Effect of hormonal contraceptives during breastfeeding on infant's milk ingestion and growth

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Objective: To measure infants' breast milk intake and infant growth when their mothers initiated either combined oral contraceptive (COC), levonorgestrel-releasing intrauterine system, or etonogestrel-releasing implant, or copper intrauterine device (IUD) as a reference group.
Design: Prospective trial.
Setting: University-based hospital.
Patient(s): On postpartum day 42, 40 women initiated a contraceptive method according to their choice.
Intervention(s): Deuterium (D_2O; 0.5 g/kg mother's weight) was ingested by mothers on postpartum days 42, 52, and 63 as a marker of total body fluid.
Main Outcome Measure(s): Infants' milk intake from 42 to 63 postpartum days was assessed by measurement of D_2O levels in infants' saliva and infant growth by measuring their body weight, height, and tibia length. Women recorded all infant feed and changes of diapers wet with urine. Breastfeeding continuation was assessed at 6 months postpartum.
Result(s): Infant mean milk intake, mean growth increase, mean number of breastfeeding episodes, daily wet diaper changes, and mean duration of exclusively breastfeeding (~5 months) were similar in the four groups.
Conclusion(s): Use of a COC, the two progestin-only contraceptives, or copper IUD did not affect the amount of infant milk intake and growth up to 9 weeks of age. The incidence of full breastfeeding and breastfeeding continuation was similar with contraceptive hormonal use and no use.
Clinical Trials Registration Number: NCT01388582. (Fertil Steril® 2013;100:445–50. ©2013 by American Society for Reproductive Medicine.)
Key Words: Breastfeeding, combined oral contraceptives, contraceptive implant, hormonal contraceptives, levonorgestrel-releasing intrauterine system, deuterium

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The World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use (1) states that the use of combined oral contraceptives (COCs) by breastfeeding women >6 weeks and ≤6 months postpartum is classified as category 3: a condition where the theoretical or proven risks usually outweigh the advantages of using the method. However, use of the progestin-only contraceptives, including the etonogestrel (ENG)–releasing implant and the levonorgestrel-releasing intrauterine system (LNG-IUS) is category 1 (no restriction) (1), although information during breastfeeding is limited (2–4).

The main reason for the WHO restriction of breastfeeding and COC use is concern about exogenous estrogens' effects on possible decrease in milk production (1). Another reason for this restriction was the increased risk of venous thromboembolism (VTE) associated with exogenous estrogens use (1). The Centers for Disease Control and Prevention (CDC) reviewed the WHO recommendations (5) and

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classified COCs as category 4 (unacceptable health risk) for use during the first 21 days postpartum independently from breastfeeding status because of the increased risk of VTE. However, beyond 1 month postpartum, use of COCs is classified as category 2 by the CDC in both breastfeeding and nonbreastfeeding women: advantages generally outweigh the risks if there are no other risk factors for VTE (5).

Evidence demonstrating the negative effect of COC upon milk production in breastfeeding was obtained many years ago and was based mainly on decreases of infant growth or milk production by pump expression with maternal COC use (6–9). One study (10) compared the ingestion of COC with a progestin-only pill (POP), administered daily at 2 weeks postpartum by evaluating breastfeeding and infant growth up to 6 months. At 8 weeks, breastfeeding was maintained by 64.1% and 63.5% of the women in the COC and POP groups, respectively, without an effect on infant growth by either agent. At 8 weeks postpartum, only 28.3% of the women were exclusively breastfeeding, a common incidence in the U.S. (10–12).

Earlier publications (2–4, 6–9) evaluating breastfeeding milk intake by infants relied mainly on measurement of infant growth based on the assumption that the infants ingest only their mothers' milk. For this reason, many studies are now using markers such as deuterium (D_2O) to determine infant breast milk intake, because D_2O is dissolved and disseminated throughout the total fluid in the body, allowing the detection of fluid intake other than the mother's milk by the infant. These studies addressed the effect of nutrition on total body fluid volume or breast milk intake by infants (13–17) and established the validity and safety of D_2O for quantifying breast milk production. However, there are no reports that have used maternal D_2O intake to assess the effect of maternal contraceptive use on breast milk intake and infant growth.

