

THE EFFECTS OF A PROGESTIN-ONLY ORAL CONTRACEPTIVE
(LEVONORGESTREL 0.03 mg) ON BREAST-FEEDING

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ABSTRACT

This study was a non-randomized clinical trial which compared the breast-feeding experience of 250 Argentine women taking levonorgestrel 0.03 mg daily (begun one week after delivery) with that of 250 women using non-hormonal contraceptives. Weight gain of unsupplemented infants, the most important of the several criteria used to assess breast-feeding performance, was similar for the two contraceptive groups. Levonorgestrel users began supplementary feeding of their infants significantly later than did non-hormonal users; levonorgestrel users were also somewhat less likely to discontinue breast-feeding during the study period. The two contraceptive groups were similar with regard to several other measures of breast-feeding performance: growth of all infants (regardless of supplementation), patterns of contraceptive discontinuation, mothers' subjective impressions of breast-milk sufficiency, and comparison of supplementation initiation with previous experience.

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INTRODUCTION

Although breast-feeding provides some contraceptive protection, this protection is not always complete. A breast-feeding woman cannot know precisely when ovulation has resumed, and once it has resumed she is at risk of pregnancy. Auxiliary contraceptive methods are therefore needed, particularly in the later months of breast-feeding.

Many breast-feeding women throughout the world are using hormonal contraceptives, primarily estrogen-progestin combinations. Unfortunately, considerable evidence indicates that combined pills, including those with relatively low dosages, have a small negative effect on lactation (1-7). In contrast, studies of progestin-only contraceptives, administered orally or parenterally, generally indicate no negative impact on breast-feeding performance (1-3). Among the many previous studies of progestin-only contraceptives among lactating women, only two have included formulations containing norgestrel or levonorgestrel (2,3), which are currently among the most widely available progestin-only oral contraceptives.

The present study examined the effect on breast-feeding performance of levonorgestrel 0.03 mg taken daily, beginning within a week after delivery. It was conducted in a private medical practice in Buenos Aires, Argentina, in collaboration with Family Health International.

MATERIALS AND METHODS

Study Design

The study was a non-randomized clinical trial comparing 250 women taking levonorgestrel 0.03 mg daily with 250 women using non-hormonal contraceptives. Study subjects were enrolled within seven days after delivery, beginning in February 1981 and continuing through January 1982 for the hormonal group and through July 1982 for the non-hormonal control group. Women who agreed to participate were enrolled if they met the following selection criteria: age 30-35 years; parity 2-6 (including the current delivery); history of successful breast-feeding; generally healthy, with no chronic illnesses and with blood pressure less than 140/100; had an uncomplicated, full-term delivery of one healthy infant, weighing at least 2000 grams; planned to breast-feed the infant at least nine months, with no supplementary feeding for at least four months.

Eligible women were then asked to choose between the progestin-only oral contraceptive (POC) and the various non-hormonal contraceptives otherwise available to them. Women in the hormonal group began taking their pills within a week after delivery; a two-month supply of pills was provided at study admission and at each monthly follow-up visit. Although studies of postpartum hormonal contraceptive use often delay method initiation until six weeks after delivery, it was decided to initiate pill-taking earlier in this study, for two reasons. Early initiation may be desirable in some settings where delivery is the only time a woman is in contact with the health care system and therefore it is important to determine whether such early initiation affects the establishment of lactation; furthermore, if no adverse effects of early initiation were found in the study, then it would be unlikely that later initiation would be detrimental. For women who wanted IUDs, the devices (Copper-T or Lippes Loop) were inserted about one month postpartum. The IUDs were not inserted earlier, to parallel early pill initiation, because immediate postpartum insertion was not feasible and therefore the only medically acceptable timing was several weeks later. The other, coitus-related methods were all begun whenever coitus was resumed.

