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Combined Hormonal Contraception with Low-Dose Ethinylestradiol is Associated with Modest Reduction of Breast Milk Volume when Administered Vaginally, but Not Orally

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Abstract

Background: Combined hormonal contraception (CHC) is habitually not prescribed to breastfeeding women due to concerns of decreased milk production. This habit is based on inconclusive studies that examined lactation suppression of CHC with high-dose Ethinylestradiol (EE ≥ 30 μg/day). Notably, the effect of oral CHC with current low-dose EE (20 μg/day EE), and of vaginal rings (15 μg/day EE), has not yet been studied. Here, we examine their effect on breastmilk production.
Study Design: This study included 172 breastfeeding women, and evaluated self-reported breastmilk production, with and without hormonal contraception. Breastfeeding women using CHC with low-dose EE, either orally ($N = 20$), or vaginally ($N = 32$), were asked to complete a questionnaire, at two time-points: (1) Before starting CHC, and (2) some 7–10 days after. The questionnaire recorded 12 variables linked with breastfeeding. As a control group, breastfeeding women using progestin-only pills (POP, $N = 54$) with Desogestrel 75 μg/day, were used. As another control group, breastfeeding women using no hormonal contraception ($N = 66$) were also asked to complete the same questionnaire.
Results: Vaginal rings, but not oral CHC pills, containing low-dose EE, are associated with a reduction of self-reported expressed breastmilk volume by 20%. Likewise, vaginal rings, but not oral pills, are correlated with impairment of 5 out of 12 breastfeeding variables, namely: (1) breastfeeding interval, (2) self-expressed milk volume, (3) use of milk substitutes, (4) number of night-feedings, and (5) full diapers.
Conclusion: Vaginal rings with low-dose EE (15 μg/day) are associated with a modest, yet significant, decrease in self-expressed breastmilk volume. In contrast, oral CHC pills with low-dose EE (20 μg/day) are not associated with a significant impact on breastmilk production. These findings may have clinical implications for prescribers and patients.

Keywords: combined hormonal contraception, progestin-only pill, progesterone-only pill, breastfeeding, ethinyl, estradiol, ethinylestradiol

Introduction

Breastfeeding is beneficial for both mothers and infants.[1] For mothers, breastfeeding is associated with long intervals between pregnancies, and with low risks of developing diabetes, breast and ovarian cancers, as well as postpartum depression.[2,3] For infants, breastfeeding is associated with low morbidity and mortality,[4] as well as better scores in intelligence tests.[5] In addition, breastfed infants benefit from a low risk of becoming overweight, and of developing diabetes, later in life.[6] As such, breastfeeding is highly encouraged.

Combined hormonal contraception (CHC) contains an estrogen and a progestin. The most used estrogen is ethinylestradiol (EE), and commonly used progestins include levonorgestrel,

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norgestrel, and norethindrone. While most studies suggest progestins have little or no impact on breastmilk production,[7] estrogens are historically associated with lactation suppression. It all began in the 1970s, when CHC injections containing high-dose estrogens (16 mg estradiol) were used to suppress lactation in women, who did not wish to breastfeed.[8] Likewise, CHCs containing high-dose estrogens (100 μg/day mestranol) were used to reduce breast engorgement in women, who did not wish to breastfeed.[9] To date, CHCs containing high-dose estrogens are no longer in use and have been replaced by lower-dose formulations (EE ≤ 20 μg), primarily to reduce the risk of thromboembolic and adverse effects. Nevertheless, CHC remains historically associated with lactation suppression.

Importantly, CHC is associated with an increased risk of venous thromboembolism (VTE). Therefore, during the first 3 weeks after delivery, breastfeeding women should not use CHC due to the increased risk of VTE[10] Likewise, breastfeeding women with other risk factors for VTE should not use CHC until 6 weeks after delivery. Yet, even beyond this period, CHC is still perceived by many clinicians to suppress lactation. As a result, when asked to prescribe CHC to a breastfeeding woman, 3 months after delivery, 50% of physicians hesitate due to potential concerns over lactation suppression.[11] Instead, they prefer to prescribe progestin-only pills (POP), which insignificantly impact breastmilk production.