The objective of the present study was to assess whether there is any difference in breast milk intake and infant growth among infants whose mothers were fully breastfeeding and on postpartum day 42 started use of a low-estrogen COC, an LNG-IUS or an ENG-releasing implant compared with mother-infant pairs in which the mother started use of a copper IUD. Measurements of these parameters were continued to postpartum week 9, and the incidence of full breastfeeding continuation was assessed until 6 months postpartum.

MATERIALS AND METHODS

This was a prospective study conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Campinas, Campinas, Brazil. The Institutional Review Board approved the study and each of the women signed an informed consent form. The trial was registered at ClinicalTrials.gov: NCT01388582.

Subjects

Parous women aged ≥ 18 and <45 years of age who delivered infants from February to October 2011 at our hospital were invited shortly after the birth of the infant to participate in the study. The inclusion criteria were: healthy noncomplicated pregnancy, term vaginal delivery (>37 weeks), previous experience of postpartum breastfeeding, willingness to breastfeed on infant demand during the study period, and planning to use one of the four contraceptive methods of the study. Exclusion criteria included: delivery of a small-for-gestational-age newborn and a newborn with a major congenital anomaly. Additional exclusions were conditions established as exclusion by WHO for use of each of the four contraceptives evaluated (1). Eligible women were instructed to return to the clinic on postpartum day 42 to initiate the study and to receive the contraceptive method of their choice. Mothers were also instructed to give no food, liquid or solid, to the babies from birth until the end of the study while breastfeeding.

Procedures

On day 42, each woman initiated use of her desired contraceptive. The COC contained 150 μg levonorgestrel (LNG) and 30 μg ethinyl-estradiol (EE) (Microvlar; Bayer). The COC was given daily for 21 days followed by 7 days of no medication. The LNG-IUS releases 20 μ/d LNG (Mirena; Bayer), and the ENG implant releases 40 μ/d ENG (Implanon; Merck). The copper IUD used was the TCu380A (Optima; Injeflex). The women were weighed before starting the contraceptive methods.

Milk intake was measured orally by determining the amount of D_2O in the saliva of the infants. Deuterium (99.9% pure, 0.5 g/kg mother's weight; Cambridge Isotope Laboratories) (13, 14) was administered orally with a single ingestion by the mothers on day 42 1 hour before contraceptive initiation. Before and 30 minutes after the D_2O administration, a saliva sample from the mother was self-collected and a sample from the infant was collected by the mother. Additionally, saliva samples from both mothers and infants were collected in plastic sterile vials (5 mL) by the mothers 30 minutes after a breastfeeding episode in the middle of the morning on postpartum days 43, 44, 45, 52, 53, 54, 56, 58, 60, and 63 at home. The mothers were instructed to collect ~2 mL of the infants' saliva with a disposable syringe when they observed more intense saliva production following deposit of two drops of lemon juice on the infants' lips. Each saliva sample was brought to the clinic within 2 hours for analyses, were centrifuged (5 minutes at 1,200 rpm), and the supernate frozen at -80°C until the assays were performed.

The infants' weights and heights were measured on postpartum day 42 (baseline) with the use of dedicated calibrated scales, and a caliper rule was used to measure the length of the left tibia. All measurements were performed in duplicate by two professionals, and a third measurement was undertaken if the first two were not in agreement (within 0.1 kg for weight, within 1.0 cm for height, and within 1.0 cm for tibia length). On days 52 and 63 after delivery, the mother-infant pairs returned to the clinic and additional D_2O ingestion by the mothers and measurement of growth parameters of the infants were done. At enrollment the women were instructed to maintain a diary to record each feeding episode and change of wet diapers with urine from the infant. These analyses were done to decide whether the

study should be stopped if users of COC caused any deleterious effect on breastfeeding frequency. At 6 months postpartum, the women were contacted by telephone to determine the duration of exclusive breastfeeding.

Deuterium Evaluation

Deuterium concentration in the mother and infant was calculated from the integral of D_2O nuclear magnetic resonance (NMR) spectra of deuterated water (4.75 ppm) against the acetonitrile signal (1.98 ppm) used as a standard reference (1 μL/tube) (17, 18). D_2O spectrum was obtained in a sample containing 500 μL saliva and 1μL acetonitrile in a Bruker Avance III spectrometer at 76.73 MHz, with the use of 90-degree pulse experiment with 64 scans and 1 second as a repetition delay. The final spectrum was processed with the use of exponential apodization with line broadening of 1 Hz. The personnel who evaluated the amount of D_2O in saliva were blinded to treatment assignment and if the sample come from the mother or the infant.

