BREASTFEEDING MEDICINE
Volume 11, Number 4, 2016

DOI: 10.1089/bfm.2016.0017

Association of Etonogestrel-Releasing Contraceptive Implant with Reduced Weight Gain in an Exclusively Breastfed Infant: Report and Literature Review

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Abstract

Background: Studies have not found that hormonal contraceptive implants adversely affect breastfeeding, but theoretical concerns exist.
Methods: We reported a case of reduced weight gain in an exclusively breastfed infant in association with placement of (ENG)-releasing contraceptive implant (Nexplanon) to the FDA Adverse Events Reporting System (FAERS). We further queried reports to FAERS and reviewed published studies of the ENG implant during breastfeeding.
Results: A breastfeeding mother received an ENG implant at 4 weeks postpartum. Her infant was exclusively breastfeeding. One month after implant placement, the infant had lost 145 g, dropping from the 44th percentile to the 6th percentile for growth. During this period, the mother had not returned to work or decreased frequency of feeding. During a 2-year period of FAERS reports, we found one other report of reduced milk supply following ENG implant placement. Among 108 breastfeeding women studied while using the ENG implant, there was one case of lactation failure. If this were not due to chance, the estimated risk of lactation failure with the ENG implant would be 0.9% (95% confidence interval 0.2–5.1%).
Conclusion: Given uncertainty regarding the true effect of ENG implants on lactation, it seems prudent for providers to counsel each woman about a possible effect on milk supply so that she can monitor her infant for signs of impaired milk transfer. Patient-centered counseling approaches are needed that allow each woman to assess her own individual tolerance of risk of unplanned pregnancy versus possible risk of lactation failure.

Introduction

A HEALTHY 22-YEAR-OLD African American G1P0 presented in spontaneous labor at 39 weeks 2 days. She progressed to complete and had an uncomplicated spontaneous vaginal birth of a 3.316 kg male infant with Apgar scores of 9 and 9. During the maternity stay, she exclusively breastfed, and mother and infant were discharged home on postpartum day 1 with a weight of 3.090 kg, 6.8% below birth weight. Mother and infant presented for pediatric follow-up on postpartum day 4. The infant's weight was 3.125 kg, and mother reported breastfeeding every 1–2 hours, with four wet diapers and four stools in the past 24 hours. At a follow-up visit on postpartum day 20, the infant's weight was 4.075 kg, and the mother reported nursing 14 times a day with numerous wet and soiled diapers.

At this time, the mother was planning to return to work as a manager at a fast food restaurant within a few weeks. She discussed with the lactation consultant that her supervisor allowed on-the-clock smoking breaks, but she would have to clock out to pump. As there was no private place to pump in her workplace, she planned to express milk in her car. She subsequently decided to defer returning to work until at least 2 months postpartum, so that she could continue to breastfeed exclusively.

At 32 days postpartum, she presented to the emergency department with vaginal bleeding, which was evaluated and felt to be consistent with resumption of her menstrual cycle. She had resumed intercourse, and her plan for Nexplanon placement at her postpartum visit was discussed. She presented 2 days later for her postpartum visit, and reported

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having had intercourse 9 days previously. She was counseled that early pregnancy could not be excluded at that time, and a follow-up visit for Nexplanon placement was scheduled for 1 week later.

On postpartum day 35, the infant presented for a 1-month well-child check, and was noted to be breastfeeding every 2 hours during the day, and every 4 hours at night. His weight had increased to 4.600 kg.

The next week, on postpartum day 39, she had the implant placed in the OB clinic, where it was documented that she was exclusively breastfeeding. She was counseled regarding possible side effects of implant placement, including ''irregular spotting for the full 3 years, potential difficulty in removal, and the need to palpate the implant after placement and intermittently over the next three years.''

One week later, on postpartum day 46, the infant presented to pediatrics clinic for evaluation of a rash, which was consistent with neonatal acne. It was documented that he was breastfeeding well without issues, and his weight was 4.93 kg. The infant review of systems documented no fevers, vomiting, or diarrhea.

