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Title

Immediate versus delayed postpartum use of levonorgestrel contraceptive implants: a randomized controlled trial in Uganda

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Condensation: Immediate postpartum initiation of contraceptive implants improves contraceptive utilization at six months.

Short Title: Immediate initiation of postpartum contraceptive implants

Abstract

Background: Use of long acting highly-effective contraception has the potential to improve women's ability to avoid short interpregnancy intervals, which are associated with an increased risk of maternal morbidity and mortality, and preterm delivery. In Uganda, contraceptive implants are not routinely available during the immediate postpartum period.

Objective: The purpose of this study was to compare the proportion of women using levonorgestrel contraceptive implants at six months after delivery in women randomized to immediate or delayed insertion.

Study Design: This is a randomized controlled trial among women in Kampala, Uganda. Women who desired contraceptive implants were randomly assigned to insertion of a two-rod contraceptive implant system containing 75 mg of levonorgestrel immediately following delivery (within five days of delivery and before discharge from hospital) or delayed insertion (six weeks postpartum). The primary outcome was implant utilization at six months postpartum.

Results: From June to October 2015, 205 women were randomized, 103 to the immediate group and 102 to the delayed group. Ninety-three percent completed the six-month follow-up visit. At six months, implant use was higher in the immediate group compared to the delayed group (97% versus 68%; $p<0.001$), as was the use of any highly effective contraceptive (98% versus 81%; $p=0.001$). Women in the immediate group were more satisfied with the timing of implant placement. If given the choice, 81% of women in the immediate group and 63% of women in the delayed group would choose the same timing of placement again ($p=0.01$). There were no serious adverse events in either group.

Conclusions: Offering women the option of initiating contraceptive implants in the immediate postpartum period has the potential to increase contraceptive utilization, decrease unwanted

pregnancies, prevent short interpregnancy intervals, and help women achieve their reproductive goals.

Keywords: contraception, immediate postpartum contraception, levonorgestrel contraceptive implants, postpartum

Introduction

Contraception is rarely offered immediately after delivery in low resource settings, like Uganda, so many women will not access contraception at all. Uganda has the third highest unmet need for contraception in the world [1] and one of the highest excess fertility rates in the world. [2] Contraceptive implants are safe, highly effective, long-acting, and reversible yet are not routinely available during the immediate postpartum period in Uganda. [3] The *Ugandan Policy on Family Planning* does not currently support immediate postpartum implant use for breastfeeding women within six weeks of delivery. [4] In a qualitative study among pregnant women in Uganda, participants expressed interest in long-acting, reversible contraceptives and desire for family planning to space pregnancies. [5]

Globally, postpartum implant placement has traditionally occurred at a postpartum visit six weeks after delivery. [6] This timing of the postpartum visit, and initiation of postpartum contraception, is based on historical precedent and does not have a clinical rationale. [6] In fact, non-breastfeeding women have been shown to ovulate as early as 25 days postpartum, [7] and 30% will have ovulated by eight weeks.[6] Studies in Uganda show that 22-58% of women resume sexual activity by six weeks after birth. [8-10] Median time to contraceptive use among postpartum women in Uganda is estimated to be 19 months after resumption of sexual intercourse.[11] Implants are offered immediately postpartum in many US hospitals. [12-15] Waiting six weeks to initiate contraception puts women at risk for unintended pregnancy and short interpregnancy intervals. Short interpregnancy intervals of less than 18-24 months are associated with an increased risk of maternal morbidity and mortality, [16] preterm delivery, and low birth weight infants. [17]

We are not aware of any studies to date evaluating immediate postpartum implant insertion among women in Africa. The purpose of this study is to evaluate the effect of immediate postpartum levonorgestrel (LNG) contraceptive implant placement compared to contraceptive implant placement at six weeks postpartum on six-month utilization among women in Uganda.

Materials and Methods

This is a randomized controlled trial conducted between June 2015 and May 2016 at Mulago Hospital in Kampala, Uganda. Mulago Hospital is the national teaching and referral hospital. There are approximately 32,000 deliveries per year at Mulago Hospital of which approximately 22% are cesarean deliveries. [18] All women delivering at Mulago hospital are offered comprehensive contraceptive counseling by nurse midwives before discharge. While permanent sterilization is available in the immediate postpartum period, copper intrauterine devices (IUDs) are the only reversible method of contraception available for initiation in the immediate postpartum period. Women are counseled to initiate all other methods of contraception when they return for their routine postpartum visit approximately six weeks after delivery.

