Comparison of levonorgestrel level and creatamatocrit in milk following immediate vs. delayed postpartum insertion of levonorgestrel IUD: a pilot randomized controlled trial

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Abstract

**Background:** Both breastfeeding and the use of postpartum contraception critically influence infant and maternal health outcomes. In this pilot study, we explore the effects of timing and duration of postpartum levonorgestrel exposure on breastfeeding through objective assessments of milk lipid and levonorgestrel content to establish baseline data for future research.

**Methods:** This substudy includes thirty-two participants from multiple clinical sites in Salt Lake City, Utah. All participants planned to breastfeed, and self-selected for this sub-study from among 259 women enrolled in a parent randomized controlled trial comparing immediate to delayed (4-8 weeks) postpartum levonorgestrel IUD insertion. Participants provided two milk samples: first at 4-8 weeks postpartum (before IUD placement for the delayed group) and second four weeks later. Participants were paired by group assignment, and we used the Wilcoxon rank sum (inter-group) and signed rank (intra-group) tests to compare milk lipid content (creamatocrit) and levonorgestrel levels between groups and time points.

**Results:** Fifteen participants were allocated to the immediate group and 17 to the delayed group. Initially, median levonorgestrel concentration of the immediate group (n=10) (32.5 pg/mL, \( IQR: 24.8, 59.4 \)) exceeded that of the delayed group (n=12) (17.5 pg/mL, \( IQR: 0.0, 25.8 \)) (p=0.01). Four weeks later, the values aligned: 26.2 pg/mL (\( IQR: 20.3, 37.3 \)) vs. 28.0 pg/mL (\( IQR: 25.2, 40.8 \)). Creamatocrits were similar between both groups and timepoints.

**Conclusions:** Immediate postpartum levonorgestrel IUD placement results in steady, low levels of levonorgestrel in milk without significant effects on lipid content. These findings support the safety of immediate postpartum levonorgestrel IUD initiation, and future research should assess time-based meaningful outcome changes to capture clinically significant differences.

**Trial Registration:** This randomized controlled trial was registered with ClinicalTrials.gov (registry number NCT01990703) on November 21, 2013.

**Background**

Both breastfeeding and the use of postpartum contraception critically influence not only infant but also maternal health outcomes (1, 2). Immediate postpartum initiation of highly effective, long-acting contraception eliminates the risk of early pregnancy and avoids the need to return to the clinic for (typically less comfortable) intrauterine device (IUD) insertion (3). Understanding the effect of immediate postpartum hormonal contraception on breastfeeding through objective assessments of milk production and exogenous progestogen content can inform counseling and decision-making.

Four decades ago, researchers used an accurate but logistically challenging radioimmunoassay to assess levonorgestrel levels in milk from women with high-dose levonorgestrel IUDs (4). Using a new commercially-available enzyme immunoassay for levonorgestrel as well as traditional creamatocrit measurements, we sought exploratory data to assess differences in milk levonorgestrel and lipid content.
over time to provide point estimates for future research on exogenous progestogen and creamatocrit lipid levels among women receiving an early versus delayed postpartum levonorgestrel IUD.

Methods

Design

This exploratory secondary analysis derives from the Breastfeeding Levonorgestrel IUD Study, a randomized controlled noninferiority trial comparing breastfeeding continuation at eight weeks postpartum between women who received immediate (within 30 minutes) post-placental levonorgestrel IUD placement and delayed (4-8 weeks postpartum) placement. Thus, criteria for eligibility for this sub-study were prior consent and enrollment in the parent study. Parent study details, including randomization allocation and other relevant recruitment data, have been previously reported (5). All sub-study participants enrolled in Salt Lake City, Utah. The Institutional Review Board at the University of Utah approved the study [IRB#_00062844]. This sub-study adheres to the CONSORT guidelines for randomized trials.

From January 2014 through November 2016, research personnel used medical records to approach potential participants at multiple clinical sites in Salt Lake City. All participants had plans to breastfeed and a stated interest in the levonorgestrel IUD. Study participants provided written consent, and opted in to the sub-study using a checkbox on the parent study's consent documents. Figure 1 details the study timeline by assignment group. We asked all sub-study participants to provide self-expressed milk samples at both the first postpartum visit (at 4-8 weeks) and the second four weeks later. In this exploratory study, we compared both levels of levonorgestrel and creamatocrit—a simple measure of lipid content in milk that can provide insight into the fat and energy content of human milk (6)—in the milk samples of women who received IUDs at different timepoints.

