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Original Research

# Effect of Progestin Compared With Combined Oral Contraceptive Pills on Lactation: A Randomized Controlled Trial

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### Abstract

**OBJECTIVE:** To estimate the effect of progestin-only compared with combined hormonal contraceptive pills on rates of breastfeeding continuation in postpartum women. Secondary outcomes include infant growth parameters, contraceptive method continuation, and patient satisfaction with breastfeeding and contraceptive method.

**METHODS:** Postpartum breastfeeding women who desired oral contraceptives were

randomly assigned to progestin-only and combined hormonal contraceptive pills. At 2 and 8 weeks postpartum, participants completed in-person questionnaires that assessed breastfeeding continuation and contraceptive use. Infant growth parameters including weight, length, and head circumference were assessed at 8 weeks postpartum. Telephone questionnaires assessing breastfeeding, contraceptive continuation, and satisfaction were completed at 3–7 weeks and 4 and 6 months. Breastfeeding continuation was compared between groups using Cox proportional hazards regression. Differences in baseline demographic characteristics and in variables between the two intervention groups were compared using  $\chi^2$  tests, Fisher exact test, or two-sample  $t$  tests as appropriate.

**RESULTS:** Breastfeeding continuation rates at 8 weeks (progestin-only 63.5%; combined hormonal 64.1%), contraceptive continuation, and infant growth parameters did not differ between users of progestin-only and combined hormonal contraceptive pills. Infant formula supplementation and maternal perception of inadequate milk supply were associated with decreased rates of breastfeeding in both groups.

**CONCLUSION:** Choice of combined hormonal or progestin-only contraceptive pills administered 2 weeks postpartum did not adversely affect breastfeeding continuation.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, [www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT01465022.

**LEVEL OF EVIDENCE:** I

Contraception for breastfeeding women should be highly effective and not impair lactation. Prompt initiation of contraception after delivery reduces the likelihood of unintended pregnancy and, in low-resource settings, reduces maternal and infant morbidity and mortality.<sup>1,2</sup> Progestin-only pills are traditionally the oral contraceptive of choice because of concerns that combined pills may reduce breast milk production and, in turn, result in early discontinuation of breastfeeding or poor infant growth.<sup>3–7</sup> In nonbreastfeeding women, combined pills are known to have several advantages over progestin-only pills, such as fewer side effects, better efficacy, and higher continuation rates.<sup>8,9</sup> Nonetheless, if combined pills diminish the quality or quantity of breast milk in a clinically meaningful way, then progestin-only pills will be preferable for most breastfeeding women desiring oral contraception. If combined pills have a negligible clinical effect on breastfeeding outcomes, then combined pills are a better contraceptive choice for most breastfeeding women.

Our aim was to estimate the effect of postpartum use of progestin-only pills compared with combined pills on breastfeeding continuation at 8 weeks postpartum. Secondary outcomes included infant growth, contraceptive method continuation, and patient satisfaction with both breastfeeding and the assigned oral contraceptive.

## **MATERIALS AND METHODS**

This double-blind randomized trial was conducted at the University of New Mexico between January 2005 and June 2008. The University of New Mexico Human Research Review Committee approved the study and all women gave written informed consent. We enrolled postpartum women aged 15–45 years who delivered at the University of New Mexico Hospital who intended to breastfeed, planned to use oral contraceptives as their family planning method, and were willing to be randomized to either progestin-only pills or combined pills. Women were excluded if they had: 1) medical contraindications to combined pills, including a history of venous thromboembolism, uncontrolled hypertension, or complex migraine headaches; 2) preterm birth (less than 37 weeks); 3) a small-for-gestational-age (less than 2,500 g) or large-for-gestational-age (more than 4,500 g) newborn; or 4) a newborn with a major congenital anomaly.