Sample Size and Statistical Analysis

The goal of the study was to determine whether there was a 10% difference in breast milk intake between each hormonal contraceptive and a copper IUD. The sample size was estimated to detect that 10% difference in breast milk intake. A two-sided statistical test with a significance level of .05 was used, which corresponds to a z value of 1.96. The acceptance error was 0.20, giving a power of 80%, which corresponds to a z value of 1.28, with a sample estimated to be 9.4 per group. The tests used were Student t test or Mann-Whitney test for quantitative variables and Fisher exact test for qualitative variables. Significance was established at $P<.05$.

RESULTS

Forty women were enrolled, ten in each group. There were no early discontinuations or protocol violations. The main demographic characteristics of the women in the four groups are presented in Table 1. All variables showed no significant differences between copper IUD users and the other three groups. All of the women were in amenorrhea at the initiation of the study; however, those who choose COC presented a bleeding episode during the first free-pill interval. The mean duration of exclusively breastfeeding before entering the study was 5.2 months, and at the 6-month evaluation it ranged from 5.0 to 5.6 months in the four groups. Male infants represented 55% of the sample.

The mean increase of infants' growth variables between postpartum day 42 and 63 for weight ranged from 0.5 to 0.8 kg with no significant differences among the groups; infant height increases ranged from 2.0 to 2.6 cm with no significant differences between the groups. Increase of length of the left tibia ranged from 0.6 to 1.3 cm with a significantly lower increase observed only when the implant but not the COC or LNG-IUS group was compared with the IUD group ($P=.030$; Table 2).

Mean D_2O measurement in mothers' saliva 30 minutes after ingestion increased from 2.6 ng/mL at basal time to 5.6 ng/mL. The mean amount of D_2O in the mothers' saliva at each point of evaluation was similar among the four groups of contraceptive users (Fig. 1A). The mean D_2O amount in the infants' saliva was significantly higher in the LNG-IUS versus IUD group on day 45 ($P=.020$) and significantly lower in the COC versus IUD group on day 56 ($P=.015$; Fig. 1B). All other mean D_2O levels were not significantly different among the 4 groups at any time.

The mean number of breastfeeding episodes (Fig. 2A) was significantly higher with COC versus IUD use on 7 out of 21 days (days 48, 49, 50, 51, 52, 54, and 55; $P<.05$) and significantly higher with implant versus IUD use on days 48, 49, 51, and 61 ($P<.05$). The mean number of diapers with urine changed each day (Fig. 2B) was significantly higher with COC versus IUD use only on days 42 and 46 ($P<.05$) and significantly higher with implant versus IUD use on days 43, 44, 45, 46, and 49 ($P<.05$). There were no other significant differences of the parameters on the four groups.

TABLE 1

Demographic characteristics of the participating women and infants according to the contraceptive method used.

Variable	COC (n = 10)	Implant (n = 10)	LNG-IUS (n = 10)	Copper IUD (n = 10)
Age (y)	24.8 ± 2.1	27.9 ± 1.4	27.0 ± 2.1	28.5 ± 1.8
P value[a]	.206	.797	.594	
No. of pregnancies	2.2 ± 0.3	2.7 ± 0.4	2.0 ± 0.3	2.4 ± 0.5
P value[b]	.969	.475	.605	
BMI (kg/m^2)	24.2 ± 1.0	24.7 ± 1.0	25.9 ± 1.2	25.9 ± 1.5
P value[a]	.356	.528	.981	
Months of exclusive breastfeeding	5.0 ± 0.4	5.1 ± 0.4	5.6 ± 0.3	5.4 ± 0.3
P value[b]	.317	.544	.745	
Infants' weight at birth (g)	3,317.5 ± 108.4	3,443.0 ± 142.9	3,287.0 ± 97.0	3,453.5 ± 127.8
P value[a]	.443	.957	.313	
White ethnicity (n)	4	2	2	5
P value[c]	>.999	.315	.315	
Male infants (n)	5	6	4	7
P value[c]	.650	>.999	.370	

Note: Values are presented as mean ± SEM or n. COC = combined oral contraceptive; implant = etonogestrel-releasing implant; IUD = intrauterine device; LNG-IUS = levonorgestrel-releasing intrauterine system.

[a,b,c] Comparison of each method with IUD: [a] t test; [b] Mann-Whitney test; [c] Fisher exact test.

