



Original research article

# The effect of immediate postpartum levonorgestrel contraceptive implant use on breastfeeding and infant growth: a randomized controlled trial <sup>☆,☆☆</sup>

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## ABSTRACT

**Objective:** This study assessed whether immediate postpartum insertion of levonorgestrel contraceptive implants is associated with a difference in infant growth from birth to 6 months, onset of lactogenesis, or breastfeeding continuation at 3 and 6 months postpartum compared to delayed insertion at 6 to 8 weeks postpartum.

**Study design:** We conducted a randomized trial of women in Uganda who desired contraceptive implants postpartum. We randomly assigned participants to receive either immediate (within 5 days of delivery) or delayed (6 to 8 weeks postpartum) insertion of a two-rod levonorgestrel contraceptive implant system. This is a prespecified secondary analysis evaluating breastfeeding outcomes. The primary outcome of this secondary analysis was change in infant weight; infants were weighed and measured at birth and 6 months. We used a validated questionnaire to assess onset of lactogenesis daily in person while participants were in the hospital, and then daily by phone after they left the hospital, until lactogenesis was documented. We used interviewer-administered questionnaires to assess breastfeeding continuation and concerns at 3 months and 6 months postpartum.

**Results:** Among the 96 women randomized to the immediate group and the 87 women to the delayed group, the mean change in infant weight from birth to 6 months was similar between groups: 4632 g in the immediate group and 4407 g in the delayed group ( $p=.26$ ). Among the 97 women who had not experienced lactogenesis prior to randomization, the median time to onset of lactogenesis did not differ significantly between the immediate and delayed groups (65 h versus 63 h;  $p=.84$ ). Similar proportions of women in the immediate and delayed groups reported exclusive breastfeeding at 3 months (74% versus 71%;  $p=.74$ ) and 6 months (48% versus 52%;  $p=.58$ ).

**Conclusion:** We found no association between the timing of postpartum initiation of levonorgestrel contraceptive implants and change in infant growth from birth to 6 months, onset of lactogenesis, or breastfeeding continuation at 3 or 6 months postpartum.

**Implications:** This study provides evidence that immediate postpartum initiation of contraception implants does not have a deleterious effect on infant growth or initiation or continuation of breastfeeding.

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## 1. Introduction

Providing effective postpartum contraception helps women achieve their reproductive goals and prevent short interpregnancy intervals. Short interpregnancy intervals are associated with an increased risk of

maternal and infant morbidity and mortality, preterm delivery and low birth weight infants [1–4]. When contraception is not offered immediately after delivery, many women do not access contraception at all, particularly in low-resource settings like Uganda [5,6].

Women in Uganda who receive contraceptive implants prior to leaving the hospital report higher satisfaction with the timing of implant placement and higher utilization of implants at 6 months postpartum compared to woman who receive implants after discharge from the hospital [7]. However, the *Ugandan Policy on Family Planning* does not currently support immediate postpartum contraceptive implant use for breastfeeding women within 6 weeks of delivery [8].

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Because progesterone withdrawal postpartum may contribute to the onset of lactogenesis, there is theoretical concern that early postpartum use of contraceptives containing progestins could inhibit initiation of breastfeeding and establishment of breastmilk supply [9]. Data on postpartum use of the etonogestrel-releasing contraceptive implant initiated within hours to days of delivery suggest that there is no effect on onset of lactogenesis [10], quantity or composition of breastmilk [11, 12], duration of exclusive breastfeeding at 12 weeks postpartum [13] or infant growth [14]. However, data are lacking on the effect of immediate insertion of the modern two-rod levonorgestrel (LNG)-releasing subdermal contraceptive implant system on breastfeeding initiation and duration and infant growth. LNG implants are commonly used worldwide in low-resource settings where challenges with breastfeeding have the potential to be most detrimental to infants.

This is a prespecified secondary analysis evaluating whether immediate postpartum insertion of LNG contraceptive implants is associated with a difference in infant growth from birth to 6 months, onset of lactogenesis, or breastfeeding continuation at 3 or 6 months postpartum compared to delayed insertion at 6 to 8 weeks postpartum.