When mother and infant returned to the clinic on postpartum day 70, the infant weighed 4.785 g, down 145 g since the last visit 24 days previously (Figure 1). The mother noted that her milk supply had decreased, and she was now able to pump only 1–2 oz at a time, down from 4–5 oz previously. She was breastfeeding every 2–4 hours, usually for 10–15 minutes, having previously breastfed for 45 minutes. She reported that her baby was not content, and was fussy and whining more than usual. A pre- and postweight feed was performed, and the infant transferred 54 mL. Formula supplementation was recommended, and the infant took 2 oz from a bottle. The review of systems documented that there was no vomiting, diarrhea, increased work of breathing, or sweating during feeds.

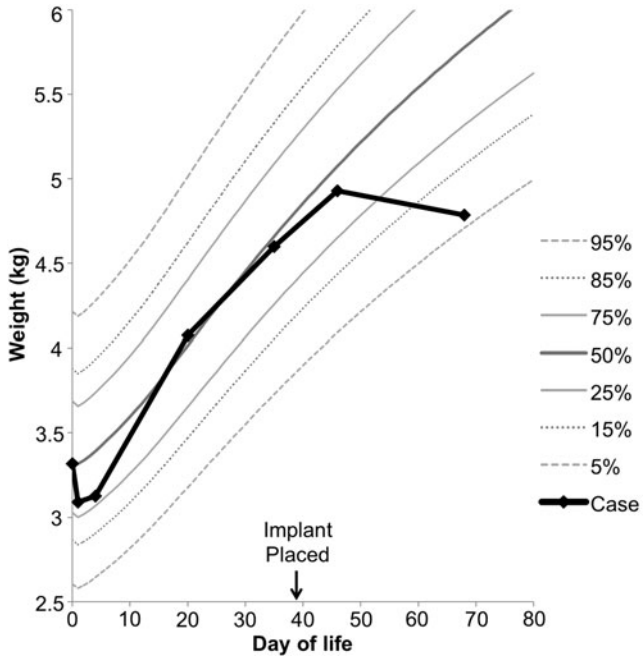

FIG. 1. Infant weight trajectory before and after placement of an etonogestrel-releasing contraceptive implant, compared with WHO growth percentiles for exclusively breastfed male infants.

TABLE 1. FAERS REPORTS, JULY 2013–JUNE 2015

	Etonogestrel	*All reports*
FAERS cases reported	6,036	1,928,561
Suppressed lactation	0	122
Lactation disorder	2	75
Breastfeeding	10	131

FAERS, FDA adverse events reporting system.

One week later, the mother and infant returned for a lactation visit. She had begun taking fenugreek. She was supplementing with 1–2 oz of formula after each breastfeeding, and the infant had gained 70 g. One month later, she transitioned completely to formula feeding.

Discussion

We report a case of abrupt change in growth of an exclusively breastfed infant, coincident with maternal initiation of the etonogestrel (ENG) implant. In this case, the woman experienced a substantial decrease in her breast milk supply, and subsequent decrease in infant growth, shortly after starting the ENG-releasing contraceptive implant. This may have been coincidence; however, it appears that no other significant factors, such as returning to work or decreasing frequency of feeding, contributed to her decrease in milk supply.

We reported this case of lactation suppression to the FDA Adverse Event Reporting System. To determine whether others have reported lactation suppression in the setting of ENG, we obtained quarterly data files from the FDA Adverse Event Reporting System from July 2013 to June 2015.[1] A total of 1,928,561 reports were filed in this 2-year period, of which 6,036 were related to ENG (Table 1). The most common adverse events reported for ENG were product quality issues ($N = 701$) and medical device complication ($N = 657$). Among ENG reports, there were 10 cases where breastfeeding was noted, 2 cases of lactation disorder, and no cases of lactation suppression.