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TABLE 2

Weight, height, and length of the tibia of the infants according to the contraceptive method in use by the mother by exclusively breastfeeding mothers from days 42–63 postpartum.

	Days after delivery				
	42	52	63	Δ[a]	*P* value
Weight (kg)					
COC	4.6 ± 0.1	5.2 ± 0.1	5.3 ± 0.2	0.7 ± 0.1	.613[b]
Implant	4.9 ± 0.2	5.3 ± 0.2	5.6 ± 0.2	0.8 ± 0.1	.678[b]
LNG-IUS	4.9 ± 0.3	5.2 ± 0.2	5.4 ± 0.3	0.5 ± 0.2	.241[c]
IUD	4.9 ± 0.2	5.5 ± 0.3	5.7 ± 0.3	0.8 ± 0.1	
Height (cm)					
COC	55.6 ± 0.5	56.9 ± 0.6	58.2 ± 0.7	2.6 ± 0.3	.583[b]
Implant	57.2 ± 0.5	58.3 ± 0.7	59.2 ± 0.7	2.0 ± 0.3	.824[b]
LNG-IUS	56.6 ± 0.5	57.3 ± 0.6	58.7 ± 0.8	2.0 ± 0.6	.891[b]
IUD	57.1 ± 0.8	58.1 ± 0.6	59.3 ± 0.6	2.2 ± 0.7	
Length of tibia (cm)					
COC	14.6 ± 0.2	14.9 ± 0.2	15.3 ± 0.2	0.8 ± 0.2	.097[b]
Implant	14.9 ± 0.2	15.2 ± 0.2	15.5 ± 0.1	0.6 ± 0.2	.030[c]
LNG-IUS	14.4 ± 0.3	15.1 ± 0.2	15.3 ± 0.2	0.8 ± 0.3	.110[c]
IUD	14.1 ± 0.3	15.1 ± 0.3	15.4 ± 0.2	1.3 ± 0.2	

Note: Values presented as mean ± SEM. Abbreviations as in Table 1.
[a] Measure at day 63 − measure at day 42.
[b,c] Comparison of each method with copper IUD: [b] Student *t* test; [c] Mann-Whitney test.

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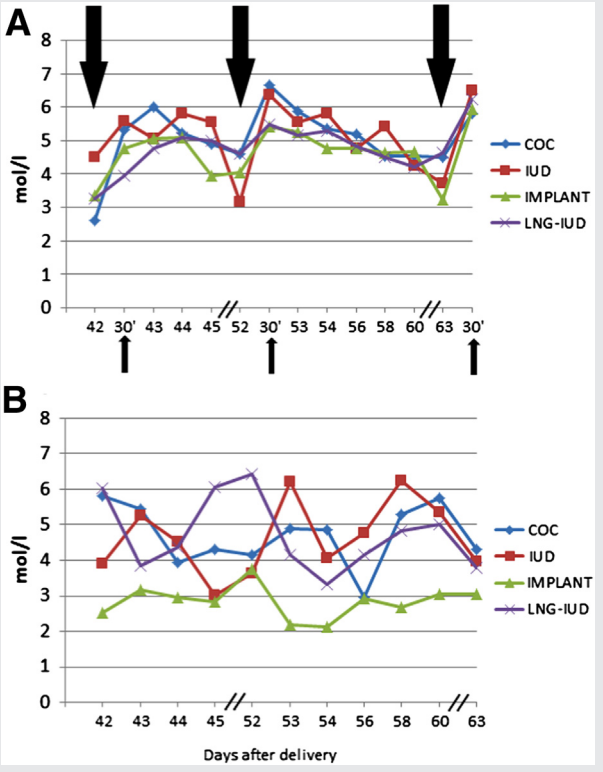
FIGURE 1



Mean D_2O amount (mol/L) in the saliva of (A) the mothers and (B) the infants from postpartum day 42 to 63 according to each contraceptive method. The *large arrows* indicate D_2O intake by the mothers, and the *small arrows* indicate D_2O measurement in saliva of the mothers 30 minutes after intake. COC = combined oral contraceptive; implant = etonogestrel-releasing implant; IUD = intrauterine device; LNG-IUS = levonorgestrel-releasing intrauterine system. (A) No analysis performed; (B) LNG-IUS versus IUD (day 45): *P*=.020; COC versus IUD (day 56): *P*=.015.