Several reviews have noted the poor, inconsistent, and outdated associations of CHC with lactation suppression. In 2015, a Cochrane review of 11 studies highlighted the inconsistent effect of CHC on breastmilk production.[12] Most of the 11 studies were out-of-date and used CHC with high-dose EE (≥50 μg), no longer available. Of the 11 studies, only 2, authored by Tankeyoon et al. of 1984,[13] and Espey et al. of 2012,[14] evaluated CHC with medium-dose EE (30–35 μg), which are closer to current low-dose EE (≤20 μg).

Tankeyoon et al. reported a fall of milk volume of 42% with CHC (30 μg EE, 150 μg Levonorgestrel), of 12% with POP (75 μg Norgestrel), and of 6% without any contraception.[13] Importantly, neither CHC nor POP delayed infant growth, as measured by weight, length, ponderal index, arm circumference, triceps skinfold thickness, and head circumference.[13] On the other hand, Espey et al. observed no difference in breastmilk production after 8 weeks (end-point) with CHC (35 μg EE, 1 mg Norethindrone) and with POP (350 μg Norethindrone), and 64% of women were still breastfeeding in both groups alike.[14] Neither CHC nor POP delayed infant growth, as measured by weight, length, and occipitofrontal measurements.[14]

More recently, a 2016 review in Contraception noted that of 13 available studies, most were decades-old and inconsistent.[15] Most studies examined the effect of CHC with different estrogen doses, and exhibited poor methodologies. The review emphasized the lack of studies with low-dose estrogen, and with alternative delivery routes, such as vaginal rings.[15] The review found no effect on infant weight gain, if CHC was started 6 weeks after delivery.

Most recently, a 2023 review in Breastfeeding Medicine summarized the 2 systematic reviews cited above, 1 clinical guideline from the CDC, 6 professional association recommendations, and 28 publications identified through an updated literature review.[16] The review concluded that while POPs continue to demonstrate safety in breastfeeding patients, low-quality evidence may support concerns of decreased milk supply with CHC.[16] Taken together, all these reviews agree that only poor, inconsistent, and out-of-date evidence supports the clinical practice of prescribing POP, instead of current CHC with low-dose EE (≤20 μg) to breastfeeding women, 6 weeks after delivery.

POP is not without disadvantages either, and progesterone is associated with a higher incidence of breakthrough bleeding (BTB).[17] While medically insignificant, BTB can evoke frustration, and lead to POP discontinuation in 25% of cases. In turn, the risk of POP-stop is associated with an increased risk of unintended postpartum pregnancies.[18] Irregular bleeding presents a particular challenge for religious Jewish patients. According to Jewish law (Halakha), a couple must refrain from intercourse, not only during menstruation, but also for an additional seven "clean" days after menstruation, and only resume intercourse after the woman immerses in a ritual bath (Mikveh).[19] Jewish law does not distinguish between menstrual bleeding and irregular bleeding (i.e., withdrawal bleeding [WB], BTB, spotting, etc.), and both can render a woman ritually impure (Niddah) depending on the circumstances.[20] As a result, religious Jewish couples frequently consult both physicians and rabbinic authorities to determine the implications of irregular bleeding. Notably, over 50% of Jewish religious women using POP reported that bleeding associated with the pill negatively impacted their marital life due to these religious considerations, often leading to early POP stop.[21] While POP (40%) is more associated with irregular bleeding than CHC (10%),[22] its combinations with low-dose EE (30 μg), and even with very low-dose EE (15–20 μg) regularize bleeding patterns in a dose-dependent manner.[23] Thus, while POP is less associated with breastmilk suppression, it is more associated with irregular bleeding and potential frustration.