Sample

Of the 259 women who enrolled in the parent study, a portion self-selected to participate in this sub-study. All participants were age 18-40 years and had delivered a healthy term infant (³ 37 weeks gestation). Sub-study participants returned for a follow-up visit four weeks after IUD insertion. We planned to cease recruitment when we obtained 12 paired (initial and four-week follow up) samples from each group. We oversampled by 25% in case of loss to follow-up (7).

Creamatocrit Measurement

Participants provided two mid-feeding milk samples (10ml each) at a 4-8 week postpartum clinic visit and second samples at home approximately four weeks later. For those in the delayed group, initial sample collection occurred at the same clinic visit as IUD placement. All other samples were collected after IUD placement, as in Figure 1. Research personnel transported samples to an -80 °C freezer within one hour of expression. Later, a research team member (NGH) blinded to group assignment thawed each
sample and measured lipid levels using the creamatocrit method twice and reported mean values for analysis (6). Samples were returned to the −80 °C freezer to await the subsequent levonorgestrel assay.

**Levonorgestrel Assay**

We shipped frozen milk samples to Arbor Assays in Ann Arbor, Michigan, for analysis. There, technicians processed each sample using Arbor Assay DetectX Levonorgestrel Enzyme Immunoassay Kit instructions (8). Samples were run in duplicate with a known levonorgestrel standard. SoftMax® 4 parameter logistic fitting software (Molecular Devices, San Jose, CA) was used to calculate results. See Supplement A for assay details and commentary.

**Data Analysis**

Participants were paired by group assignment, and data analysis was blinded. Using Stata 15 statistical software (StataCorp LP, College Station, TX USA), we conducted the Wilcoxon rank sum (inter-group) and signed rank (intra-group) tests to compare levonorgestrel levels and creamatocrit between groups and times. We also conducted a sensitivity analysis to compare outcomes among those who experienced IUD expulsions (and subsequent reinsertion) (expulsion in delayed group=1 [5%], expulsion in immediate group=2 [9%]) and no expulsion (n=19, [86%]).

**Results**

**Participant Characteristics**

Table 1 presents participant characteristics. In total, 32 participants provided an initial milk sample at the first postpartum visit. Of these, 22 (immediate=12, delayed=10) provided a second sample, and we limit analyses to this group. Ten participants (immediate=5, delayed=5) did not provide a second sample for reasons including discontinuing breastfeeding and IUD expulsion without reinsertion.
**Table 1. Demographics of BLIS* participants providing milk samples, by randomization arm (N=22)**

| Variables                        | Early Insertion | Delayed Insertion |
|----------------------------------|-----------------|-------------------|
|                                  | n=12            | n=10              |
|                                  | n (%)           | n (%)             |
| Age<sup>a</sup>                  |                 |                   |
| 18-24                            | 4 (33)          | 2 (22)            |
| 25-29                            | 4 (33)          | 3 (33)            |
| 30-34                            | 3 (25)          | 2 (22)            |
| 35-39                            | 1 (8)           | 2 (22)            |
| Full-time employment             |                 |                   |
| Yes                              | 1 (8)           | 1 (10)            |
| No                               | 11 (92)         | 9 (90)            |
| History of obesity               |                 |                   |
| Yes                              | 2 (20)          | 0                 |
| No                               | 8 (80)          | 10 (100)          |
| Gravidity                        |                 |                   |
| None                             | 0               | 0                 |
| 1                                | 1 (8)           | 0                 |
| ≥2                               | 11 (92)         | 10 (100)          |
| History of prior breastfeeding    |                 |                   |
| Yes                              | 11 (92)         | 9 (90)            |
| No                               | 1 (8)           | 1 (10)            |
Initial breastfeeding duration goal

|         | < 6 months | > 6 months |
|---------|------------|------------|
|         | 1 (8)      | 11 (92)    |
|         | 1 (10)     | 9 (90)     |

* BLIS stands for Breastfeeding Levonorgesterel Intrauterine Device Study.

\[\text{a} \quad \text{One participant in the delayed insertion group did not provide age.}\]

**Levonorgestrel Concentrations**

At the first postpartum visit, the median levonorgestrel concentration of the immediate group was 32.5 pg/mL (IQR: 24.8, 59.4), and the delayed group was 17.5 pg/mL (IQR: 0.0, 25.8), (p=0.01). Four weeks later, the values aligned: 26.2 pg/mL (IQR: 20.3, 37.3) in the immediate group and 28.0 pg/mL (IQR: 25.2, 40.8) in the delayed group. No difference was found in the immediate group’s levonorgestrel concentrations between postpartum visits (p=0.38). Sensitivity analysis described above in Methods: Data Analysis did not significantly alter results.