## 2. Materials and methods

We conducted a randomized trial to investigate utilization of LNG implants at 6 months after delivery among women randomized to immediate or delayed implant insertion (Clinical Trial Registration number: NCT02341027). The trial was conducted between June 2015 and May 2016 at Mulago Hospital in Kampala, Uganda, and the results are described elsewhere in detail [7]. We found that implant use was higher in the immediate group compared to the delayed group at 6 months postpartum (97% vs. 68%;  $p < .001$ ) [7]. In this prespecified secondary analysis, we evaluated the effect of immediate postpartum initiation of LNG implants on infant growth, breastfeeding initiation and continuation.

Briefly, women who wanted contraceptive implants for postpartum contraception were 18 years and older, spoke English or Luganda, had a vaginal or cesarean delivery at Mulago Hospital within the prior 5 days and could demonstrate that they had a working cellular telephone were eligible. We excluded women who had a medical contraindication to

implant use or who were taking the antiretroviral Efavirenz due to concern for decreased contraceptive efficacy [15]. For this analysis, we excluded perinatal mortalities (stillbirths and deaths within the first week of life) because these events are unlikely to be a result of poor breastfeeding, but perinatal mortalities can affect breastfeeding outcomes. We also excluded multiple births since multiples can affect breastfeeding outcomes.

We randomly assigned women in the hospital during their postpartum stay to immediate insertion (within 5 days of delivery) or delayed insertion (at a 6–8-week postpartum visit) of the two-rod LNG implant system. All participants provided written consent prior to enrollment. At enrollment, participants completed a baseline demographics questionnaire. Hospital nurses measured infant birth weight, length and head circumference on day of birth and recorded this information in the participant's medical chart. Study personnel transcribed this information from the chart at study enrollment. At enrollment, study nurses inserted contraceptive implants for women randomized to immediate insertion.

During lactogenesis stage II (referred to as lactogenesis), colostrum transitions to mature milk. It typically occurs between 36 and 72 h postpartum [10,16,17]. While in the hospital, research nurses assessed daily for lactogenesis, in person, using maternal perception, which has been validated as an indicator of the timing of the onset of lactogenesis compared to the standard of test-weighing infants before and after each feed. Nurses asked, "Has your milk come in yet?" and if the response was yes, then they asked, "When did your milk come in?" [16]. If lactogenesis had not occurred by the time a participant left the hospital, study staff phoned her daily and asked these two questions until she confirmed lactogenesis occurred or until 148 h postpartum when women meet criteria for lactogenesis failure [18]. Women who underwent lactogenesis prior to randomization in the study were excluded from the lactogenesis analysis.

We interviewed all participants by telephone at 3 months after delivery. We completed in-person visits with mothers and infants at 6 months after delivery. If a woman was unable to return in person with her infant, we offered the option to complete the 6-month visit by phone. At both time points, trained research nurses asked participants