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DISCUSSION

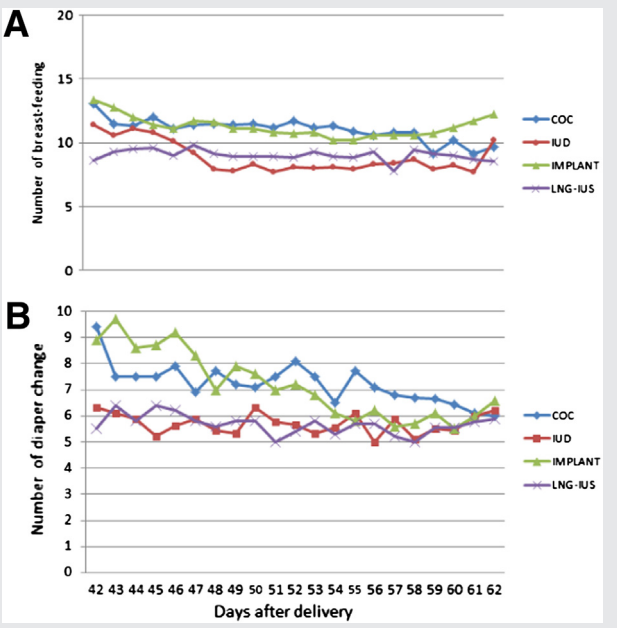
Our results show that fully breastfed infants whose mothers received a 30 μg-EE/150 μg-LNG COC pill or an LNG-IUS or ENG-releasing implant had breast milk intake (according to the values of D_2O in infants' saliva) and infant growth (delta variation of body weight, height and length of left tibia between baseline and the end of the study) similar to infants breastfed by mothers with a copper IUD during postpartum days 42–63. These findings indicate there is no effect of contraceptive steroids either combined with estrogen or progestin alone on infant growth or milk intake by fully breastfeeding infants. The most relevant finding was that the use of a low-EE COC administered from postpartum day 42 to day 63 did not alter the amount of milk ingested by the fully breastfeeding infants from their mothers.

Our results of exclusive breastfeeding duration are different from the Brazilian rates. The prevalence of exclusive breastfeeding in Brazil in children aged up to 6 months averaged 41.0% in the country overall (ranging from 27.1% to 56.1% in different regions). The median duration of exclusive breastfeeding was 1.8 months, and the median non-exclusive breastfeeding was 11.2 months (19). The duration of breastfeeding at the 6-month evaluation was similar among the four groups in the present study. However, we have to take into account that the participants had a previous successful experience of breastfeeding.

Our results had good validation because calculation of infant milk ingestion was performed by D_2O enrichment and quantified by NMR compared with earlier studies in which milk intake was evaluated indirectly by measuring infant growth (2–4, 6–9). Maternal D_2O intake has been used in other studies mainly to assess infant breast milk intake (13–17), but many of those studies on breastfeeding did not use NMR to quantify D_2O (17, 18). Since 1979 (20) D_2O has been used as a noninvasive test for tracking milk transfer from breastfeeding mothers to infants and the common method for assessment was Fourier-transform infrared spectroscopy (21, 22). Nevertheless, this method requires sample preparation with specialized analytical manipulations, in contrast to NMR which is a more workable approach (18). The advantage of NMR is that it is a noninvasive and nondestructive technique and can make the determination without degrading the sample.

The results obtained in this study are not in agreement with the most important two studies (9, 23), conducted by WHO, which compared the same COC used here and POP intake on milk production by breastfeeding women. Maternal milk volume was measured by breast pump expression and was analyzed by documenting breastfeeding frequency, time to introduction of supplemental feed, and infant growth. The infants were followed to 24 weeks postpartum. The investigators observed a reduction of volume of milk in the COC group although infant growth and breastfeeding continuation were not affected. The explanation by the investigators for this discrepancy was

FIGURE 2



Mean number of (A) breastfeeding episodes and (B) mean number of diaper change wet with urine from postpartum day 42 to 63 according to each contraceptive method. Abbreviations as in Figure 1. (A) COC versus IUD: $P<.05$ on days 48, 49, 50, 51, 52, 54, and 55; implant versus IUD: $P<.05$ on days 48, 49, 51, and 61. (B) COC versus IUD: $P<.05$ on days 42 and 46; implant versus IUD: $P<.05$ on days 43, 44, 45, 46, and 49.