Mother-infant pairs in both the POC and non-hormonal control groups were observed once a month for a maximum of nine months. Information was recorded concerning the health of the mother and infant, growth of the infant, infant feeding patterns, and contraceptive use. Subjects were terminated from the study nine months after delivery or before nine months if the woman ceased all breast-feeding, discontinued the study contraceptive method, became pregnant, or was lost-to-follow-up.

Data Analysis

The following criteria were used for assessing breast-feeding performance:

1. growth of infants (all infants, and unsupplemented infants alone),
2. initiation of supplementary feeding;
3. discontinuation of breast-feeding;
4. discontinuation of the study contraceptive for reasons related to breast-feeding; and
5. maternal reports of decreased milk production.

Of these criteria, weight gain of unsupplemented infants is the most direct and objective measure (8).

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Infant growth was measured by weight, length, and head circumference, with the mean values of these measurements at each month compared between the contraceptive groups. In addition, the rate (or velocity) of infant growth was computed in two ways. Between two consecutive observations, the absolute weight gain was divided by the number of days between those two observations to obtain the average daily velocity. Between birth and the four-month visit, weight velocity was calculated as the slope of a straight line fitted to the data points of weight by infant age, using least-squares linear regression. Velocities for the two contraceptive groups were compared by the Student's t-test. Confounding was evaluated by stratification on potential confounders and by analysis of covariance.

The time between birth and the initiation of supplementary feeding was analyzed by the Kaplan-Meier product-limit technique for the estimation of the survival curves, using the Breslow test statistic for comparison of the survival times between the two contraceptive groups (9,10). Pregnancy rates were analyzed by the Kaplan-Meier survival technique (9). The rates of intermittent bleeding were compared by Chi-square analysis. Baseline characteristics of the contraceptive groups were compared by Student's t-test and Chi-square statistics. Throughout this analysis, a comparison was deemed statistically significant if it had a p-value of less than 0.05.

RESULTS

Baseline Characteristics

The POC and non-hormonal groups had remarkably similar baseline characteristics. None of the comparisons between these two contraceptive groups were significantly different with regard to maternal sociodemographic characteristics, breast-feeding history, or infant sex distribution and anthropometry.

More than half (54.8%) of the women in the control group chose to use IUDs. The remainder used coitus-related methods (foam, diaphragm, and/or jelly, 25.6%; condom, 18.8%; withdrawal and/or rhythm, 0.4%; and no method, 0.4%).

Study Terminations

The rate of loss-to-follow-up was similar for the two contraceptive groups (about 40% at six months and about 55% at nine months). The women who were lost-to-follow-up in each contraceptive group had baseline characteristics similar to both (a) the

women in the same contraceptive group who were either followed-up for nine months or terminated from the study for other reasons; and (b) the women in the other contraceptive group who were lost-to-follow-up.

Very few women discontinued use of their chosen contraceptive (4 pill users and 2 in the non-hormonal group). None discontinued because of inadequate breast-milk production. Abnormal vaginal bleeding was cited as the reason for discontinuation by all four of the women who discontinued pill use and by one of the two women who discontinued their non-hormonal method.

Women in the non-hormonal group were somewhat more likely than women taking levonorgestrel to discontinue breast-feeding during the study period. Three times as many non-hormonal as hormonal users discontinued breast-feeding (22 and 7, respectively). Furthermore, three times as many non-hormonal users (15 and 5, respectively) cited decreased milk production as the reason for discontinuation. Breast-feeding discontinuations were distributed throughout the follow-up period.