We recruited women who wanted the contraceptive implant after receiving comprehensive contraceptive counseling and they were assessed for eligibility. Patients who were 18 years and older, who spoke English or Luganda, had a vaginal or cesarean delivery at Mulago Hospital within the past five days, and could demonstrate that they had a working cellular telephone were eligible for entry into the study. We excluded women who had a medical contraindication to progestin-only contraceptives or were taking Efavirenz medication as part of their HIV antiretroviral treatment.

Women were randomized to immediate insertion (within five days of delivery and before leaving the hospital) or delayed insertion (at the routine six-week postpartum visit, the current standard of care in Uganda).

All devices were placed by nurses with training and experience in contraceptive implant placement. The device used is a commercially-available two-rod contraceptive implant system. Each rod is 2.5 mm x 43 mm, and contains 75 mg of the progestin, levonorgestrel (LNG). The implants are approved for five years of continuous use. [19]

All women received routine postpartum care according to the standard of care. Participants in both groups were scheduled for a routine six-week postpartum visit. There was no additional six-week study visit scheduled, but women who returned for their six-week visit were asked to complete a brief questionnaire. Clinic attendance records were also used to verify if a woman returned for her six-week visit.

Women randomized to delayed insertion had implants placed at the clinic when they came for their postpartum follow-up visit. Prior to implant placement, women in the delayed group were screened for pregnancy with a urine pregnancy test. In addition, they were asked about unprotected intercourse and frequency of breastfeeding. Any woman considered to be at risk for pregnancy was counseled about the possibility and offered a home pregnancy test to take in two weeks.

All participants were contacted by telephone at three months after delivery. In-person interviews were completed at six months after delivery. Multiple attempts were made to assist the participant to come in person. If the participant was unable to return due to extenuating circumstances then the interview was conducted by phone. Attempts were made to reach the participants until four months past the delivery date for the three-month survey and up to eight

months past the delivery date for the six-month survey. We excluded from analysis any surveys inadvertently conducted after these time frames. Both follow-up surveys assessed whether participants were using the implant or another method of contraception. Modern methods of contraception was defined as condoms, combined hormonal contraceptives, progestin-only contraceptives (including implants, injections, pills and IUDs), copper IUDs, sterilization and lactational amenorrhea at less than 6 months according to the WHO definition. [20] Highly effective methods of contraception were defined as methods with typical use pregnancy rates of < 10% in the first year (WHO tier 1 and 2 methods) which included combined hormonal contraception, progestin only pills, implants, injections, IUDs, and sterilization.[21] Additionally, we assessed bleeding patterns by asking participants how many days after delivery they had bleeding at least once per day (days of lochia), how many days of bleeding in the last month required a pad or a tampon and how many days participants had bleeding in the last month that did not require a pad or tampon according to the standardized recommendations for defining bleeding in contraceptive trials. [22] We measured satisfaction by asking participants how satisfied they were with their current method overall based on a five-point Likert scale. If they had an implant placed, we asked if they would choose the same timing of initiation again or earlier or later. To ascertain adverse events we asked participants if they have been diagnosed with bleeding or infection at implant site, deep implant placement, pregnancy, blood clots in lungs or legs or any other new medical condition. A nurse evaluated the implant site at the follow-up visit.

We estimated 100% of women in the immediate group would have an implant placed. Based on the results of a previous trial of postplacental IUD placement at Mulago Hospital we estimated that 60% of women in the delayed group would return for a postpartum visit and have an implant

placed. [23] We opined that greater than or equal to a 20% difference between the two groups is clinically meaningful. To detect this effect with 80% power assuming a two-sided alpha of 0.05, and assuming a 20% discontinuation rate we estimated that 184 women (92 women in each group) would be required. We planned to recruit a total of 204 participants to account for 10% loss to follow-up.

Randomization was performed using blocks of four and six which were varied randomly. Sequential, numbered, opaque envelopes containing a card with computer-generated assignment information were prepared by a statistician not involved in randomization. The envelopes were opened in consecutive order.

During follow-up, attempts were made to blind the research assistant collecting data to the group to which the patient had been randomized. There were no questions on the three-month or six-month study instruments that directly asked when the patient received her implant.