**Creamatocrit**

We observed similar median creamatocrit values at the initial (4-8 weeks) postpartum visit [immediate=5.9% (IQR: 2.8%, 8.1%); delayed=5.1% (IQR: 3.4%, 7.4%)] and four weeks later [immediate=4.7% (IQR: 3.9%, 7.7%); delayed=3.9% (IQR: 3.6%, 4.9%)]. Additionally, intragroup median creamatocrits were similar between the two time points for the immediate or delayed groups. Sensitivity analysis described in section 2.5 did not significantly alter results.

**Discussion**

This exploratory study provides point estimates for milk levonorgestrel levels and lipid levels in postpartum individuals initiating levonorgestrel IUD contraception immediately and 4-8 weeks later. We found that women receiving delayed IUD placement eventually have similar levonorgestrel milk levels and similar milk lipid content compared to those receiving immediate postpartum IUD placement. Our findings align with previous research, which suggests the temporal stability of levonorgestrel levels in milk (4).

It is unclear why some participants in the delayed group had trace amounts of levonorgestrel in their initial milk sample before the insertion of a levonorgestrel IUD. Notably, our results are consistent with those from the assay development, which also identified trace amounts of levonorgestrel in urine samples of individuals (including males) not using a levonorgestrel-containing product (8). While these findings may represent contamination or cross-reactivity of the assay, further research investigating background levonorgestrel levels in human milk may help clarify the significance of this finding.
Study limitations include small sample size and limited power to detect small differences between groups, between primiparous and multiparous women, across BMI, across body fat distribution, and across time by the number of weeks postpartum. Furthermore, all participants identified as Latina. Thus, although ethnicity likely does not affect lipid or hormone levels in human milk, results from this study may not be generalizable. Initially, we planned to obtain infant plasma levonorgestrel levels; however, no participants agreed to an infant blood draw. Moreover, at follow-up, many participants reported changes in breastfeeding behavior such as bottle feeding, supplementation, or exclusive artificial milk feeding. Breastfeeding behavior affects milk composition, and these changes may have influenced lipid levels. Lastly, crematocrit has traditionally been used as a proxy measure of milk energy content. However, we now know that a variety of factors, including the time of day collected, time since the last feeding, whether fresh or stored, and whether foremilk or hindmilk may influence crematocrit (9).

**Conclusion**

Overall, our study provides evidence that immediate postpartum levonorgestrel IUD placement results in steady, low levels of levonorgestrel in milk without significant effects on lipid content. These findings add to the growing body of literature supporting the safety of immediate postpartum levonorgestrel IUD initiation. While not powered to detect noninferiority, our study presents baseline data to inform future research. Future studies examining differences between immediate and delayed contraceptive use should assess time-based meaningful outcome changes to capture clinically significant differences.

**Abbreviations**

IUD
intrauterine device

**Declarations**

*Ethics and Approval and Consent to Participate*

The Institutional Review Board at the University of Utah approved the study [IRB# .00062844].

*Consent for Publication*

Not applicable.

*Availability of Data and Materials*

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

*Competing Interests*
The University of Utah Department of Obstetrics and Gynecology Program in Family Planning receives research funding from Bayer Women’s Health Care, Merck & Co. Inc., Cooper Surgical, Sebela Pharmaceuticals, and Medicines 360. DKT serves as a consultant for Sebela Pharmaceuticals. The other authors report no conflicts of interest.

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Authors’ Contributions

NGH contributed to conception, design, acquisition, analysis, and interpretation in addition to drafting and critically revising the manuscript. RGS contributed to analysis, interpretation, drafting, and critically revising the manuscript. JS contributed to conception, design, acquisition, analysis, and interpretation in addition to critically revising the manuscript. KW contributed to conception, design, acquisition, analysis, and interpretation in addition to critically revising the manuscript. SMJ contributed to conception, design, acquisition, analysis, and interpretation in addition to critically revising the manuscript. EE contributed to conception and design in addition to critically revising the manuscript. DTK contributed to conception, design, acquisition, analysis, and interpretation in addition to drafting and critically revising the manuscript. All authors read and approved the final manuscript and agree to be both personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Authors' Information (optional)

Not applicable.
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Figures
Figure 1

Timeline of participant intrauterine device (IUD) placement and milk collection by assignment group

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement1ELISAandCVs20200420FINAL.docx