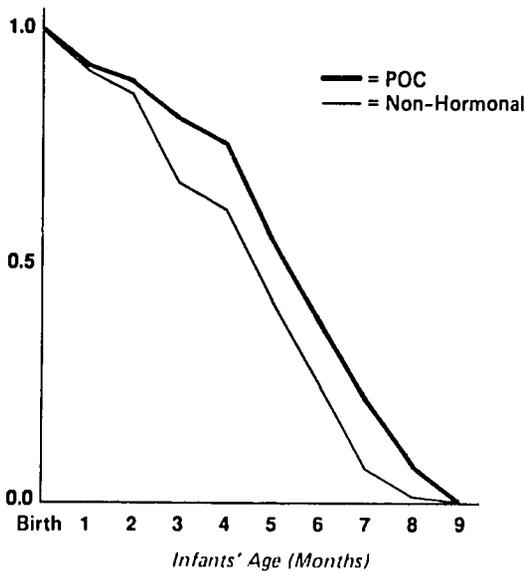
The cumulative life table pregnancy rate at nine months after delivery was 3.9 per 100 women in the POC group. IUD users had a pregnancy rate of 1.9, which was statistically similar to that of POC users. Women in the control group who were using methods other than IUDs had a pregnancy rate of 22.8, which was significantly higher than that of POC users. (The number of pregnancies associated with each type of contraceptive was as follows: POC, 3; IUD, 1; condom, 3; foam, diaphragm and /or jelly, 1; withdrawal and/or rhythm, 1.) All pregnancies occurred toward the end of the study period, when both the contraceptive effect of lactation and compliance with the contraceptive regimen may have been waning.

Infant Supplementation

Mothers in the POC group introduced supplementary foods later than did mothers in the control group. As displayed in Figure 1, the cumulative proportion of infants not yet supplemented was significantly higher for the hormonal group than for the non-hormonal group throughout the follow-up period. The median infant age at supplementation was 5.4 months for the POC group and 4.6 months for the control group.

Comparison of the time to initiation of supplementary feeding during the study with the woman's previous experience uses each woman as her own control. While 31 percent of the POC group mothers supplemented their study infant earlier than their previous infant, a larger percentage (42%) of control group women began supplementary feeding of their study infant earlier.

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NOTE: The two curves are significantly different (Kaplan-Meier survival analysis; Breslow test, $p < 0.05$).

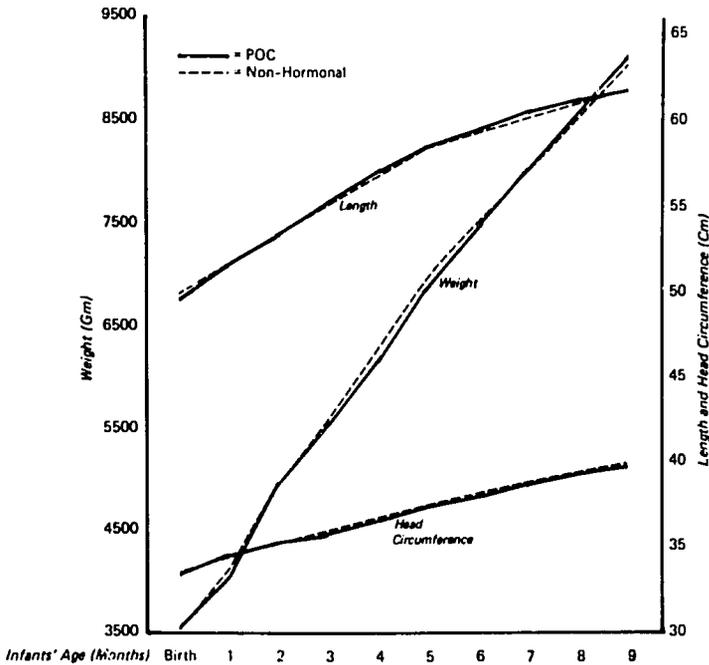
Figure 1. Proportion of infants not yet supplemented, by contraceptive group.

Maternal Assessment of Milk Production

Maternal reports of decreased milk production occurred with similar frequency in the two contraceptive groups, when supplementation status is controlled for by stratification into supplemented and unsupplemented groups. In contrast, analysis of maternal complaints that did not control for supplementation status found that control group mothers were more likely to complain. Because of the effects of supplementation, only the stratified analysis, which found no differences between contraceptive groups, should be considered valid.