The past decades have seen the emergence of the current CHC with low-dose estrogen (EE ≤ 20 μg), and in addition to oral pills, vaginal and transdermal formulations have been approved. NuvaRing is a monthly CHC vaginal ring that releases 15 μg of EE, and 120 μg of Etonogestrel daily. The transdermal patch is a weekly CHC that delivers 20 μg EE, and 150 μg Norelgestromin daily. Both, NuvaRing and the transdermal patch were designed to provide a sustained dose, to attain steady serum concentrations, and to improve medical compliance.[24] Each of the three formulations elicit different pharmacokinetic serum concentrations, and the pill, the ring, and the patch could potentially induce distinctive responses of lactation suppression.[24]

Here, we evaluate the effects of CHC with low-dose EE (≤20 μg) on milk production, and distinguish between oral (EE, 20 μg/day) and vaginal (EE, 15 μg/day) formulations. In particular, we measure 12 different perceived variables associated with breastmilk production, and compare them to those of women using either POP (Desogestrel, 75 μg/day) or no hormonal contraception.

Methods

Study design

This prospective cohort study included 172 breastfeeding women divided in 4 groups: (1) The first group ($N = 20$) used oral CHC pills containing low-dose estrogen (EE 20 μg/day,

Desogestrel 150 μg/day). (2) The second group ($N = 32$) used vaginal CHC rings containing low-dose estrogen (EE 15 μg/day, Etonogestrel 120 μg/day). (3) The third group ($N = 54$) was a control group, and used oral POP (Desogestrel 75 μg/day). (4) The fourth group ($N = 66$) was also a control, and used no hormonal contraception at all. First, the study compared before versus after CHC use in the same groups, without controls. Then, the study compared after CHC use, versus after POP use (control), versus no-hormone use (control).

Setting and subjects

All group participants were breastfeeding, and were 6 weeks to 6 months after delivery. The study was noninvasive, and the authors did not prescribe any contraception. The medical and legal responsibility for prescribing POP and CHC, and for ruling out potential contraindications, was under the sole discretion of attending physicians, unrelated to this study. The participants were referred to this study by their attending physicians, or approached us directly, after reading ads on social networks.

Data collection

All participants in all groups received the same questionnaire. The questionnaire recorded demographic, medical, and obstetric data, as well as 12 breastfeeding variables such as the self-reported expressed milk volume, and the duration (Supplementary Table S1). The participants of the oral and vaginal CHC groups completed the questionnaires twice: (1) before CHC start, and (2) some 7–10 days after CHC start. The participants of the control group using POP completed the questionnaire once, at recruitment only, after using POP for at least 7–10 days. The participants of the second control group, using no hormonal contraception, completed the questionnaire once, at recruitment.

Importantly, the questionnaire instructed participants to express breastmilk at their own discretion, at least 3 hours after breastfeeding, and to record the self-expressed milk volume in milliliters, and duration in minutes. Finally, the 12 breastfeeding variables, including the self-reported milk-volume were compared between oral and vaginal groups, before and after CHC use. Likewise, 12 perceived breastfeeding variables after oral and vaginal CHC use, were compared with those of each control group.

Statistical analysis

Numerical scale data were analyzed using means and standard deviations, while binary scale data were analyzed using frequency tables and percentages. One-way analysis of variance was employed to compare data among groups (CHC, POP, and no-contraception), followed by *post hoc* LSD tests. Paired *t*-tests were used to compare data between two time-points in the same CHC group (before and after). Chi-square tests were utilized to compare categorical data among groups, and to examine the association between categorical variables. A statistical significance level of 5% was required, and the analysis was performed using SPSS software version 28. The sample size was calculated using the GPOWER 3.1.9 software. Assuming an effect size of 0.35, power of 80%, and a significance level of 5%, the minimal sample size was calculated to 17 participants in each group.

Ethical approval

This prospective cohort study received approval from the Ethics Committee of the Faculty of Medicine, Bar Ilan University, Safed, (IRB Ref #: 01-2022, Approval date: July 31, 2022).

Results

Demographic, medical, and obstetric data

Table 1 lists the demographic, medical, and obstetric data of our 172 participants in the study. All participants are breastfeeding, for >6 weeks, and for <6 months, following delivery. The participants are divided into four groups: (1) An oral CHC test group, $N = 20$, using pills (EE 20 μg/day, Desogestrel 150 μg/day); (2) A vaginal CHC test group, $N = 32$, equipped with a NuvaRing (EE 15 μg/day, Etonogestrel 120 μg/day); (3) An oral POP control group, $N = 54$, using pills (Desogestrel 75 μg/day); and (4) A no-use control group, $N = 66$, using no hormonal contraception whatsoever. As shown by the multiple *p* values, there are no statistical differences in terms of demographic, obstetric, and medical data between any of the groups. Likewise, as shown by the paired *p* values, there is no statistical difference between the oral and vaginal CHC subgroups, except for age (Table 1).