Study information was distributed using a flyer at the 35-week visit to women receiving prenatal care at University of New Mexico Health Sciences-affiliated clinics and who planned to deliver at University of New Mexico Hospital. Research nurses approached eligible participants after delivery and provided details about the study. Monetary compensation of \$20 was provided at enrollment, 2 weeks and 2 months postpartum, for a total of \$60 for women who completed the entire study.

Consented participants completed a questionnaire that included patient characteristics including insurance type, smoking history, breastfeeding history, and history of contraceptive use. Infant length, weight, and head circumference (occipitofrontal) measurements were obtained using a study-dedicated scale throughout the patient's participation to avoid measurement inconsistencies. At enrollment, to ensure that all women had access to contraception whether or not they continued in the study, women were given an envelope containing a written prescription for the oral contraceptive of their provider's choice to be filled in case they decided against study participation.

One week postpartum, participants were contacted by telephone. Those who discontinued breastfeeding or who no longer wished to participate were encouraged to start contraception and follow-up with a routine postpartum visit. Those who continued breastfeeding and reaffirmed their interest in participation were scheduled for a 2-week study visit during which they were randomized to the study medications. The randomization sequence was generated in blocks of six by a general clinical research center biostatistician. The randomization consisted of forcing each consecutive block of six participant identifications to have precisely three treatment assignments from each of the two groups, but randomly permuting the order of those assignments using standard statistical software (SAS).

The randomization list was e-mailed to the research pharmacist, who alone had access to randomization information for the duration of the study. The research nurse notified the research pharmacist when randomizations were needed and the research pharmacist dispensed the initial supply of blinded medication that was indicated on the randomization list, assigning participants to the next available treatment.

At the 2-week study visit, participants completed a questionnaire, growth assessments of

their infants were performed, and participants received study medication. The progestin-only pills group used 0.35 mg of norethindrone once per day orally and the combined pills group took 1 mg of norethindrone and 0.035 mg of ethinyl estradiol (E2) once per day orally for 21 days, followed by 7 days of placebo pills. We chose norethindrone-containing combined oral contraceptives and progestin-only pills to eliminate the potential effect of the type of progestin on oral contraceptive continuation.<sup>10</sup> The norethindrone dose in the combined oral contraceptives was higher than that in the progestin-only pills, reflecting conventional use. The research pharmacist prepared pill packs by removing assigned pills from their blister packs and placing them in red plastic capsules. All pills were placed in identical monthly pill dispensers to disguise their appearance. Because there were 7 days of placebo in the combined pills but not in the progestin-only pills arm, the pharmacist ensured that cells were filled in the proper order, numbered from 1 through 28. Once filled by the research pharmacist, the cells were taped shut until the participant needed the product for that block of days.

At 2 weeks postpartum, participants returned to the University of New Mexico Hospital and met with the research nurse. At this visit, women completed a questionnaire regarding breastfeeding progress, including continuation, supplementation with formula, the perception of adequate milk supply, and satisfaction with breastfeeding. Infant growth parameters (weight, height, and head circumference) were obtained and plotted on a growth curve. Women received 8 weeks of the previously blinded oral contraceptives at this visit and the research nurse observed the woman taking her first pill. The research nurse instructed the participants about the importance of using the pills in order.

Participants were telephoned weekly by the research nurse between 3 and 7 weeks postpartum and completed a verbal questionnaire that addressed continuation of and satisfaction with breastfeeding, the use of supplemental formula, and satisfaction with the oral contraceptive. At 2 months postpartum, participants returned to the hospital for a follow-up visit and completed a research nurse-administered questionnaire identical to the telephone follow-up questionnaires. The infant's length, weight, and head circumference were obtained and plotted on the growth curve. Participants received an additional 4 months of oral contraceptives prepared by the research pharmacist in the same manner as the initial supply. Participants were contacted by telephone at 4 and 6 months and completed the same questionnaire.

All study personnel and participants were blinded to treatment assignment for the duration of the study. The randomization code was unlocked and revealed to the researchers only after participant recruitment and data collection were complete.