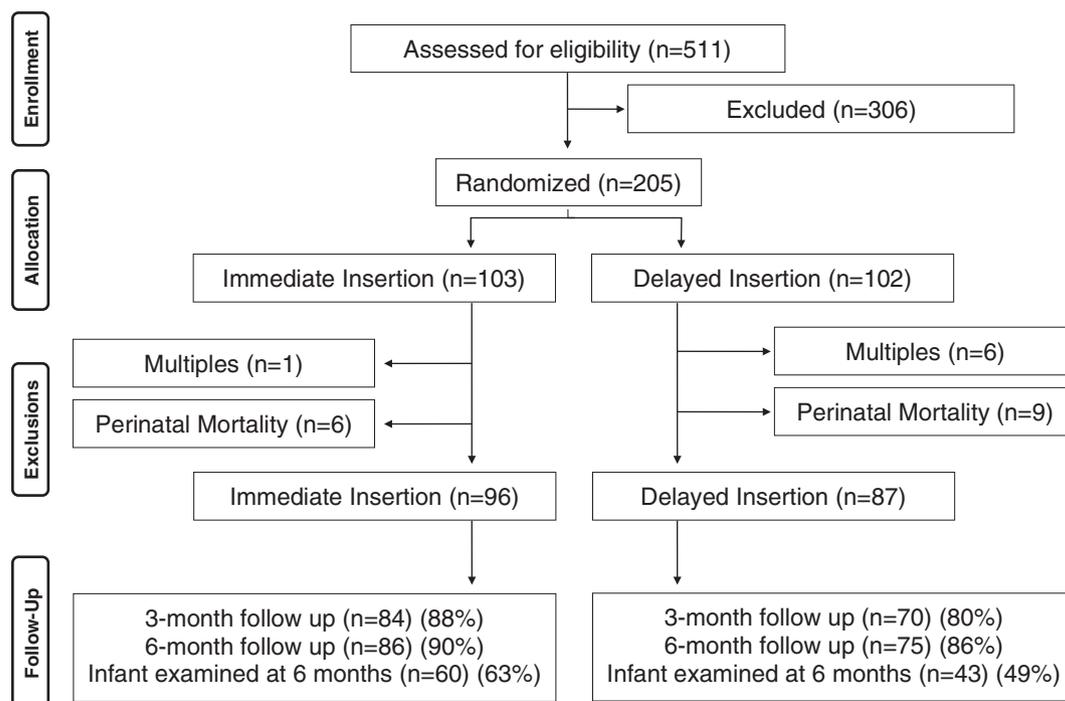
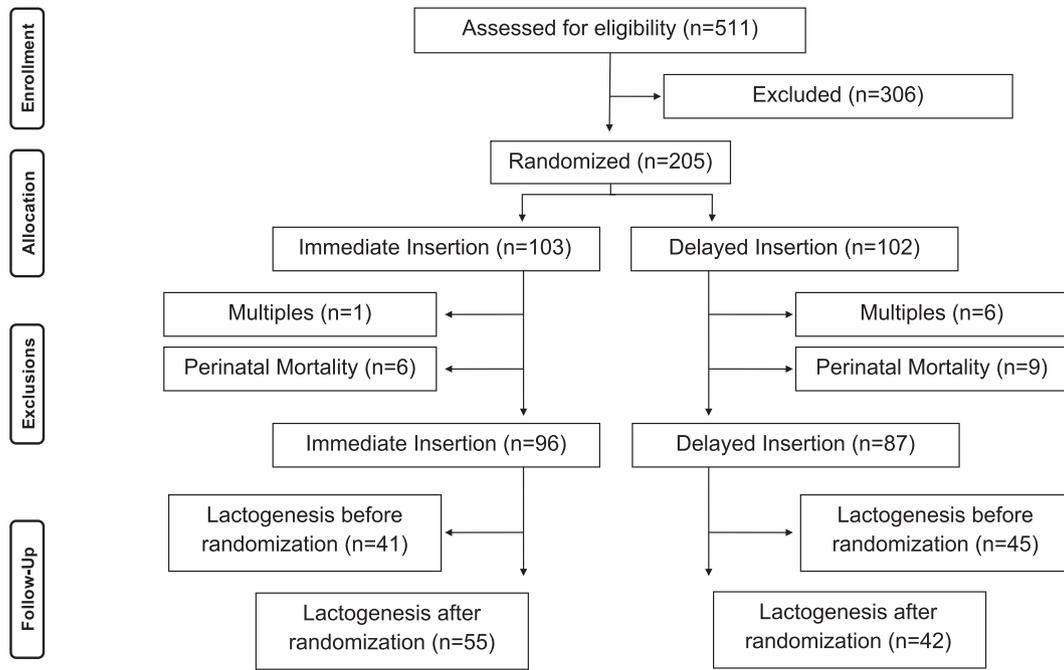


Fig. 1. Participant flow diagram for a randomized trial evaluating the effect of LNG contraceptive implants on breastfeeding continuation and infant growth among women and infants in Uganda in 2015–2016.



**Fig. 2.** Participant flow diagram for a randomized trial evaluating the effect of LNG contraceptive implants on onset of lactogenesis among women in Uganda in 2015–2016.

about breastfeeding and infant supplementation and any concerns about having enough breastmilk since delivery.

A nurse measured infant birth weight, length and head circumference at the 6-month postpartum visit according to standard guidelines if the infant was present at the in-person visit [19]. The nurse recorded one complete set of measurements. To measure length, we used a marked board with the infant recumbent and recorded to the nearest 0.1 cm. To measure weight, we used an infant scale and recorded to the nearest 0.01 kg. We calibrated clinic scales to hospital scales to ensure accuracy. We measured head circumference with a tape measure at the maximum diameter through the glabella and occiput and recorded to the nearest 0.1 cm.

Throughout follow-up, attempts were made to blind staff collecting data to the group to which the women had been randomized. There were no questions on the study instruments assessing outcomes that asked when the implant was placed.

