. One noncomparative cohort study assessed infant outcomes among children of breastfeeding mothers using the implant; all of the 60 infants had weights and heights within normal ranges over a 6-year period [29]. IQ was over 90 for all children tested. In one study, 28 HIV-negative users of SI (II) had were randomized to TDF-FTC for primary HIV prevention [31]. No pregnancies occurred up to 1 year of follow-up, and after adjusting for age, BMI and time since implant insertion, use of TDF-FTC was not associated with changes in mean LNG concentration compared

with those assigned to placebo. All mean concentrations were above the minimum LNG concentration reported for efficacy.

4.3. Limitations to the body of evidence

This body of evidence is primarily limited by the absence of studies on safety of SI (II) use among women with medical conditions or other characteristics. There were also several limitations in the quality of the existing indirect evidence. The six RCTs included in this review were generally of intermediate quality. Some of the RCTs had potential for bias due to failure to report procedures for allocation concealment and randomization sequence generation [32]. However, bias may be minimized by extremely low loss to follow-up in all the studies. The three observational studies included two cohort studies and one cross-sectional study of low to very low quality; limitations of the observational studies included poor description of study methods [23], use of multiple comparisons without adjustment [17] and high and differential loss to follow-up [20].

The body of evidence and this systematic review have limited generalizability, given that all the studies included in the review were conducted in China. Two studies have been published on SI (II) that included women from outside China. Although they did not have a comparison group and do not inform our primary question regarding the safety of SI (II) for women with medical problems, one study in Madagascar showed high efficacy and acceptability and no pregnancies [24] and another in Kenya and Pakistan showed few adverse events and few pregnancies [25]. This provides some reassurance that the method would be expected to behave similarly in non-Chinese women.

An additional limitation on the generalizability of this body of literature is that women under age 17 years and over age 40 years, those who were nulliparous or those who had medical conditions were excluded from most of the studies identified. This limited our ability to answer our primary question about the safety of the method for women with medical problems.

The scope of the problem is unknown, but duplicate publication is not uncommon in the Chinese literature [33]. We attempted to ascertain the originality of all included studies, but we may have wrongly included studies that were duplicates or excluded as duplicates studies that were in fact original.

In 2014, the WHO Expert Working Group reviewed this evidence to assess how to add SI (II) to the Medical Eligibility Criteria [34]. Although the evidence was limited regarding women with medical conditions, the Expert Working Group determined that the evidence of similarity of SI (II) to other LNG implants warranted a recommendation that SI (II) be equated with Jadelle® for the purposes of the MEC.

5. Conclusions

Multiple studies comparing SI (II) to other LNG implants found no difference in serious adverse events or for surrogate markers of disease in healthy women. Limited evidence suggests that SI (II) is not harmful and may be beneficial for women with menorrhagia.

Studies were conflicting regarding efficacy for overweight women, although very few pregnancies occurred in absolute terms. The safety and side effect profile of SI (II) appears to be comparable to that of other LNG implants. Serious adverse events were uncommon. Evidence was limited to research involving women in China. No evidence was identified comparing SI (II) to nonhormonal or other contraceptive methods.