Our primary outcome measure was the continuation of breastfeeding in women using progestin-only pills compared with women using combined pills at 8 weeks postpartum. Secondary end points included breastfeeding rates at 4 and 6 months postpartum. We chose 8 weeks as the time point for our primary breastfeeding continuation end point with the expectation that any negative effect of combined oral contraceptives on breastfeeding would

be evident by then. Secondary outcome measures were infant weight and length, and continuation and satisfaction with the contraceptive method. Additional analyses examined reasons for discontinuing breastfeeding, discontinuing oral contraceptives, and for supplementing infant feeding with formula.

Sample size calculation, based on the primary study aim, indicated that 120 participants divided equally between the two groups would provide a power of 80% at a two-sided significance level of 5% to detect a difference in continuation of breastfeeding of 35% in the combined pills group compared with 60% in the progestin-only pills group at 8 weeks postpartum. The calculation was based on the assumption that 50% of women would still be breastfeeding at 8 weeks postpartum and that the study was powered for a hazard ratio of 2. Anticipating a 20% loss to follow-up, this number was increased to 150 study participants. Recruitment was expanded to 200 women because of a higher than expected loss of participants between enrollment and randomization.

Statistical analyses were conducted using SAS 9.2. Differences in baseline demographic characteristics and in variables between the two intervention groups were compared using  $\chi^2$  tests, Fisher exact test, or two-sample *t* tests as appropriate. Significance for all analyses was set at  $P < .05$ .

A survival model was used for analysis of the primary outcome of breastfeeding duration. Continuation of breastfeeding was compared between the two groups using Cox proportional hazards regression adjusting for time-varying covariates of formula supplementation (supplemented with formula in the time period preceding each contact) and adequate milk production (the woman's perception that milk production was adequate in the time period preceding each contact). Breastfeeding duration data were censored from two sources: women still breastfeeding at the end of the study and women in the study for some number of weeks but with whom contact was lost before 6 months (loss to follow-up). Although the main study end point was 8 weeks, the survival analysis used the full 6-month follow-up period. Treatment group was fit as a factor in the model; the variables oral contraceptive history and breastfeeding history (for which there was some imbalance of groups at baseline) were entered as covariates. The time-varying covariates ("currently supplementing" and "have concerns about milk supply") were entered as well (for the previous time period). For the time-varying covariates, when there was a missing value for a time period, the last available value was carried forward. No similar data imputation was needed for the primary outcome of breastfeeding duration.

Although contact times were discrete (weeks 2–8 and months 4 and 6), an exact date for breastfeeding discontinuation was determined by the interviewer, allowing times until stopping breastfeeding to be treated as a continuous variable. Participants who discontinued breastfeeding before 8 weeks were discontinued from the study and infant growth parameters were not obtained at 8 weeks.

Two-sample *t* tests were used to analyze the two groups for measures of infant length and weight. Measures of oral contraceptive continuation and satisfaction were assessed by

logistic regression after adjusting for previous use of oral contraceptives.

## RESULTS

A total of 197 postpartum women who met inclusion criteria were enrolled before discharge from the hospital. At the 1-week phone call, 127 (63%) remained eligible and were randomized; 64 received combined pills and 63 received progestin-only pills. Outcomes of study participants are summarized in a flow diagram ([Fig. 1](#)). Seventy enrolled patients were not randomized, most commonly because they did not keep their follow-up appointment. Women who were not randomized were less likely to be high school graduates and less likely to be employed than those who were randomized ([Table 1](#)).



Fig. 1 Table 1

Patient characteristics were similar between the two groups, except that combined pill users were more likely to have used oral contraceptives previously, whereas progestin-only pills users were more likely to have breastfed previously ([Table 1](#)). At 2 weeks postpartum, before initiation of pills, the number of women exclusively breastfeeding and the number of women who perceived inadequate milk supply did not differ between groups ([Table 1](#)); 63.8% of all study participants were exclusively breastfeeding and 22% perceived inadequate milk supply. No protocol deviations occurred.