Table 1. Demographic, Medical, and Obstetric Data of the 172 Breastfeeding Women Used in This Study

	Test groups			*Control groups*		
Variable	*Oral CHC* (N = *20*)	*Vaginal CHC* (N = *32*)	*Paired* p *value*	*Oral POP* (N = *54*)	*No use* (N = *66*)	*ANOVA* p *value*
Age (year)	26.4 ± 4.9	30 ± 5.9	0.01[a]	28.5 ± 5.1	29.4 ± 4.8	0.571
Parity	3.1 ± 1.2	3.4 ± 2	0.373	3.0 ± 1.9	3.4 ± 2.2	0.518
Week postpartum	13.5 ± 4	13.8 ± 4.7	0.397	15.7 ± 4.9	14.7 ± 6.0	0.140
Employment			0.794			0.475
Maternity leave	13 (65%)	23 (72%)		32 (59%)	42 (64%)	
Work resumed	7 (35%)	9 (28%)		22 (41%)	24 (36%)	
Body mass index	25.5 ± 3.4	26.3 ± 3.7	0.992	24.6 ± 4.7	24.5 ± 5.3	0.992

[a]Statistic significance ($p < 0.05$).
CHC, combined hormonal contraception; POP, progestin-only pill.

Vaginal and oral CHC groups (before vs. after)

Remarkably, vaginal CHC ($N = 32$), but not oral CHC ($N = 20$), is associated with reduced lactation by up to 20%, when comparing two timepoints—before, and after CHC. Table 2 lists the breastfeeding variables before and after starting CHC, either with a vaginal ring or with oral pills. After starting CHC, a significant, yet small, reduction of breastmilk volume is associated with vaginal CHC use ($N = 32$), but not with oral CHC use ($N = 20$). In the vaginal CHC group, 5 out of 12 self-reported breastfeeding variables differ, before and after NuvaRing use: (1) the number of breastfeedings per night increases from 1.9 to 2.3 ($p = 0.031$); (2) the breastfeeding interval decreases from 3 hours and above, to 3 hours and below ($p = 0.001$); (3) the self-expressed milk volume decreases from 114.1 to 91.8 mL ($p = 0.002$); (4) the number of self-reported full diapers drops from 97% to 81%. ($p = 0.001$); and (5) the use of milk substitutes increases from 12% to 28% ($p = 0.001$) (Table 2). Remarkably, in the oral CHC group, no significant differences are associated with any of the breastfeeding variables, before and after pill use.

Vaginal and oral CHC groups (test vs. ontrol)

Remarkably, vaginal CHC, but not oral CHC, is associated with a significant, yet small, reduction of expressed milk volume (<20%) in comparison with oral POP ($N = 54$). Likewise, a similar reduction of breastmilk volume is evident, in contrast to no use of contraception at all ($N = 66$). Table 3 lists the breastfeeding variables of the vaginal and oral test groups—after CHC—and compares them with the two control groups, namely oral POP, and no use of contraception. Note that the oral and vaginal groups—after CHC—are identical to those listed earlier in Table 2, columns 3 and 6. When comparing oral CHC, with oral POP, the differences are insignificant. When comparing vaginal CHC, with oral POP group, then 3 out of 12 variables are significantly different: (1) The self-expressed milk volume with oral POP is 123.7 ± 38.8 mL, but decreases with vaginal CHC to 91.8 ± 50.8 mL ($p = 0.014$), (2) the baby calmness with oral POP is 87%, but falls to 56% with vaginal CHC ($p = 0.006$), (3) the self-reported milk reduction with oral POP goes unnoticed by 48% of participants, but is more prominent with vaginal CHC with unnoticed suppression falling to only 16% ($p = 0.011$). As such, the vaginal CHC is associated with a minor, but significant decrease of milk volume, indicating that vaginal rings with low-dose EE (15 μg/day) may suppress lactation by up to 20%. Remarkably, the oral CHC group shows no significant difference with the oral POP group and indicates that CHC with low-dose EE (20 μg/day) is not associated with any lactation suppression.