The primary outcome was the proportion of women using a contraceptive implant at six months after delivery. Secondary outcomes included utilization of the implant at three months, postpartum bleeding, side effects and negative outcomes, and satisfaction. Bivariate comparisons were analyzed using chi ^{2} test or Fisher's Exact test for categorical variables and t-test or Mann-Whitney for continuous variables as appropriate. The primary outcome was evaluated per intent-to-treat analysis.

Sensitivity analyses were carried out to assess the potential impact of loss to follow-up on the primary outcome.

Study data were collected and managed using REDCap electronic data capture tools. Data analyses were completed using STATA (Statistical Software version 13·1).

The institutional review boards of the University of California, San Francisco and Mulago Hospital, and the Ugandan National Council for Science and Technology, approved the protocol. All participants provided written consent prior to enrollment. The CONSORT guidelines were used for reporting.[24]

Results

Enrollment occurred between June, 2015 and October, 2015. During this time, approximately 7500 women delivered at Mulago Hospital. Five hundred and eleven women (7%) who indicated that they planned to use the contraceptive implant postpartum were screened for enrollment—205 were randomized (103 to the immediate group and 102 to the delayed group) (figure 1). Protocol violations were identified in three participants after randomization (one woman was randomized greater than five days since delivery and two did not have working cellular phones) but they were included in the analysis per intention to treat.

By eight weeks postpartum, 52 women (25%) (23 in the immediate group (22%) and 29 in delayed group (28%); p=0.44) had returned to Mulago for the scheduled postpartum follow-up visit. One hundred and eighty-five women (90%) completed the three-month follow-up visit and 191 women (93%) completed the six-month follow-up visit. There was no difference in follow-up between groups at three months or six months.

Women were on average 27 years old (SD 5.4). Most women were married (48%) or in a relationship (49%) (Table 1). The average age of participant's male partners was 33 years (SD 7.9). The majority of women completed some secondary school (56%) and had two or more living children (80%). Women reported an average age at first pregnancy of 19 (SD 3.2). Thirty-three percent of women had a cesarean delivery and 3% of women delivered multiples. Seven

percent of women reported previously using the implant for contraception. Women traveled, on average, 72 minutes to seek care at Mulago Hospital (SD 41.8).

At three months and six months, implant use was higher in the immediate group compared to the delayed group: 99% immediate versus 41% delayed, p<0.001; and 97% immediate versus 68%, delayed p<0.001, as was the use of any modern contraceptive at 3 months and 6 months:100% immediate versus 52%, delayed, p<0.001; and 99% immediate versus 86% delayed, p=0.001 (Table 2). Women in the immediate group were also more likely to be using a highly effective method of contraception at three months and six months (100% immediate versus 50% delayed, p<0.001; and 98% immediate versus 80% delayed, p=0.001). One woman had a single-rod etonogestrel implant placed at an outside clinic. She was considered an implant user for the purposes of the analysis. Twenty-four women (23.5%) in the delayed group returned for implant placement between the three-month phone call and the six-month follow-up visit (Figure 1). Women who requested an implant at the six-month visit were not considered to be implant users at six months for the purpose of the analysis.

Sensitivity analyses assuming all participants lost to follow-up were implant users or all were non-implant users did not change the overall findings (data not shown). A last observation carried forward analysis assuming all participants who were observed to be using an implant at last known visit are still using an implant, and all participants who were not using an implant at last known visit are still not using an implant, did not change the overall findings (data not shown).

Two women became pregnant during study follow-up. Both women presented for delayed insertion and had a negative pregnancy test (one at 84 days postpartum and the other at 46 days postpartum). Both were diagnosed with a pregnancy within a few weeks of insertion and were

dated by ultrasound to have pregnancies that pre-dated the contraceptive action of the implant. One woman carried her pregnancy to term and the other had an abortion (she did not disclose whether the abortion was spontaneous or induced).

Among women who received an implant, satisfaction with the method was high overall, with 91% of 90 women in the immediate group reporting being 'satisfied' or 'very satisfied' with the method compared with 88% of 35 women in the delayed group at 3 months (p=0.73) and 94% of 93 women in the immediate group compared with 97% of 59 women in the delayed group at six months (p=0.53) (Table 3). However, women in the immediate group were more satisfied with the timing of implant placement. If given the choice, 90% of women in the immediate group and 51% of women in the delayed group would choose the same timing of placement again at three months (p=0.001) and 83% of women in the immediate group and 68% of women in the delayed group would choose the same timing of placement again at six months (p=0.03).