Infant Growth

Because satisfactory infant growth is the ultimate objective of satisfactory breast milk production, infant growth is a crucial criterion for assessing the effect of hormonal contraceptives on breast-feeding performance. Weight, length, and head circumference of infants (supplemented and unsupplemented combined) were virtually identical in the two contraceptive groups throughout the nine-month follow-up period, as displayed in Figure 2. Within the control group, comparison between users of IUDs and users of other non-hormonal methods also found similar overall growth patterns.

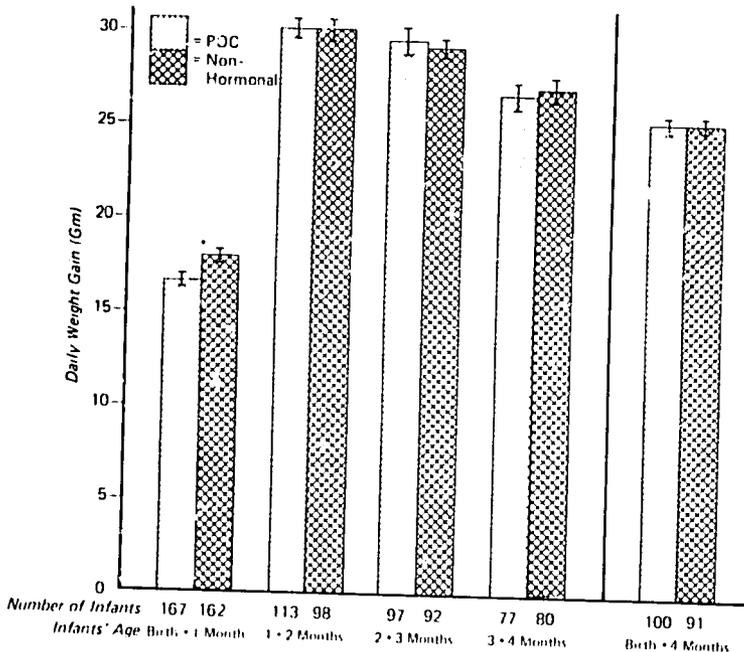


NOTE: The only comparison between contraceptive groups that was statistically significant ($p < 0.05$) was for head circumference at five months.

Figure 2. Mean infant weight, length and head circumference, by contraceptive group and infants' age.

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Growth of infants who were receiving only breast milk is the most direct measure of breast-feeding performance. The results for unsupplemented infants are shown only for the first four months in order to emphasize this early period, when the majority of infants were not yet supplemented. The weight velocity among unsupplemented infants was generally similar for the POC and non-hormonal groups (Figure 3). In three of the first four monthly periods, mean daily weight gain was not statistically different for the two contraceptive groups. In the first period the POC group infants gained weight more slowly, a difference which was statistically significant but which from a clinical perspective was quite small (1.2 grams per day).



NOTE: * $p < 0.05$.

Figure 3. Mean weight velocity (daily weight gain) and standard error of unsupplemented infants, by contraceptive group and infants' age.

In addition to the monthly growth velocities, the rate of weight gain was calculated from birth through the fourth month because of variability in the rate of short-term (i.e., monthly) growth. This four-month velocity also has the advantage of providing a single growth parameter for each infant, thus avoiding the statistical problems inherent in multiple comparisons of the same infant. From birth through four months, the average weight gain of unsupplemented infants was identical for the two contraceptive groups (25.3 grams per day). The data on four-month velocity were stratified separately on

several variables: infant illness, maternal cigarette smoking status, birthweight, infant sex, mother's education, and number of breast-feeding episodes per day in the first month. Neither interaction nor confounding was present. The only one of these variables that had any effect on weight gain was infant illness, which resulted in significantly slower infant growth in both of the contraceptive groups (suggesting that the study could have also demonstrated a clinically important effect of the POC, had such an effect been present).