In addition, when comparing women using oral CHC to those using no contraception, the only statistically significant difference was in the frequency of full diapers, which was lower in the oral CHC group (Table 3). On the other hand,

Table 2. Breastfeeding Variables of Vaginal and Oral CHC—Before vs. After

	*Vaginal CHC (*N = *32)*			*Oral CHC (*N = *20)*		
Variable	*Before use*	*After use*	*Paired* p *value*	*Before use*	*After use*	*Paired* p *value*
Breastfeedings per day	7.5 ± 1.7	8 ± 3	0.12	8.2 ± 1.5	8.5 ± 2	0.4
Breastfeeding duration (min)	15.9 ± 6.6	15.8 ± 7.9	0.923	17 ± 7.7	17.6 ± 9.9	0.594
Breastfeeding interval			0.001*			0.089
<3 hours	11 (34%)	19 (59%)		6 (30%)	11 (55%)	
≈3 hours	16 (50%)	7 (22%)		12 (60%)	7 (35%)	
>3 hours	5 (16%)	6 ((19%		2 (10%)	2 (10%)	
Breastfeeding at night			1			0.76
No	6 (22%)	7 (22%)		1 (5%)	2 (10%)	
Yes	26 (78%)	25 (78%)		19 (95%)	18 (90%)	
Breastfeeding per night	1.9 ± 1.2	2.3 ± 1.5	0.031*	1.8 ± 0.8	2.1 ± 1.1	0.107
Expressed milk volume (ml)	114.1 ± 41.7	91.8 ± 50.8	0.002*	120.4 ± 29.6	117.7 ± 39.6	0.332
Expression duration (min)	14 ± 4.9	14.4 ± 5.7	0.238	15 ± 6.8	16.2 ± 6.7	0.186
Milk suppression			0.633			0.864
No	13 (41%)	5 (16%)		11 (55%)	11 (55%)	
Maybe	15 (47%)	19 (59%)		7 (35%)	5 (25%)	
Yes	4 (12%)	8 (25%)		2 (10%)	4 (20%)	
Use of milk substitutes			0.001*			0.071
No	28 (88%)	23 (72%)		13 (65%)	15 (75%)	
Yes	4 (12%)	9 (28%)		7 (35%)	5 (20%)	
Baby calmness			0.37			0.75
No	1 (3%)	14 (44%)		0 (0%)	5 (25%)	
Yes	31 (97%)	18 (56%)		20 (100%)	15 (75%)	
Diaper-changes per day	6 ± 1.7	6 ± 2	0.418	6.2 ± 1.6	6 ± 1.7	0.190
Full diapers			0.001*			0.83
No	0 (0%)	4 (13%)		0 (0%)	1 (5%)	
Maybe	1 (3%)	2 (6%)		0 (0%)	2 (10%)	
Yes	31 (97%)	26 (81%)		20 (100%)	17 (85%)	

*Statistical significance ($p < 0.05$).
CHC, combined hormonal contraception.

Table 3. Breastfeeding Variables of Vaginal and Oral CHC (Test Groups) vs. Oral POP and No-Use (Control Groups)