At six weeks postpartum there was no difference in mean days of lochia between women who received the implant immediately after delivery and those who did not receive the implant (13.2 days in both groups, p=0.95; data not shown). Among women who had received an implant by three months, the majority of women in both groups reported no bleeding days in the month prior to the three-month visit (79% immediate versus 71% delayed; p= 0.26) and six-month visit (81% immediate versus 76% delayed; p=0.71) (Table 3).

Seven women had their implants removed during study follow-up (three (3%) in the immediate group and four (4%) in the delayed group, p=0.69). The reasons reported for implant removal included arm pain (two women), early undiagnosed pregnancy at the time the implant was placed (two women), bothersome bleeding (one woman), abdominal pain and decreased libido (one

woman), and the recommendation of her primary care provider after a new diagnosis of diabetes (one woman). There were no serious adverse events during study follow-up.

Comment

We found that contraceptive implant utilization at six months was significantly improved by providing implants immediately following delivery among women in Uganda. In addition, women were more satisfied with the timing of implant placement when the implant was placed immediately after delivery.

To the best of our knowledge, this study was the first randomized trial of immediate post-partum implant placement in Africa. The results of this study suggest that increasing access to long-acting reversible contraceptive (LARC) methods immediately postpartum, especially in low resource settings, will improve utilization. Although Uganda is a geographically restrictive population this study has application to a larger population of similar low resource settings across Africa and even globally. Postpartum LARC programs have the potential to allow women to achieve desired birth spacing and decrease maternal and infant morbidity and mortality. Postpartum LARC programs have also been shown to be cost-effective in the US setting.[25]

The effect of immediate postpartum provision of contraceptive implants on postpartum utilization may be even greater than what was seen in our study. We found that 68% of women in the delayed, or standard of care group, were using implants at six months compared to 97% in the immediate group. This is likely a conservative estimate of effect because of the clinical trial setting, which only enrolled women willing to follow-up, provided reimbursement for travel, and provided the opportunity for participants to talk on the phone to a study nurse about their contraceptive plan at three months. At eight weeks postpartum, only 25% of women had returned

to Mulago for a routine scheduled postpartum visit and by three months postpartum only 41% of women in the delayed group were using an implant. Soon after the three-month study call, a number of participants in the delayed group returned for implant placement. In observational studies of women in Uganda only 25-28% report using contraception between 3 and 12 months postpartum. [26-27]

Our findings are consistent with observational studies in the US where continuation rates after immediate postpartum placement of contraceptive implants have been shown to be greater than 95% after 6 months.[12,14] Our findings are similar to a small randomized trial conducted in the US among adolescents which showed that 70 % of women in the delayed group were using implants at three months compared to 92% in the immediate group (p=0.02).[28]

Our study has several strengths. While another observational study has shown an association between immediate postpartum insertion of contraceptive implants and implant utilization, [12] this is a randomized trial demonstrating that association. It can be difficult to know whether the differential use of implants in the observational study was due to the intervention itself or other participant characteristics associated with choosing immediate insertion. Because of randomization, our study highlights the importance of the intervention itself. Another strength of our study was the low loss to follow up which minimizes the risk of bias in our findings.

Our study has several limitations. First, it was not feasible to design this study to evaluate the effect of immediate postpartum provision of contraceptive implants on interpregnancy interval—the outcome with clear, demonstrated public health benefits. There were two pregnancies in our delayed group and none in the immediate group. Still our study was not powered to detect meaningful differences in pregnancy and our follow up was not long enough to do so. We would expect the majority of early repeat pregnancies to occur after six months, [12] especially among a

population of women known to have high exclusive breastfeeding rates in the first few months. [2] Utilization of effective postpartum contraception has been shown to decrease short interpregnancy intervals, [29] which are associated with increased maternal and infant morbidity and mortality. [16,30] Implant utilization is likely a reasonable surrogate outcome for avoidance of early repeat pregnancy.

In summary, offering women the option of initiating contraceptive implants in the immediate postpartum period in low resource settings like Uganda has the potential to decrease unwanted pregnancies, prevent short interpregnancy intervals and help women achieve their reproductive goals. Health Ministries should focus on expanding policies and protocols that facilitate immediate postpartum insertion of LARC.