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Table 1

RCTs

Author, year Support	Study design Population	Outcome Follow-up	Results	Strengths, weaknesses	Quality
Fang 1997 [20] Source of funding not stated	RCT 19,673 women aged 17–40 years, with at least 1 child, smoking less than 10 cigarettes/day 9739=SI (I) 9934=SI (II)	Serious adverse events 2 years	**Ectopic pregnancy** SI (I): 1 case, SI (II): 3 cases (statistics not reported) **Physical examination** No difference between groups at any time point in incidence of breast, pelvic or cardiovascular abnormalities on physical examination (all abnormalities <0.3% incidence)	*Strengths* –Appropriate analyses –Low loss to follow-up (5.7% over 2 years) *Weaknesses* –No description of allocation concealment or randomization procedures –Unclear how women who discontinued or were LTFU were analyzed	I, intermediate
Ni 1998 [18] Source of funding not stated	RCT 300 women, married, parous, aged under 40 years, 100=SI (I) 100=SI (II) 100=Norplant®	Weight change 2 years	**Weight** All groups increased, but no significant difference among groups; SI (I): 1.4 kg; SI (II): 0.86 kg; Norplant®: 0.77 kg Among women weighing more than 70 kg at the time of implant insertion, weight change ranged from −10 kg to +4 kg at 24 months	*Weaknesses* –No description of randomization procedures or allocation concealment –Loss to follow-up not reported –Unclear how women who discontinued or were LTFU were analyzed	I, low
Zhang 1998 [14] Source of funding not stated	RCT 1846 women ≤40 years old, parous, smoking ≤10 cigarettes/day 919=SI (I) 927=SI (II)	Weight change Blood pressure change 2 years	**Weight** Increased in both groups compared with preinsertion (0.63 kg SI (I), 0.72 kg SI (II), p<.05 for paired *t* test, comparative between groups statistics not presented) **Blood pressure** Small, statistically significant increase in systolic blood pressure in both groups; diastolic blood pressure decreased in SI (I) group, unchanged in SI (II) group	*Strengths* –Low loss to follow-up (<4% at 2 years) –Appropriate analyses *Weaknesses* –No description of randomization procedures or allocation concealment –Unclear how women who discontinued or were LTFU were analyzed	I, intermediate
Qi 2002 [17] Source of funding not stated	RCT 2297 women Phase I: 100=SI (I) 100=SI (II) 100=Norplant® Phase II: 1000=SI (I) 1000=SI (II) 2 excluded for noncompliance	Pregnancy; continuation; removal for various reasons 5 years	*Phase* I **Ectopic pregnancy** No ectopics *Phase II* **Ectopic pregnancy** SI (I): 1 ectopic, SI (II): no ectopics **Changes in blood pressure, weight, hemoglobin** 2 participants had increased blood pressure; all others were normal; average body weight increased but was the same between CLa and SI (II) groups; no significant difference in hemoglobin or platelets before and after placement, though unclear when tests occurred (p>.05) (Hemoglobin tested on a subset of 300 participants)	*Strengths* –Low loss to follow-up (0.5% over 5 years) –Appropriate analyses *Weaknesses* –No description of allocation concealment or randomization procedures –Unclear how women who discontinued or were LTFU were analyzed –Unclear if blood pressure was checked on all participants –Unclear when changes in hemoglobin measured	I, intermediate
Xing 2002 [15] Source of funding not stated	RCT 7941 women, aged 17–40 years parous, nonsmoker or<10 cigarettes/day 3932=SI (I) 4009=SI (II)	Removal for medical reasons; efficacy based on weight 5 years	**Removal for medical reasons** SI (II) group less likely to remove for medical reasons (2.1 vs. 1.5, p<.05) **Weight** 69 pregnancies (86% among users of SI [II]). Pregnancy rate for women ≥70 kg at baseline 2.19 vs. 0.74 for women <60 kg (statistical analysis not reported). No relation	*Strengths* –Low loss to follow-up (6.9% over 2 years, 7.7% over 5 years) –Appropriate analyses *Weaknesses* –No description of randomization procedures	I, intermediate