Survival analysis demonstrated no difference in the primary outcome of breastfeeding continuation between the two oral contraceptive groups over the full 6 months of follow-up ([Fig. 2](#)). Maternal breastfeeding supplementation with formula (“supplementing”) or maternal concern for inadequate milk supply (“milk concerns”) was predictive of breastfeeding discontinuation ([Table 2](#)). At the primary end point of 8 weeks, the number of women continuing to breastfeed between the two groups was not different: 64.1% of women in the combined pills group and 63.5% in the progestin-only pills group were still breastfeeding ([Fig. 3](#)).



Fig. 2 Table 2 Fig. 3

Over the 8-week study period, growth parameters between infants did not differ between groups, either in percent change in weight ( $P=.56$ ), length ( $P=.41$ ), or head circumference ( $P=.79$ ) ([Fig. 4](#)). The box plots in [Figure 4](#) demonstrate considerable overlap for the distributions of these variables between the two groups. At weekly time points between 2-week and 8-week visits, breastfeeding women did not differ in the percentage who continued to use pills. Of those continuing to breastfeed at 8 weeks, 98% of participants

assigned to combined pills and 100% assigned to progestin-only pills continued their pills (Fig. 3). Additionally, the number of women lost to follow-up was similar between the two groups at 8 weeks ( $P>.99$ ).

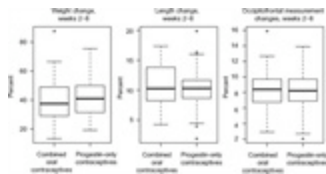


Fig. 4

Groups did not differ in reasons cited for discontinuing breastfeeding or contraceptive pills during the 6 months of the study (Table 3). Of women who discontinued breastfeeding, 44% of the progestin-only pills group and 55% of the combined pills group reported stopping because of a perceived lack of milk supply ( $P=.80$ ). Of those who discontinued their oral contraceptive, 23% of progestin-only pills users and 21% of combined pill users reported stopping because of a perceived negative effect of the assigned oral contraceptive on milk supply. Other reasons women gave for discontinuation of breastfeeding or oral contraceptives are shown in Table 3.

Reason	Combined Pill (n=100)	Progestin-Only Pill (n=100)	P-value
Lack of milk supply	55	44	.80
Negative effect on milk supply	21	23	.75
Other reasons	24	33	.12

Table 3

Groups at 2 and 8 weeks did not differ in satisfaction with breastfeeding, oral contraceptive use, perception of adequate milk supply, or supplementation with formula ( $P>.05$ ). At 8 weeks, all women who continued to breastfeed were somewhat or very satisfied with their oral contraceptive and 93% of combined pills users and 95% of progestin-only pills users were somewhat or very satisfied with breastfeeding. There were no pregnancies reported in the first 8 weeks in those continuing in the study and no adverse events reported during the 6 months of the full follow-up period.

## DISCUSSION

We found that breastfeeding duration and infant growth did not differ between women who initiated progestin-only pills compared with combined pills at 2 weeks postpartum. Reasons cited for discontinuing breastfeeding did not differ between groups; maternal perception of inadequate milk supply was the most common reason cited. We found that introduction of supplementation with formula or a perceived lack of milk supply correlated with breastfeeding discontinuation, whereas type of OCP used had no effect. Even at 2 weeks postpartum, approximately one third of women were already supplementing with formula

and one fifth perceived inadequate milk supply.