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Table 1: Demographics and baseline characteristics of women randomized to delayed and immediate contraceptive implant initiation

	Total N= 205 N (%)	Immediate Start N=103 N (%)	Delayed Start N= 102 N (%)
Age, years (Mean/SD)	26.9 (5.4)	26.3 (5.2)	27.5 (5.5)
Marital status			
Single	4 (2.0)	3 (2.9)	1 (1.0)
Married	98 (47.8)	52 (50.5)	46 (45.1)
Divorced/Separated/Widowed	3 (1.5)	0 (0)	3 (2.9)
In a relationship	100(48.8)	48 (4.6)	52 (51.0)
Age of Partner, years (Mean/SD)[b]	32.9 (7.9)	32.4 (8.3)	33.4 (7.5)
Education Completed			
No formal schooling	6 (2.9)	2 (1.9)	4 (3.9)
Some primary school	64 (31.2)	33 (32.0)	31 (30.4)
Some secondary school	115 (56.1)	60 (58.3)	55 (53.9)
Some university	20 (9.8)	8 (7.8)	12 (11.8)
Number of living children			
0	29 (14.1)	16 (15.5)	13(12.7)
1	13 (6.3)	8 (7.8)	5 (4.9)
2	52 (25.4)	29 (28.2)	23 (22.5)
≥3	111 (54.1)	50 (48.5)	61 (59.8)
Age at first pregnancy (Mean/SD)	18.9 (3.2)	18.7 (3.0)	19.1 (3.3)
Cesarean delivery	68 (33.2)	37 (35.9)	31 (30.4)
Delivery of multiples[c]	7 (3.4)	1 (1.0)	6 (5.9)
Prior Implant Use	15 (7.3)	5 (4.9)	10 (9.9)
Time traveled to Mulago (min) (Mean/SD)	72.4 (41.8)	69.5 (38.7)	75.4 (44.6)

a. 17 participants reported age of partner unknown
b. 6 sets of twins and 1 set of triplets

Table 2: Utilization after immediate versus delayed postpartum initiation of contraceptive implants at 3 months and 6 months (intent to treat)

3 months postpartum	**Immediate N=91 (%)**	**Delayed N=85 (%)**	**Risk Difference (95%Cl)**	**P-value**
Using Implant at 3 months	90 (98.9)	35 (41.2)	57.7 (47.05-68.40)	<0.0001
Using Implant or other modern method* at 3 months	91 (100)	44 (51.8)	48.2 (37.61-58.86)	<0.0001
Using Implant or other highly effective method* at 3 months	91 (100)	42 (49.4)	50.6 (39.96-61.22)	<0.0001
6 months postpartum	**Immediate N=96 (%)**	**Delayed N=87 (%)**	**Risk Difference (95%Cl)**	**P-value**
Using Implant at 6 months	93 (96.9)	59 (67.8)	29.1 (18.64-39.47)	<0.001
Using Implant or other modern method* at 6 months	95 (99.0)	75 (86.2)	12.8 (5.22-20.28)	0.001
Using Implant or other highly effective method* at 6 months	94 (97.9)	70 (80.5)	17.4 (8.65-26.27)	0.001
Pregnancies at 6 months	0 (0)	2 (2.3)	2.3 (0.01-5.58)	0.23

Data presented as N(%) analyzed with X^2 or Fisher's exact test

- Modern methods include: implant pill, injection, IUDs, condoms, sterilization (and lactational amenorrhea at 3 months)
- Highly effective methods include: implant, pill, injection, IUDs and sterilization