The primary outcome was change in infant weight from birth to 6 months. Secondary outcomes included time to lactogenesis, breastfeeding continuation at 3 and 6 months, and change in infant head circumference and length from birth to 6 months. We chose change in infant weight as our primary outcome to capture a measure of any effect of change in breastfeeding on infant health. In order to investigate mediators of potential effects on infant health, we also investigated breast feeding outcomes. We estimated that we would need 154 infants (77 in each group) to detect a 10% change in infant weight between groups from birth to 6 months. We based this estimation on our assessment that a 10% difference between the two groups is clinically meaningful. For the secondary outcome of lactogenesis, we assumed a mean onset of lactogenesis to be 65 h with a standard deviation of 20 h based on a previous study of postpartum implant users [10]. We estimated we would require 90 women (45 in each group) to have an 80% power to detect a difference of 12 h between groups assuming a two-sided alpha of 0.05. We considered a difference of more than 12 h clinically meaningful because other studies have shown common labor and delivery interventions, such as epidural anesthesia and cesarean delivery, to delay onset of lactogenesis by up to 13 h [20].

We analyzed bivariate comparisons using chi-squared test or Fisher’s Exact test for categorical variables and *t* test or Wilcoxon rank-sum for continuous variables. We evaluated the primary outcome per intent-to-treat analysis. We assessed time to lactogenesis using a

Kaplan–Meier survival analysis with a log-rank test to compare the distribution between groups.

We carried out sensitivity analyses stratified to assess the potential impact of the intervention among women with a premature birth (defined as birth weight  $\leq 2500$  g in this setting) and among women with a term birth. We also carried out sensitivity analyses for the infant growth and breastfeeding continuation outcomes, excluding participants who were randomized after the onset of lactogenesis. We conducted a per-protocol analysis to assess the effect of the intervention among women who received the implant as planned by randomization.

We collected and managed the data using REDCap electronic tools housed at the University of California, San Francisco, and we used STATA software (version 14) to analyze the data. The ethics review boards of the University of California, San Francisco, and Mulago Hospital, and the Ugandan National Council for Science and Technology approved the protocol. We used the CONSORT guidelines for reporting.

**Table 1**  
Baseline characteristics of women randomized to immediate and delayed two-rod LNG contraceptive implant initiation

	All participants N=183	Immediate placement N=96	Delayed placement N=87
	N (%)	N (%)	N (%)
Age (mean, SD)	26.8 (5.4)	26.2 (5.1)	27.4 (5.6)
Education completed			
No formal schooling	4 (2.2)	2 (2.1)	2 (2.1)
Some primary school	60 (32.8)	31 (32.3)	29 (33.3)
Some secondary school	102 (55.7)	57 (59.4)	45 (51.7)
Some university	17 (9.3)	6 (6.3)	11 (12.6)
Previous breastfeeding experience	134 (73.2)	70 (72.9)	64 (73.6)
Number of living children			
3 or more	100 (54.6)	48 (50.0)	52 (59.8)
Cesarean delivery	60 (32.8)	34 (35.4)	26 (29.9)
Premature delivery	16 (8.7)	6 (6.3)	10 (11.5)
Days from delivery to implant placement <sup>a</sup> (mean, SD)	23.0 (35.2)	1.4 (1.1)	68.3 (28.1)

<sup>a</sup> Data on time of implant placement were available for 90 women in the immediate placement group and 43 women in the delayed placement group.

**Table 2**  
Infant growth from birth to 6 months of age among infants born to women randomized to immediate and delayed two-rod LNG contraceptive implant initiation

Intention-to-treat analysis				
	Immediate placement	Delayed placement		
	N=60	N=43	Difference	
	Mean (SD)	Mean (SD)	(95% CI)	p value
Weight (g)	4631.7 (1020.0)	4407.0 (957.3)	224.7 (−169.5 to 618.8)	.26
Head circumference (cm)	9.3 (2.6)	9.5 (2.7)	0.2 (−0.8 to 1.2)	.70
Length (cm)	14.7 (5.3)	15.2 (5.1)	0.5 (−1.6 to 1.3)	.63
Analysis restricted to women randomized before onset of lactogenesis				
	N=39	N=24		
Weight (g)	4555.4 (1039.1)	4570.8 (950.3)	15.4 (−506.7 to 537.6)	.95
Head circumference (cm)	9.7 (2.6)	9.4 (2.5)	0.3 (−1.1 to 1.6)	.69
Length (cm)	14.2 (6.6)	15.4 (5.0)	1.2 (−1.9 to 4.4)	.43