Details of the two lactation disorder reports were requested from the FDA. Both cases were patient reports initially filed with Merck, the manufacturer of the implant. In one case, a patient reported experiencing a reduction in breast milk production following placement of an ENG implant. In the second case, a patient had an ENG implant placed immediately following an abortion. She reported that a month after implant placement, she was still lactating and also having some spotting.

Strengths of our case report include documentation of infant weights at multiple time points, as well as documentation of stable breastfeeding frequency over time. This is the only case report to our knowledge of lactation suppression coincident with initiation of the ENG implant.

This case raises several important issues that need to be considered to enable women to both achieve their infant feeding goals and adequately space future pregnancies. The use of hormonal contraceptives in breastfeeding is controversial. Progesterone withdrawal following delivery is thought

to trigger secretory activation and onset of milk production,[2] raising biologically plausible concerns that early initiation of hormonal contraception may decrease milk supply. There is also evidence that a subsequent pregnancy, which increases progesterone, may affect the growth of breastfed children. In a small study in rural Bhutan, children of women who became pregnant again before weaning had slower growth than age-matched children of mothers who weaned while not pregnant.[3] However, published studies have found similar breastfeeding durations and infant weight gain among women using hormonal versus nonhormonal contraception. A recent Cochrane review noted that the quality of evidence regarding hormonal contraception and lactation was moderate overall and low for three of four placebo-controlled trials.[4]

The contraceptive implant available in the United States contains ENG, a synthetic progesterone analogue. Serum levels peak at 1,200 pg/mL within the first 2 weeks after insertion and then gradually decline to 202 pg/mL at 12 months.[5] Based on serum and milk levels in a prospective study of 42 mother–infant dyads, breastfed infants are expected to receive about 19.9 ng/kg of ENG daily at 1 month, 15.1 ng/kg daily at 2 months, and 10.5 ng/kg daily at 4 months after insertion.[6]

Of note, doses, formulations, and serum levels vary among hormonal contraceptive methods. For example, while ENG levels decline to 202 pg/mL by 12 months after ENG implant placement, with the extended release ENG and ethinyl estradiol insert (Nuvaring), ENG levels range from 1,578 pg/mL in week 1 to 1,374 pg/mL in week 3 of the 4-week cycle.[7] Different formulations may also have different effects on breast physiology. For example, there is evidence that formulations of estrogen and progestin differentially affect breast cell proliferation in postmenopausal women.[8] These results suggest that effects for one progestin or estrogen may not be generalizable to other formulations.

Two recent randomized controlled trials have measured breastfeeding outcomes among women receiving the ENG implant. In a randomized controlled trial (RCT) comparing early insertion (1–3 days postpartum) with standard insertion ($n=69$), there was no difference in hours to lactogenesis (mean difference, −1.4 hours, 95% CI −10.6 to 7.7 hours) or lactation failure (early: 1/34 vs. standard 0/35, risk difference 0.03, 95% CI −0.02 to 0.08) between the two groups.[9] The study was powered based on a baseline lactation failure rate of 5% in both groups, with sufficient power to detect a failure rate of 20% or higher in the early placement group. There was no difference in the percentage of women partially or completely breastfeeding at 3 or 6 months. A second small RCT ($n=24$) used deuterium to index milk ingestion among healthy term newborns of mothers randomized to immediate postpartum ENG implant placement ($n=12$) or 6-week placement ($n=12$).[10] Participation was limited to nonobese women who had previously breastfed for at least 3 months. No differences were found in milk intake between the two groups.

An open-label, randomized pilot study of 40 exclusively breastfeeding women compared early postpartum insertion (24–48 hours postdelivery) of the ENG implant with 6-week postpartum DMPA administration.[11] The authors found no differences in infant growth or rates of breastfeeding between the two groups. In the implant group ($n=20$), one woman had stopped breastfeeding exclusively by 6 weeks postpartum, compared with three who had stopped in the group assigned to receive DMPA at 6 weeks ($n=20$). At 12 weeks postpartum, infant growth was greater in the implant group than the DMPA group, and rates of exclusive breastfeeding were similar (Implant: 85% vs DMPA: 75%). An earlier open-label group comparison study measured milk composition and infant growth among 80 fully breastfeeding women and their infants. Women chose to receive either an ENG implant ($n=42$) or a copper intrauterine device ($n=38$) at 28–56 days postpartum.[6,12] There were no differences between group means in 24-hour milk production, fat content, or infant growth.