The final point to be made regarding infant weight gain is that loss-to-follow-up did not appear to affect the growth comparisons between the contraceptive groups. For each monthly follow-up period, the previous month's weight gain was compared between infants who were lost-to-follow-up and infants who were not lost-to-follow-up. The infants who were lost-to-follow-up had not been consistently gaining weight more or less rapidly than those who continued in the study, in either contraceptive group.

Intermittent Bleeding

The most common side-effect of progestin-only contraception is intermittent bleeding. Compared with users of non-hormonal methods other than IUDs, women taking POCs were significantly more likely to report intermittent bleeding. In contrast, compared with IUD users, women in the POC group were less likely to report intermittent bleeding; the percentage of POC users ever reporting intermittent bleeding during the study period (68.2%) was significantly lower than the corresponding percentage of IUD users (82.8%). In the first few months about one-third of POC users reported each month that they had experienced intermittent bleeding, declining to about 20 percent in later months.

DISCUSSION AND CONCLUSIONS

Do progestin-only oral contraceptives affect breast-feeding performance? Specifically, does levonorgestrel 0.03 mg, taken daily beginning within a week after delivery, adversely affect milk production among patients in a private medical practice in Buenos Aires, Argentina?

Strength and Direction of the Association

There is no evidence in this study of an adverse effect of levonorgestrel on breast-feeding performance. Weight gain of unsupplemented infants, the best measure of lactation, was generally similar for the POC and non-hormonal control groups. This was true whether weight gain was quantified as monthly weight velocity or as weight velocity from birth through the fourth month.

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The other criteria for assessing breast milk production showed either no association or the suggestion of a positive association with levonorgestrel. Time to supplementation was significantly longer for the POC group. Hormonal group mothers were somewhat less likely than control group mothers to supplement their study infant earlier than their previous infant; time to supplementation for the previous infant found that only one-third of the POC group infants began receiving supplementary foods earlier than had their older siblings. Three times as many control group infants discontinued breast-feeding during the study, with inadequate milk production being the major reason cited for discontinuation of breast-feeding. Very few women discontinued the study contraceptive, and none of them cited inadequate milk production as a reason for discontinuation. When asked for their subjective assessment of milk production, the percentage of women who reported decreased milk production was similar for the two contraceptive groups, once supplementation status was controlled for.

Internal Validity

Selection bias does not appear to be present in this study. Both contraceptive groups were recruited from the same source, a private medical practice, during the same period of time. Their admission characteristics were remarkably similar. Selective loss-to-follow-up was potentially a large source of selection bias as the study progressed, but it did not occur. The rate of loss-to-follow-up was high, but it was similar for the POC and control groups. Furthermore, the admission characteristics of women lost-to-follow-up in each contraceptive group were similar both (a) to those in the respective contraceptive groups who continued in the study, and (b) to those lost-to-follow-up in the other group.

Information bias also does not appear to have occurred in this study. Information was collected in the same manner for both of the comparison groups. Infant growth measurements, the most important criteria for assessing lactation, are objective measurements, and they were made by pediatricians who presumably had less of an interest in the comparison of the contraceptives than a gynecologist might. The more subjective criteria, including the decisions to initiate supplementation or to discontinue breast-feeding, have greater potential for bias. This bias could be different for the two contraceptive groups, because these decisions could be affected by what the woman and/or her physician think about the possible effects of the hormonal contraceptive. However, instead of indicating an adverse effect on lactation, which might be expected if the woman is concerned about an adverse effect, these more subjective criteria suggest no effect or even a positive effect.

Confounding, usually considered inevitable in a non-randomized clinical trial, is minimal here. As stated above, the baseline characteristics of the contraceptive groups

were remarkably similar. Analysis of infant growth was not confounded by supplementation status, as the absence of consistent differences between the POC and control groups was found regardless of whether the data were stratified by supplementation status. Neither is there interaction between infant weight gain and supplementation status. None of the other variables considered in the analysis of four-month weight velocity were found to be either confounders or effect modifiers. Only in the analysis of the mother's subjective impressions of breast milk production was supplementation status found to be a confounder; only the analysis which stratified for supplementation status should be considered valid.