### 3. Results

Initially, we randomized 205 women to the immediate group ( $n=103$ ) and to the delayed group ( $n=102$ ) (Fig. 1). After excluding multiple births and perinatal mortalities, we analyzed the data from the remaining 96 women in the immediate group and the remaining 87 women in the delayed group for the infant growth and breastfeeding continuation outcomes. After excluding those who underwent lactogenesis prior to enrollment, we analyzed the data from 55 women in the immediate group and 42 women in the delayed group for the lactogenesis analysis (Fig. 2). Eighty-six women in the immediate group and 75 in the delayed group participated in a follow-up visit at 6 months. Sixty infants in the immediate group and 43 infants in the delayed group presented for follow up at 6 months.

The majority of women had three or more live children (55%) (Table 1). Thirty-three percent of women had a cesarean delivery, and 73% reported prior experience breastfeeding. The mean time from delivery to implant placement was 34 h (range 4–108 h) in the immediate group and 68 days in the delayed group (range 44–121 days).

#### 3.1. Change in infant growth

In both groups, we found similar changes in infant weight, head circumference and length from birth to 6 months. Infants in the immediate group gained 4632 g compared to 4407 g in the delayed group,  $p=.26$

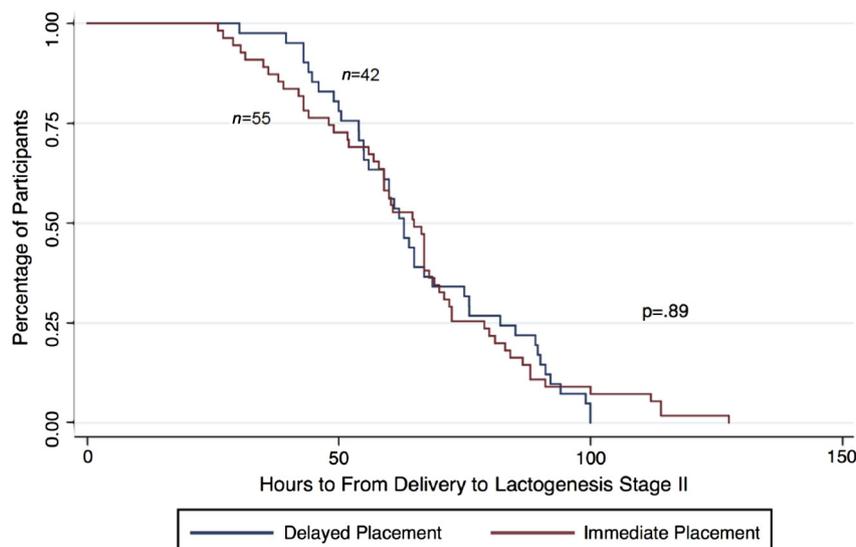
(Table 2). The head circumference of infants in the immediate group increased 9.3 cm compared to 9.5 cm in the delayed group,  $p=.70$ . Infants in the immediate group grew 14.7 cm in length compared to 15.2 cm in the delayed group,  $p=.63$ .

The sensitivity analyses did not change the overall findings, with the exception of the effect of the intervention among women with a premature birth. Infant weight from birth to 6 months increased in the immediate group compared to infants in the delayed group: premature infants in the immediate group gained 6033 g compared to 4563 g in the delayed group,  $p=.006$ . The overall findings did not change when premature infants were excluded (data not shown).

Infant growth from birth to 6 months was similar between groups after excluding participants who were randomized before the onset of lactogenesis. Among women who were randomized prior to lactogenesis, infants in the immediate group gained 4555 g compared to 4571 g in the delayed group,  $p=.99$ . The head circumference of infants in the immediate group increased 9.7 cm compared to 9.4 cm in the delayed group,  $p=.69$ . Infants in the immediate group grew 14.2 cm in length compared to 15.4 cm in the delayed group,  $p=.63$  (Table 2).

#### 3.2. Lactogenesis II

We found no difference in median time to lactogenesis among women who had not undergone lactogenesis at the time of



**Fig. 3.** Kaplan–Meier survival curve of time to onset of lactogenesis among women in a randomized trial evaluating the effect of LNG contraceptive implants on breastfeeding outcomes in Uganda in 2015–2016, restricted to women randomized before onset of lactogenesis.