Author, year Support	Study design Population	Outcome Follow-up	Results	Strengths, weaknesses	Quality
			between duration of implant use and pregnancy among women ≥70 kg (statistical analysis not reported)	–Unclear how women who discontinued or were LTFU were analyzed	
Fan 2004 [21] National Population and Family Planning Commission	RCT 2999 women, aged 18–40 years, parous 1001=SI (I) 1000=SI (II) 998=Norplant®	Removal for medical reasons; renal/hepatic function tests; efficacy based on weight 5 years	**Ectopic pregnancy** No ectopic pregnancies in any group **Removal for medical reasons** Including headache, skin problems, mammary hyperplasia, cardiovascular disease, uterine tumor, ovarian cyst, weight increase, diabetes, cancer, pulmonary cardiomyopathy: no difference among groups (p>.05) **Hepatic function** 50 cases selected from each group for hepatic and renal tests; all indices normal at 1, 2 and 5 years postinsertion (results not reported) **Weight** No relation seen between weight and pregnancy (only 8 pregnancies occurred); unclear how this analysis was performed	*Strengths* –Low loss to follow-up (0.2% over 5 years) *Weaknesses* –No description of allocation concealment or randomization procedures –Unclear how cases were selected for measurement of hepatic function –Pregnancy/weight analysis not stratified by method used –Unclear how women who discontinued or were LTFU were analyzed	I, intermediate

Table 2

Observational studies

Author, year Support	Study design Population	Outcome Follow-up (if applicable)	Results	Strengths Weaknesses	Quality
Han 1998 [22] Source of funding not stated	Prospective cohort 89 women, parous, with normal menstruation 29=SI (I) 30=SI (II) 30=Norplant®	Change in mean blood loss, hemoglobin 1 year	**Mean blood loss** All groups had decreased MBL after implantation compared with before SI (II) users had significantly decreased MBL at 3rd cycle compared with before implantation; no significant difference at 6th or 12th cycle, although both SI (I) and Norplant® users had significantly decreased MBL at 12th cycle **Mean blood loss among women with MBL ≥ 80 mL preinsertion** MBL decreased from mean 113 mL to 51 at 3rd cycle (p<.05), 106 at 6th cycle (p>.05), 61 at 12th cycle (p<.05) **Hemoglobin changes** Hemoglobin increased in all groups, including SI (II), from preinsertion to 12th cycle; no significant difference between groups. Among women with MBL≥80 mL, Hb increased from mean 109 to 133 g/L (statistics not provided)	*Strengths* –Rigorous, quantitative measurement of mean blood loss *Weaknesses* –Little description of methods for recruitment into study –Key information not presented stratified by method used –Loss to follow-up not described	II-2, low
Shen 1998 [16] Source of funding not stated	Cross-sectional 166 women using method for ≥3 years 37=SI (I) 41=SI (II) 45=Norplant® 43=nonuser (no hormonal contraceptives in prior year)	Bone mineral density and surrogate markers of bone health	**Bone mineral density** No difference among groups **Bone metabolism markers** SI (II) no different from control Hydroxyproline/creatinine and calcium/ creatinine ratio higher in Norplant® group than other groups (p<.01) (indicative of bone formation); Serum calcium, phosphorus, Alk phosphatase, osteocalcin (BGP): no difference among groups **Estrogen** No difference among groups **Osteocalcin (BGP)** SI (II) no difference from control Osteocalcin lower vs. control in women aged 35–39 years and ≥40 years using Norplant®	*Strengths* –Compared with both other implants and nonhormonal control –Methods well-described *Weaknesses* –Cross-sectional design –Multiple comparisons without a priori explanations	II-2, low
Liu 2000 [19] Source of funding not stated	Prospective cohort 315=SI (II) 302=nonuser (using no method or a nonhormonal method)	Blood pressure change Weight change 3 years	**Blood pressure** At 3 years, both systolic and diastolic higher in control than SI (II) (mean 14.1/9.4 kPa for SI (II), mean 14.8/9.9 control, p<.05) **Weight** No difference between groups at initiation; both groups gained weight, control>SI (II) (mean gain 1.3 kg SI (II), 2.7 kg control, p<.05) **Ovarian cysts/uterine myomas** SI (II) group more likely to develop cysts seen on ultrasound, all of which resolved; less likely to develop myomas seen on ultrasound	*Strengths* –Loss to follow-up clearly described –Statistical analyses/comparisons clearly described *Weaknesses* –High and differential loss to follow-up (19% and 28% SI (II) at 2 and 3 years, 42% and 50% at 2 and 3 years control)	II-2, very low