	Test groups		*Control group (1)*		*Control group (2)*	
Variable	*Vaginal CHC (*N = *32)*	*Oral CHC (*N = *20)*	*Oral POP (*N = *54)*	*ANOVA* p *value*	*No Use (*N = *66)*	*ANOVA* p *value*
Breastfeedings per day	8 ± 3	8.5 ± 2	8.4 ± 2	0.83	8.35 ± 2	0.824
Breastfeeding duration (min)	15.8 ± 7.9	17.6 ± 9.9	17.2 ± 9.5	0.15	17.2 ± 9.5	0.746
Breastfeeding interval				0.15		0.114
<3 hours	19 (59%)	11 (55%)	24 (45%)		25 (38%)	
≈3 hours	7 (22%)	7 (35%)	25 (46%)		30 (45%)	
>3 hours	6 (19%)	2 (10%)	5 (9%)		11 (17%)	
Breastfeeding at night				0.13		0.294
No	7 (22%)	2 (10%)	5 (9%)		12 (18%)	
Yes	25 (78%)	18 (90%)	49 (91%)		54 (82%)	
Breastfeedings per night	2.3 ± 1.5	2.1 ± 1.1	2.2 ± 1	0.219	2.19 ± 1	0.781
Expressed milk volume (ml)	91.8 ± 50.8	117.7 ± 39.6	123.7 ± 38.8	0.014[a]	125.2 ± 53.2	0.032[a]
Expression duration (min)	14.3 ± 5.6	16.2 ± 6.7	18.2 ± 4	0.14	15.5 ± 6.1	0.675
Milk suppression				0.011[a]		<0.001[a]
No	5 (16%)	11 (55%)	26 (48%)		37 (56%)	
Maybe	19 (59%)	5 (25%)	23 (43%)		25 (38%)	
Yes	8 (25%)	4 (20%)	5 (9%)		4 (6%)	
Use of milk substitutes				0.57		0.143
No	23 (72%)	15 (75%)	44 (82%)		58 (88%)	
Yes	9 (28%)	5 (20%)	10 (18%)		8 (12%)	
Baby calmness				0.006[a]		<0.001[a]
No	14 (44%)	5 (25%)	7 (13%)		6 (9%)	
Yes	18 (56%)	15 (75%)	47 (87%)		60 (91%)	
Diaper-changes per day	6 ± 2	6 ± 1.7	6.1 ± 1.5	0.8	6.1 ± 1.5	0.958
Full diapers				0.97		0.013[b]
No	4 (13%)	1 (5%)	1 (2%)		0	
Maybe	2 (6%)	2 (10%)	0		0	
Yes	26 (81%)	17 (85%)	53 (98%)		66 (100%)	

[a]Statistical significance ($p < 0.05$) between vaginal CHC and control groups.
[b]Statistical significance ($p < 0.05$) between vaginal CHC, oral CHC, and control groups.
CHC, combined hormonal contraception; POP, progestin-only pill.

when comparing vaginal CHC with no contraception, then 4 out of 12 variables are significantly affected: (1) The self-expressed milk volume with no CHC is 125.2 ± 53.2 mL, but decreases with vaginal CHC to 91.8 ± 50.8 mL ($p = 0.032$), (2) the baby calmness with no CHC is 91% but falls to 56% with vaginal CHC ($p < 0.001$), (3) the self-reported milk suppression with no CHC goes unnoticed by 56% of participants, but only in 16% of vaginal CHC ($p < 0.001$), (4) Full diapers are reported in 100% of no CHC group, but only in 81% of vaginal CHC (0.013).

Notably, the self-expressed milk volume of women, before CHC use, and after, are statistically correlated (R = 0.67, $p = 0.001$), suggesting that participants express little breastmilk, or a lot, consistently. In addition, the self-expressed milk volume and breastfeeding variables of the oral POP group, and of women using no hormonal contraception, are statistically correlated (R > 0.8), suggesting that POP is unassociated with milk reduction, as reported in the literature,[17]

Discussion

Here, we examine the effects CHC with low-dose EE (≤20 μg/day), on breastmilk production. Notably, we distinguish between oral pills (EE 20 μg/day) and vaginal rings (EE 15 μg/day), currently in-use, in breastfeeding women. We find that vaginal CHC ($N = 32$), but not oral CHC ($N = 20$), is associated with a 20% reduction of self-expressed milk-volume. Moreover, vaginal CHC, but not oral CHC, is associated with an impairment of <5 out of 12 self-reported breastfeeding variables. As a control group, we use breastfeeding women taking POP, ($N = 54$). As another control group, we use breastfeeding women taking no hormonal contraception whatsoever ($N = 66$). Our hypothesis is grounded in the pharmacodynamic principles of drug action, and presumes that CHC use for 7–10 days is associated with a decrease of breastmilk-volume. To capture this association, we administer the two questionnaires: (1) before, and (2) after 7–10 days of CHC use. All 172 participants are breastfeeding women >6 weeks, and < 6 months, postpartum.