**Table 3**  
Breastfeeding continuation among women randomized to immediate and delayed two-rod LNG contraceptive implant initiation (intention to treat)

	Immediate placement	Delayed placement	Risk	p value
	N=84 (3 months)	N=70 (3 months)	Difference	
	N=86 (6 months)	N=75 (6 months)	(95% CI)	
	N (%)	N (%)		
Exclusive breastfeeding				
3 months	62 (73.8)	50 (71.4)	2.4 (−11.8 to 16.5)	.74
6 months	41 (47.7)	39 (52.0)	4.3 (−11.1 to 19.8)	.58
Any breastfeeding				
3 months	83 (98.8)	70 (100.0)	1.2 (−1.1 to 3.5)	.54
6 months	83 (96.5)	75 (100.0)	3.5 (−0.4 to 7.4)	.25
Any concerns about breastmilk supply				
3 months <sup>a</sup>	21 (25.6)	16 (23.9)	1.7 (−12.2 to 15.6)	.81
6 months <sup>b</sup>	27 (31.4)	27 (37.0)	5.6 (−9.2 to 20.4)	.46

<sup>a</sup> Eighty-two women in the immediate placement group and 67 women in the delayed placement group answered this question.

<sup>b</sup> Seventy-three women in the delayed placement group answered this question.

randomization: 65 h in the immediate group (IQR 48–79, range 26–128) and 63 h in the delayed group (IQR 51–82, range 1–100),  $p=.84$ . Both groups had a mean time to lactogenesis of 65 h (Fig. 3). No women reported lactogenesis failure.

### 3.3. Breastfeeding continuation and concerns

A similar proportion of women reported exclusive breastfeeding between groups at 3 months: 74% in the immediate group and 71% in the delayed group,  $p=.74$ ; and 6 months: 48% in the immediate group and 52% in the delayed group,  $p=.58$  (Table 3). Almost all women (>96%) reported some breastfeeding at 3 and 6 months. We found no statistically significant differences between groups in the proportion of women reporting a concern about breastmilk supply.

The overall finding did not change when stratifying by premature or full-term delivery, or restricting to women randomized prior to lactogenesis (data not shown).

### 3.4. Per-protocol analysis

When we evaluated the infant growth and breastfeeding continuation outcomes among women who received the implant as planned at the time they were randomized to, the results did not change (Table 4).

### 3.5. Infant deaths

One infant died between the first week of life and 6 months. This infant weighed 1500 g at birth, and the infant's mother received an immediate postpartum implant.

## 4. Discussion

This study found that infant growth, onset of lactogenesis and breastfeeding continuation were similar between women randomized to immediate postpartum initiation of LNG implants and women randomized to delayed insertion at 6 to 8 weeks postpartum. We found no difference between groups in either infant weight or breast feeding outcomes that would be on the pathway to changes in infant weight. These findings are consistent with the preponderance of literature supporting the hypothesis that progestin-containing contraceptives do not compromise a woman's ability to initiate or sustain breastfeeding and do not adversely affect infant growth [21]. Our findings support the safety of initiating LNG implants, a method commonly used worldwide, immediately after delivery among breastfeeding women.

Our results are consistent with studies demonstrating no harmful effect of immediate postpartum insertion of the etonogestrel-releasing contraceptive implant on onset of lactogenesis II [10], exclusive breastfeeding [13] or infant growth [14]. A number of prior studies

**Table 4**  
Per-protocol analysis among women receiving delayed and immediate two-rod LNG contraceptive implants

Infant outcomes	Immediate placement	Delayed placement	Risk difference	p value
	N=57	N=17	(95% CI)	
	Mean (SD)	Mean (SD)		
Weight (g)	4580.7 (1007.4)	4682.4 (1121.0)	101.7 (−467.8 to 671.1)	.72
Head circumference (cm)	9.03 (2.4)	9.62 (2.0)	0.6 (−0.7 to 1.8)	.36
Length (cm)	15.2 (4.7)	16.4 (5.6)	1.16 (−1.7 to 4.0)	.42
Maternal outcomes	N=80 (3 months)	N=21 (3 months)		
	N=82 (6 months)	N=23 (6 months)		
	N (%)	N (%)		
Exclusive breastfeeding				
3 months	59 (73.8)	17 (81.0)	7.2 (−12.2 to 26.6)	.50
6 months	40 (48.8)	15 (65.2)	16.4 (−5.8 to 38.7)	.16
Any breastfeeding				
3 months	79 (98.8)	21 (100.0)	1.2 (−1.2 to 3.7)	.61
6 months	79 (96.3)	23 (100.0)	3.7 (−0.4 to 7.7)	.35
Any concerns about breastmilk supply				
3 months <sup>a</sup>	21 (26.6)	5 (23.8)	2.8 (−17.9 to 23.4)	.52
6 months	26 (31.7)	6 (26.1)	5.6 (−15.0 to 26.2)	.60