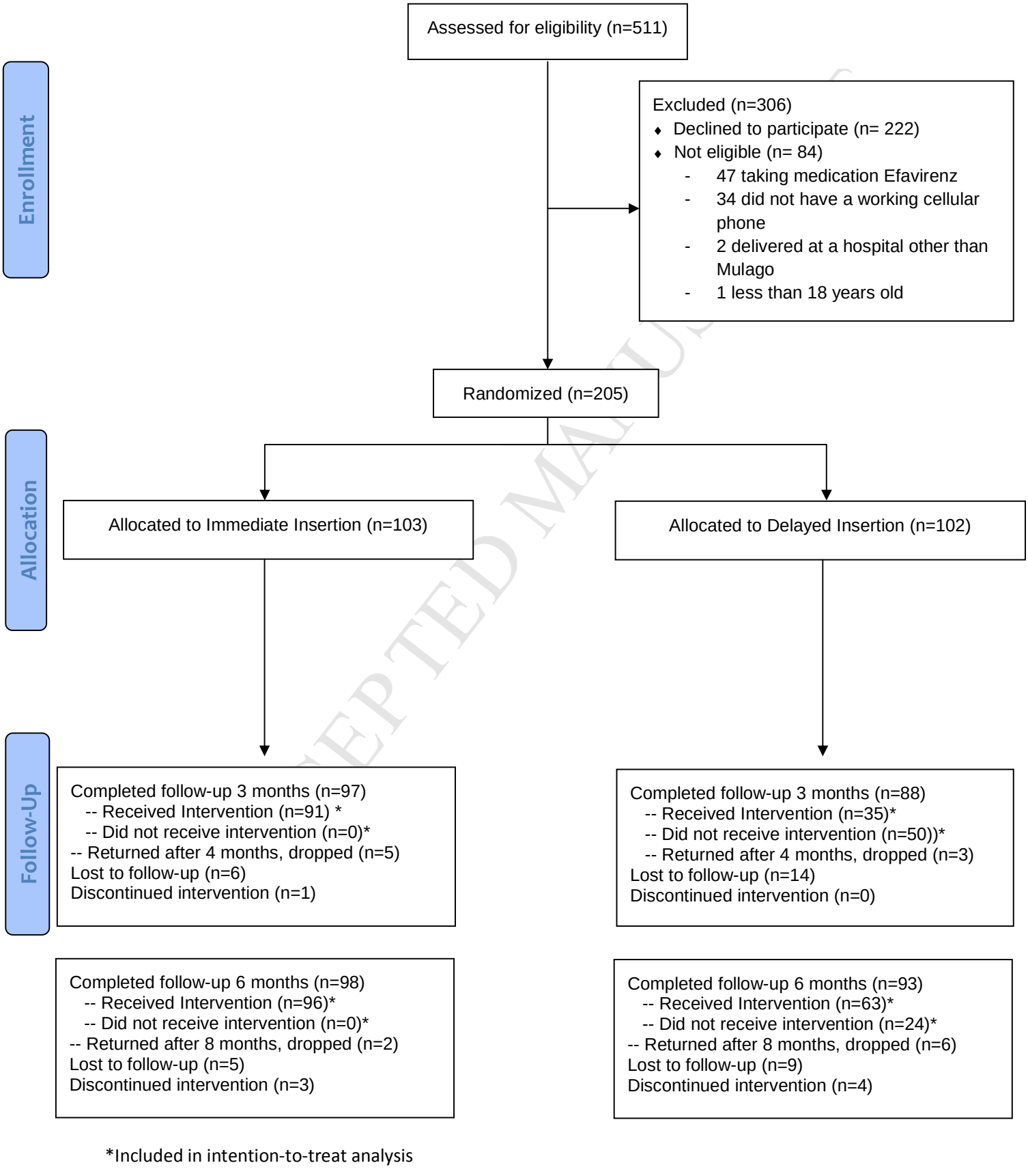
Table 3: Bleeding and satisfaction among implant users among women with immediate versus delayed postpartum initiation of contraceptive implants

Implant users, 3 months postpartum	**Immediate N= 90 (%)**	**Delayed N= 35 (%)**	**P-value**
Overall satisfaction with implant			
Very or somewhat satisfied	82 (91.1)	30 (88.2)	0.73
Satisfaction timing of placement			
Would choose same timing	81 (90.0)	18 (51.4)	0.001
Bleeding days in last month			
None	71 (78.9)	25 (71.4)	0·26[a]
1-6 days per month	14 (15.6)	6 (17.1)	
> 6 days per month	4 (4.4)	4 (11.4)	

Implant users, 6 months postpartum	**Immediate N= 93 (%)**	**Delayed N= 59 (%)**	**P-value**
Overall satisfaction with implant			
Very or somewhat satisfied	89 (93.7)	60 (96.7)	0.53
Satisfaction timing of placement			
Would choose same timing	77 (82.8)	40 (67.8)	0.03
Bleeding days in last month			
None	75 (80.7)	45 (76.3)	0.71[a]
1-6 days per month	14 (15.1)	12 (20.3)	
> 6 days per month	4 (4.3)	2 (3.4)	

a. Fisher's exact test

Figure 1: CONSORT Flow Diagram



*Included in intention-to-treat analysis