Unlike vaginal CHC, oral CHC is not significantly associated with reduced volume of self-expressed breastmilk. The different effects of oral and vaginal CHC is attributed to variations in dosage and formulation. With the vaginal ring, the CHC dose is released continuously over a period of 28 days, and a steady-state plasma concentration is achieved within hours after insertion. With oral pills, the CHC dose is taken

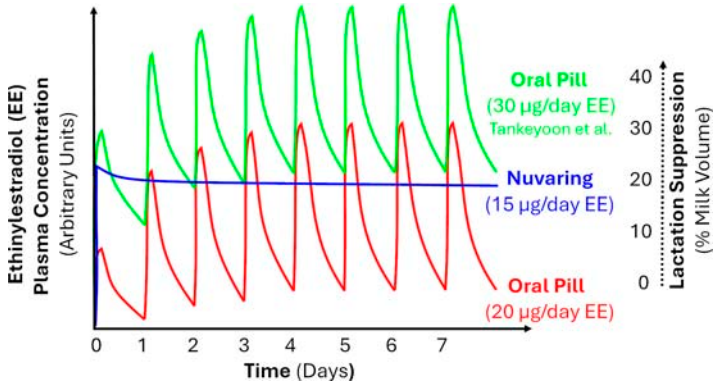

FIG. 1. Pharmacokinetics of oral and vaginal CHC formulation. Shown are theoretical plasma concentrations of Ethinylestradiol (EE) over time, of vaginal (*in blue*), and oral (*in red and green*) CHC formulations. Vaginal EE reaches a steady concentration, but oral EE fluctuates with each dose. The green curve corresponds to oral doses (30 µg/day EE) associated with ~40% milk reduction, as reported by Tankeyoon et al.[13] The blue and red curves correspond to vaginal (15 µg/day EE), and oral doses (20 µg/day EE) associated with ~20% and ~0% milk reduction, respectively, described in this study. Note that the green and blue curves, as well as their relative proportion, were adapted from reference.[24]

once per day, and plasma concentrations fluctuate between peak-and-trough throughout the day. Figure 1 shows the tentative pharmacokinetic profile of three CHC formulations, one vaginal (NuvaRing, 15 µg/day EE), and two oral (20 and 30 µg/day EE). With the oral formulation, potential breastmilk-suppression rises and falls, with the peak and trough plasma-concentrations. Potential lactation-suppression is most pronounced when estrogen peaks, shortly after taking the pill. Later, as estrogen-concentrations decline, potential lactation-suppression abates, and breastmilk-production resumes. In contrast, the vaginal ring retains a constant plasma-concentration of EE, and exerts a sustained effect on potential lactation-suppression.

Early reports disputing the potential risk of lactation-suppression with CHC have used different doses. Consequently, health care organizations have issued different guidelines for the use of CHC while breastfeeding.[12–16] Table 4 lists their current recommendations. The American College of Obstetricians and Gynecologists supports breastfeeding compatibility with CHC, from 6 weeks after delivery.[28] Likewise, the Center for Disease Control and Prevention (CDC) categorizes CHC as compatible with breastfeeding, starting 6 weeks postpartum.[26] On the other hand, the Royal College of Obstetricians and Gynecologists (RCOG) categorically rejects breastfeeding compatibility with CHC, 6 weeks after delivery.[29] Likewise, the World Health Organization categorizes CHC as moderately safe during breastfeeding, 6 weeks postpartum.[25] Notably, the breastfeeding incompatibility at 6 weeks after delivery relies on studies with high-dose EE (>30 µg/day), no longer in use. To the best of our knowledge, no study has been performed with oral CHC containing low-dose EE (20 µg/day), or with vaginal rings (20 µg/day), thus highlighting the importance of our study. Moreover, our study exhibits a dose-dependent effect, and uses two control groups.

Historically, estrogens have been used to suppress lactation. In particular, high doses of estrogens have a suppressive effect on milk production.[30] Several studies have explored the impact of estrogen on breast tissue and the mammary gland. In cows, estradiol injections disrupt mammary tight junctions, leading to the leakage of lactose from milk into plasma or urine.[31] Estradiol reduces breast milk production by enhancing apoptosis in bovine mammary epithelial cells.[32] The historical association between estrogens and lactation-suppression is important but must not confound the compatibility of CHC with low-dose EE with breastfeeding.