External Validity

The findings of this study are consistent with those of other studies which have examined the effect of progestin-only oral contraceptives on lactation (1-3). These studies also found no negative impact or, in some cases, a modest positive impact. Two of these studies involved levonorgestrel: levonorgestrel 0.03 mg was evaluated in Hungary and in Thailand (2) and levonorgestrel 0.05 mg was studied in India (3). In both of these studies oral contraceptive use began six weeks postpartum, rather than within the first week of delivery. They both found that breast-feeding performance of women taking levonorgestrel was similar to that of the non-hormonal controls and greater than that of women using estrogen-progestin contraceptives. Several criteria were used to assess breast-feeding in these two studies, but neither study analyzed the weight gain of unsupplemented infants, which is the best criterion. Only one of them measured weight gain, but without control for supplementation (2). The study in Hungary and Thailand also examined the breast milk lipid and fatty acid composition, finding little apparent effect of levonorgestrel (11).

Several recent studies of levonorgestrel administered by other routes support these findings regarding orally-administered levonorgestrel. Two studies of Norplant subdermal levonorgestrel implants (12, 13) and one study of a levonorgestrel-releasing IUD (14) found no evidence of an adverse effect of the hormone on lactation performance.

The growth of the infants in this study is also consistent with that demonstrated in other studies that have computed growth velocities of infants in advantaged populations (15,16). The rates of weight gain in these other studies were of the same order of magnitude as those reported in the present study and displayed a similar pattern, with a lower rate in the period immediately after birth, the peak rate in the next month, and a gradual decline thereafter.

Implications

The present study indicates that it is reasonable to promote progestin-only contraceptives as the formulation of choice for breast-feeding women who wish to use hormonal contraception, as no adverse effects of levonorgestrel 0.03 mg daily on

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breast-feeding performance were found. That no adverse effect was found even when levonorgestrel was begun within a week after delivery is particularly encouraging, as the period when lactation is being established might be particularly vulnerable. However, the women in this study were a socially advantaged group, and so the results should be generalized cautiously until results of studies in less advantaged populations, including on-going studies being conducted by Family Health International, are available.

This study did not address the question of whether the progestin has any adverse effect on the infant other than effects on growth. The limited available data indicate that only a small fraction of the maternal dose is transferred to the infant, that it is readily metabolized, and that it does not have any effect on the infant (1,17-19). No long-term studies of infants whose mothers used levonorgestrel contraceptives during breast-feeding have yet been reported, although two long-term studies of medroxyprogesterone acetate (20,21) and one long-term study of estrogen-progestin combined oral contraceptives (22) found no adverse effects. Any risk to the infant of the steroid itself is much smaller and more speculative than the very real risk to the mother of conceiving again, which could have many adverse effects on both the mother and the infant, including cessation of breast-feeding. Thus it seems reasonable that, rather than denying hormonal contraceptives to breast-feeding women who wish to use them, a progestin-only contraceptive (such as levonorgestrel) should be provided.

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REFERENCES

1. McCann MF, Liskin LS, Piotrow PT, Rinehart W, Fox G. Breast-feeding, fertility, and family planning. *Population Reports* 1984; Series J., no. 24.
2. WHO Special Programme of Research, Development, and Research Training in Human Reproduction, Task Force on Oral Contraceptives. Effects of hormonal contraceptives on milk volume and infant growth. *Contraception* 1984; 30:505-22.