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that the mothers could have compensated for decreased milk production by supplementary feeding the infants or by intense and prolonged suckling episodes (9, 23).

Other authors compared the intake of the same COC used in our study with a nonhormonal contraceptive beginning on postpartum day 30 (24, 25). The COC users had a lower proportion of women who maintained full and exclusive breastfeeding at the third and sixth postpartum months than those using nonhormonal contraceptive. Lower infant mean weight increase occurred in the COC group than the nonhormonal group at the second, third, and fourth months of age; nevertheless, the infant mean weight at 1 year was similar in both groups. The results of these studies (9, 23–25) are often used as justification for preventing COC use by breastfeeding women.

Our results are in agreement with a recent study (10) in which no deleterious effect was observed on breastfeeding and infant growth among mothers who initiated use of a COC during the second week after delivery. The principal criticism of that study is that at 14 days after delivery the intake of COC poses a high risk of VTE. For this reason COC use is not begin at this time. We begin COC use at 42 days postpartum because this is the time recommended to initiate use of a progestin-only contraceptive or the copper IUD (1).

In addition, to avoid the possibility that a reduction in milk intake occurred before the D_2O measurement was performed, we measured the number of breastfeeding episodes and the diaper change frequency. Decreased breast milk production of each feeding episode could be masked by an increase in the breastfeeding frequency to maintain total volume of milk. Our results showed no significant differences in the amount of breast milk ingestion by infants on several days among the four groups evaluated. The results of this study showed that infants in the COC and implant groups had significantly more breastfeeding episodes than the IUD group only 7 and 4 days after study initiation, respectively.

Wet diaper change frequency can also reflect breastfeeding adequacy. If the infant feeds more frequently but fails to make wet diapers, then it suggests that the breast milk volume was inadequate. However, if the infant was fed frequently and makes many wet diapers, the findings suggest that the infant is simply a good feeder. The number of changes of wet diapers was significantly higher in the COC and implant groups only on 2 and 5 days after study initiation, respectively. These findings reinforce the conclusion that there is no influence of hormonal contraceptives with or without estrogens on breastfeeding amount or infant growth between 6 and 9 weeks of age.

Regarding the two groups of women who received LNG-IUS and ENG-releasing implants, the results of breastfeeding were as expected because there are no restrictions by WHO or CDC to initiate progestin-only contraceptives immediately after delivery (1, 26). A systematic review (27) on the effect of progestin-only contraceptives on breastfeeding and milk production, mainly with mothers who were using injectable contraceptives or a progestin-only pill, showed that most studies did not show a deleterious effect on breastfeeding, growth, or development from 6 months to 6 years of age with use of these steroids.

Regarding the use of LNG-IUS, we were able to identify one study (4) in which fully breastfeeding mothers inserted the device at 6–8 weeks postpartum and breastfeeding parameters were compared with mothers who received a copper IUD. There were no significantly differences in mean breastfeeding duration (149 vs. 160 days) for the mothers using LNG-IUS versus copper IUD, respectively. Additionally, no significant differences were observed between the groups regarding infant growth and development. Regarding the ENG implant, three studies (2, 28, 29) evaluated frequency and duration of breastfeeding and milk composition when the implant was inserted at 28–56 days postpartum, and no differences were observed compared with copper IUD users (2, 24). Others (3, 29) inserted an ENG-releasing implant 24–48 hours after delivery and did not observe differences in milk production or infant weight compared with nonusers.

The main strength of the present study was the technique used to assess milk intake and the fact that we compared three hormonal contraceptive methods, including one COC, with a nonhormonal method. The main limitations are that we were unable to allocate the women at random owing to ethical limitations and that we can not extrapolate the results to other COCs because we tested only one formulation, albeit one that is widely used worldwide. Nevertheless, the findings of no

effect on breastfeeding with this COC could be applied to COC formulations with lower amounts of EE. Many women may wish to use a COC despite the fact that they are fully breastfeeding due to fear of insertion of an IUD or implants or lack of supplies of other contraceptive methods. Consequently, the possibility to offer COC at postpartum day 42 could improve contraceptive access and reduce unintended pregnancies. In conclusion, the use of a COC containing 150 μg LNG and 30 μg of EE did not affect fully breastfeeding infants' milk intake compared with two progestin-only contraceptives or the copper IUD from 6 to 9 weeks postpartum.

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