Limitations

As a potential limitation of this study, the breastfeeding variables are self-reported by the participants and could suffer from biases. It is possible that some of the breastfeeding variables are also subjective, as participants were asked to

TABLE 4. BREASTFEEDING COMPATIBILITY OF COMBINED HORMONAL CONTRACEPTION

	Time after delivery			
Guideline source	*<21 days*	*21 days–6 weeks*	*6 weeks–6 months*	*>6 months*
World Health Organization (WHO)[25]	L4	L4	L3	L2
Center for Disease Control (CDC)[26]	L4	L3 (VTE risk) L2 (no VTE risk)	L1	L1
National Health Services (NHS)[27]	Incompatible	Incompatible	Compatible	Compatible
American College of Obstetricians and Gynecologists (ACOG)[28]	Incompatible	Incompatible	Compatible	Compatible
Royal College of Obstetricians and Gynecologists (RCOG)[29]	Incompatible	Incompatible	Inompatible	Compatible

L1, Safest; L2, Safer; L3, Moderately safe; L4, Possibly hazardous, L5, Contraindicated.

visually assess full diapers, rather than weigh them. In addition, we do not claim that all women between 6 and 24 weeks exhibit similar variables, and breast milk volumes, instead we claim that the average shifts. In addition, the oral and vaginal CHC groups were relatively small, in comparison to the control groups. It is possible that different group sizes would provide different results, and this study should be considered a pilot study. For definitive conclusion, a larger sample size is required. Moreover, the interval between the two questionnaires was short, and reflected about 7–10 days use of CHC. Likewise, the control participants were surveyed at a single time point, which may not fully account for natural day-to-day variation in lactation parameters. It is possible that assessing the effect over a more extended period, with additional time points would give different results. Also, the participant's compliance and oral pill adherence is self-reported. While the vaginal-ring requires no daily action, oral CHC pills demand daily administration, which participants can forget, miss, and ignore. Possibly, sustained-release vaginal CHC is more associated with reduced milk volumes, than oral CHC pills because oral pills are more likely to be missed, reducing the effective hormone exposure. Additionally, EE release from the vaginal ring is highest during the initial week of use, and gradually plateaus over the following weeks. Given that our study is focused on 7–10 days of CHC, it is possible that reduced milk volumes are associated with the initial EE peak.

Another potential limitation of this study is the different drug brands used by participants. While all participants of the POP group used Desogestrel (75 μg/day), the brand names include Cerazette, Diamilla, and Fominic. While all participants in the vaginal CHC group used NuvaRing (EE 15 μg/day, Etonogestrel 120 μg/day), most, but not all, the participants in the oral CHC group used Feminet (EE 20 μg/day, Desogestrel 150 μg/day). While all participants of the oral CHC group used low-dose EE of 20 μg/day, some used different brands of progestin, such as Harmonet (EE 20 μg/day, Gestoden 75 μg/day), Meliane (EE 20 μg/day, Gestoden 75 μg/day), and Yaz (EE 20 μg/day, Drospirenone 3 μg/day). Although previous studies have demonstrated that different progestins do not impair breastfeeding, it is possible that different progestin brands have different effects on breastfeeding.[16] Finally, further studies with larger cohorts, and multiple time-points are required to increase the statistical significance of our results.

In the past, we have underlined the importance of discussing the potential use of CHC with patients, when POP is associated with unwanted side effects such as WB, and BTB.[11] Here, we reiterate the importance of presenting accurate information to the patient while explaining the potential decrease in milk volume.

Conclusion

Nuvaring with low-dose EE (15 μg/day), but not oral CHC pills with low-dose EE (20 μg/day), appears to be associated with a decrease in self-expressed breast milk volume.

Authors' Contributions

L.S., N.S., and A.O.S., conceived and analyzed study; wrote and revised article; L.S., G.S., H.H., and Y.B. recruited participants. L.S. collected data; B.H. performed statistical analysis; G.W. translated.

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Supplementary Material

Supplementary Table S1

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