Breastfeeding rates at 8 weeks in our study were similar to rates found in the New Mexico Pregnancy Risk Assessment Monitoring System data. Overall, 84% of women in New Mexico initiate breastfeeding; however, only 60% are breastfeeding through 2 months postpartum.<sup>11</sup> Although 64% of our randomized study participants were breastfeeding at 8 weeks, only 28.3% were exclusively breastfeeding, agreeing with findings of generally low exclusive breastfeeding rates in U.S. women between 6 and 12 weeks postpartum.<sup>12,13</sup>

Other studies examining the effect of hormonal contraceptives on lactation and growth have demonstrated mixed results.<sup>3-7,14-16</sup> The most robust was a 1988 quasi-randomized trial of progestin-only pills compared with combined pills that found a lower volume of milk expressed in the combined pill group but no differences between groups in infant growth, breastfeeding continuation, and reasons for breastfeeding discontinuation.<sup>14</sup> Earlier trials, limited by methodologic flaws, demonstrate some differences in rates of breastfeeding and few differences in infant and child outcomes.<sup>3-5,15</sup> Additionally, some trials suggest lower pregnancy rates in women using progestin-only pills.<sup>4,5</sup>

Our study has limitations. The sample size was calculated to identify a 25% difference in continuation of breastfeeding at 2 months between the two study groups. Our findings highlight the need for a large randomized controlled trial with the aim of demonstrating equivalency between progestin-only pills and combined pills; our results support the feasibility of such a study. The high loss to follow-up rate in our study is explained partly by the recruitment of many participants from clinics that serve a population of women who are undocumented and mobile. Additionally, the results may not be applicable beyond the patient population studied, who were generally Hispanic and without an identified payment source for health care. Given the extent of early supplementation of breastfeeding with formula in our population, our results apply only to women with ready access to formula. Although women randomized to progestin-only pills were more likely to have breastfed in the past, they would have skewed the results to show more, not less, of an effect on reducing breastfeeding duration; it is unlikely that this difference had an effect on the results of the study. The combined oral contraceptive used in this study contains 35 micrograms of ethinyl E<sub>2</sub>, the highest dose in current common use. The lack of an effect on breastfeeding is reassuring with regard to formulations containing lower amounts of ethinyl E<sub>2</sub>.

Recommendations for using or avoiding combined pills in postpartum breastfeeding women vary. The Centers for Disease Control and Prevention United States medical eligibility criteria for contraceptive use recently updated its guidance on initiation of combined pills for postpartum women based on evidence that the increased risk of thromboembolism persists through 21 days postpartum. In postpartum breastfeeding women, initiation before 21 days is ranked as category 4 (unacceptable health risks); initiation at 21–29 days for women at low risk for thromboembolism is rated category 3 (theoretical or proven risks generally outweigh advantages) because of concerns about a negative effect on breastfeeding, and initiation at more than 42 days is rated category 2 (advantages generally outweigh theoretical



or proven risks).<sup>17</sup> The American College of Obstetricians and Gynecologists endorses this recommendation.<sup>18</sup> The World Health Organization assigns a category 4 (unacceptable health risk) for initiation of combined pills within 6 weeks of delivery and a category 3 (theoretical or proven risks usually outweigh the advantages) for initiation of combined pills from 6 weeks to 6 months in primarily breastfeeding women.<sup>19</sup> The recommendations of the International Planned Parenthood Federation are similar to those of the World Health Organization.<sup>20</sup> In 2010, a Cochrane review concluded that current data were insufficient to make recommendations on the effect of hormonal contraception on milk quality and quantity because of a lack of methodologically sound trials.<sup>21</sup>

The lack of recent literature on the effect of combined hormonal contraception on breastfeeding is surprising given the worldwide popularity of combined oral contraceptives and the importance and prevalence of breastfeeding. If, as our study suggests, there is no difference in effect of progestin-only pills compared with combined pills on breastfeeding continuation or infant outcomes, then women who desire an oral contraceptive should be encouraged to use combined pills, initiated no earlier than 21 days postpartum because of their greater effectiveness and the negative consequences of unintended pregnancy.<sup>22</sup> This study demonstrates the feasibility of a larger equivalency study to clarify the clinical effect of combined oral contraceptive use on lactation. Our data are reassuring that combined pills do not have a major effect on breastfeeding continuation or infant growth.

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