Combining these four studies, a total of 108 breastfeeding women have been studied while using the ENG implant, with one case of primary lactation failure documented in a woman randomized to immediate postpartum ENG.[9] If this case of lactation failure were not due to chance, the estimated risk of lactation failure with the ENG implant would be 1 case among 108 women receiving ENG at some time between birth and 8 weeks postpartum, or 0.9% (95% confidence interval 0.2–5.1%). Of note, these four studies evaluated healthy women with term infants; two trials excluded women with BMI $\geq 30\ kg/m^2$. The effects of the ENG implant on lactation for women with medical problems or preterm infants are not known. In addition to published trials of ENG in lactation, we found one report of decreased milk supply following ENG implant insertion in the FAERS database over a 24-month period, suggesting that such adverse effects are uncommon. However, reporting of lactation disorders or suppressed lactation was rare in the FAERS database, and it is possible that healthcare providers do not consider an abrupt reduction in milk production to be a reportable adverse event.

In our clinical experience, we have found that women receive biased information about the potential effects of hormonal contraception on lactation. Providers focused on preventing unplanned pregnancy may dismiss concerns as anecdotal and insist that there is no risk, whereas providers who are focused on breastfeeding may dwell on the risks, dissuading women from choosing a highly effective method. In both situations, providers' competing priorities prevent open communication of relevant information, undermining patient autonomy and informed consent.[13]

Studies are needed to determine whether there is a causal relationship between hormonal contraception and suppressed lactation and, if so, whether there are identifiable risk factors that can be used to inform counseling. Potential approaches to advance this work include routine reporting of suppressed lactation to FAERS, establishment of a registry of women who experience suppressed lactation coincident with use of hormonal contraceptives, and translational studies to measure the effect of hormonal contraception on the milk transcriptome[14] and on cultured lactocytes. If an adverse effect is found, it will also be important to determine whether or not the effect is reversible.

Until such data are available, prevailing uncertainties pose challenges for healthcare providers counseling breastfeeding mother–infant dyads about ENG implants. The ENG implant is a highly effective, long-acting, reversible contraceptive method that has much higher continuation rates than pills, patches, or injectable contraception.[15] Providers, including the provider in our report, routinely counsel women about potential side effects, including irregular spotting, difficult removal, and the need to palpate the implant periodically

after placement. In the case described here, anticipatory guidance about a potential effect on milk production might have prompted the mother to take her baby in for a weight check earlier, preventing him from falling off his growth curve. However, if the events we describe here are a chance association, such counseling has the potential to unnecessarily dissuade women from choosing a highly effective contraceptive method.

Available data suggest that adverse effects of ENG implants on breast milk production are uncommon. However, more than 3 million women in the United States initiate breastfeeding each year, suggesting that even a 1-per-1,000 risk of suppressed lactation might affect a substantial number of women. The possibility of decreased breast milk from an implant may be qualitatively different for a woman intending to breastfeed than the other uncommon risks the implant may pose such as skin infection. Given uncertainty regarding the true effect of ENG implants on lactation, it seems prudent for healthcare providers to counsel each woman about a possible effect on milk supply so that she can monitor her infant for signs of impaired milk transfer. Furthermore, patient-centered counseling approaches are needed that allow each woman to assess her own individual tolerance of risk of unplanned pregnancy versus risk of possible lactation failure. Such an approach will ensure that each patient can make an informed decision that is free from coercion, pressure, or undue influence.[13]

Disclosure Statement

No competing financial interests exist.

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