<sup>a</sup> Seventy-nine women in the immediate placement group answered this question.

evaluated the effect of the previously used six-rod LNG implant system on breastfeeding outcomes and did not find a difference in breastfeeding duration, supplementation, infant growth or development [21]. However, these prior studies initiated implants at greater than 7 days, so they do not assess the effect of early initiation of LNG implants on establishment of breastfeeding.

Two prior randomized trials showed lower breastfeeding continuation among women initiating LNG-intrauterine devices (IUDs) early in the postpartum period, raising concern for a possible deleterious effect of LNG specifically on breastfeeding. The first study showed decreased breastfeeding continuation at 75 days among women initiating a LNG-IUD between 32 and 56 days, but this difference was no longer present at 6 months [22]. A secondary analysis showed that a lower proportion of women randomized to immediate postplacental LNG-IUDs breastfed at 6 months compared to women randomized to delayed (6 weeks postpartum) LNG-IUD insertion (3/50 vs. 11/46,  $p=.02$ ) [23]. However, a recent larger noninferiority randomized trial designed to evaluate the effect of immediate insertion of LNG-IUD use on breastfeeding found LNG-IUDs to have non-inferior time to lactogenesis and breastfeeding continuation at weeks ( $n=259$ ) [24]. Our study provides further evidence that early initiation of LNG-containing contraceptives does not affect initiation or continuation of breastfeeding.

Some strengths of this study include the randomized design, longitudinal follow-up and low loss to follow-up among women (<10%) [7], which minimizes the risk of bias in the outcomes which rely on follow-up of the women. Another strength is our study considered infant weight in the context of breastfeeding. If the lack of difference in infant weight gain between groups was due to increased supplementation among one group, we may have seen no difference in weight gain but would then expect decreases in breastfeeding. The fact that we saw no change in infant weight or breastfeeding together provides further evidence that early initiation of LNG-containing contraceptives does not have a harmful effect on breastfeeding outcomes.

This study had several limitations. This was a planned secondary analysis, so the study was not designed with breastfeeding as a primary outcome. Therefore, we enrolled some women in the study who had already undergone lactogenesis, which could cause bias. We excluded these women from the lactogenesis analysis. Sensitivity analyses of breastfeeding continuation and infant growth, excluding the women who underwent lactogenesis prior to randomization, were consistent with the overall findings among all women randomized. In addition, we did not power this study to assess breastfeeding outcomes among women at risk for low milk supply (such as women with premature infants), which warrants further evaluation. Because of limited power for some outcomes (i.e., concerns about supply), these confidence intervals were not narrow enough to exclude clinically meaningful differences. Therefore, there may be small differences between groups that we were underpowered to detect. Furthermore, we had greater than expected missing data for the infants at 6 months either because the mothers did not bring the infants to the 6-month follow-up visit or because the visit was conducted by phone. However, the confidence interval around the risk difference for the change in infant weight indicates that our results are consistent with, at most, an infant weight loss of 169.5 g, which is only a 4% decrease.

Another limitation of this study is that we extended follow-up to only 6 months. Thus, we cannot evaluate the long-term effects of early progestin exposure on infant growth and development; this warrants further evaluation. Many participants had three or more children, and the majority of participants had previous experience breastfeeding, thus limiting the generalizability of our findings. In addition, we chose measures of growth widely used globally, which are based on studies with methodologic limitations [25]. There may be better indicators of infant growth, such as tibial length [26]. We chose to use weight, length and head circumference, which are the standard measurements used in many large cohort studies of infant growth [27,28] as recommended by the WHO [19]. Lastly, there may be better indicators of maternal

breastmilk intake, such as deuterium [26], but studying these requires specialized equipment not easily available in Uganda.

In summary, offering women LNG implants in the immediate postpartum period has the potential to improve utilization of a highly effective contraceptive, enabling women to achieve desired birth spacing and avoid unintended pregnancies. Our study provides further evidence that this practice does not have a deleterious effect on infant growth or initiation or continuation of breastfeeding.

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