3. Gupta AN, Mathur VS, Gorg SK. Effect of oral contraceptives on the production and composition of human milk. In: Parkes AS, Thomson AM, Potts M, Herbertson MA. Fertility regulation during human lactation. *J Biosoc Sci* 1977; Suppl. no. 4.:123-33.
4. Diaz S, Peralta O, Juez G, et al. Fertility regulation in nursing women: III. Short-term influence of a low-dose combined oral contraceptive upon lactation and infant growth. *Contraception* 1983; 27:1-11.
5. Croxatto HB, Diaz S, Peralta O, et al. Fertility regulation in nursing women: IV. Long-term influence of a low-dose combined oral contraceptive initiated at day 30 postpartum upon lactation and infant growth. *Contraception* 1983; 27:13-25.
6. Peralta O, Diaz S, Juez G, et al. Fertility regulation in nursing women: V. Long-term influence of a low-dose combined oral contraceptive initiated at day 90 postpartum upon lactation and infant growth. *Contraception* 1983; 27:27-38.
7. Prema K. Duration of lactation and return of menstruation in lactating women using hormonal contraception and IUDs. *Contraceptive Delivery Systems* 1982; 3:39-46.
8. Laukaran VH. The effects of contraceptive use on the initiation and duration of lactation. *Int J Gynaecol Obstet* 1987; 25 Suppl:129-42.
9. Kaplan BL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53:457-81.
10. Breslow N. A generalized Kruskal-Wallis test for comparing k samples subject to unequal patterns of censorship. *Biometrika* 1970; 57:579-94.
11. WHO Special Programme of Research, Development, and Research Training in Human Reproduction, Task Force on Oral Contraceptives. An investigation of the influence of steroidal contraceptives on milk lipid and fatty acids in Hungary and Thailand. *Contraception* 1986; 33:159-78.
12. Diaz S, Herreros C, Juez G, et al. Effects of NORPLANT (R) subdermal implants on lactation and infant growth. In: Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ, eds. *Long-Acting Contraceptive Delivery Systems*. Philadelphia: Harper and Row, 1984; 397-403.
13. Affandi B, Karmadibrata S, Prikartono J, Lubis F, Samil RS. Effect of Norplant on mothers and infants in the postpartum period. *Adv Contracept* 1986; 2:371-80.

CONTRACEPTION

14. Heikkila M, Haukkamaa M, Luukkainen T. Contraception with a levonorgestrel-releasing IUD: Effect on lactation and child development. In: Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ, eds. Long-Acting Contraceptive Delivery Systems. Philadelphia: Harper and Row, 1984; 368-77.
15. Falkner F. Some physical measurements in the first three years of life. Arch Dis Child 1958; 33:1-9.
16. Tanner JM, Whitehouse FH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965--Parts I and II. Arch Dis Child 1966; 41:454-71 and 613-35.
17. Johansson E, Odland V. The passage of exogenous hormones into breast milk--possible effects. Int J Gynaecol Obstet 1987; 25 Suppl:111-4.
18. Shikary ZK, Betrabet SS, Patel ZM, et al. ICMR Task Force Study on Hormonal Contraception. Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. Contraception 1987;35:477-86.
19. Shaaban MM, Odland V, Salem HT, Abdullah KA, Gomaa AA. Levonorgestrel concentrations in maternal and infant serum during use of subdermal levonorgestrel contraceptive implants, Norplant, by nursing mothers. Contraception 1986;33:357-63.
20. Koetsawang S, Boonyaprabob V, Suvanichati S, Paipuekul S. Long-term study of growth and development of children breast-fed by mothers receiving Depo-Provera (medroxyprogesterone acetate) during lactation. In: Zatuchni GI, Goldsmith A, Shelton JD, Sciarra JJ, eds. Long-Acting Contraceptive Delivery Systems. Philadelphia: Harper and Row, 1984; 378-87.
21. Jimenez J, Ochoa M, Soler MP, Portales P. Long-term follow-up of children breast-fed by mothers receiving depot-medroxyprogesterone acetate. Contraception 1984; 30:523-33.
22. Nilsson S, Mellbin T, Hofvander Y, Sundelin C, Valentin J, Nygren K G. Long-term follow-up of children breast-fed by mothers using oral contraceptives. Contraception 1986; 34:443-57.