

ICMR TASK FORCE STUDY ON HORMONAL CONTRACEPTION

Transfer of Norethisterone(NET) and Levonorgestrel(LNG) from a Single Tablet into the Infant's Circulation through the Mother's Milk

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ABSTRACT

A single tablet of either of the three different types of oral contraceptive preparations, viz. "Gynovlar" containing 3000 ug norethisterone (NET) and 50 ug ethinyl estradiol (EE₂) or "Ovral" containing 250 ug levonorgestrel (LNG) and 50 ug EE₂, or a daily progestogen only type - "Minipill" containing 30 ug of LNG only, were administered to 40 normal lactating women on a random basis. The sampling schedule in all the three body fluids, i.e. the maternal sera, breast milk and the infant's sera, was kept in such a manner that the peak levels of the contraceptive steroids would be expected to be present in these fluids. The results of this study indicate that the transfer ratio of LNG or NET from the maternal sera to her breast milk was approximately 10% (6-34%) for Gynovlar, 9% (5-18%) for Ovral and 6% (2-34%) for Minipill. However, it was interesting to observe that whereas the transfer ratio of NET or LNG from breast milk to infant's sera was similar for combination pills - 8% (3-23%) for Gynovlar and 12% (3-42%) for Ovral, it was significantly higher for progestogen only Minipills - 38% (13-92%) for LNG. The precise reason for the higher transfer ratio of LNG from breast milk to infant's serum in Minipill users cannot be explained.

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INTRODUCTION

Lactation alone does not provide complete contraceptive protection to all women because the resumption of both menstruation and ovulation shows high individual variability. Our own study (1) in 204 normal post-partum women who were not using any contraceptives and were having lactation amenorrhoea and actively breast-feeding their infants, indicated that about 4 percent of them became pregnant within five months and 7 percent within 12 months of parturition. It therefore becomes necessary to provide suitable contraceptive therapy in the early postpartum period.

It is now well-established that small amounts of contraceptive steroids administered to the lactating women are transferred from the maternal plasma to her breast milk (2,3,4,5). However, the transfer of contraceptive steroids from the breast milk to the infant is incompletely understood. A study was therefore initiated to determine the amount of the contraceptive steroids transferred from the breast milk to the infants when the mothers were administered one of the three different types of contraceptive pills on a random basis.

SUBJECTS AND METHODS

Forty normal healthy postpartum lactating women in the age group of 20-30 years who had delivered normal healthy full-term babies and were not receiving any medication were selected for this study. The age of the infants ranged from 6 to 20 weeks. They were randomly allocated into the following groups:

- Group I : 15 women were given a single tablet of "Gynovlar" containing 3000 ug NET and 50 ug EE₂.
- Group II : 15 women were given a single tablet of "Ovral" containing 250 ug LNG and 50 ug EE₂.
- Group III : 10 women were given a single tablet of "Minipill" containing 30 ug of LNG only.

All these women were advised to report to the clinic at 9.00 A.M. after a good breakfast. They were then advised to feed their babies. Thereafter, each woman was given a single tablet of one of the above type of contraceptive pill, according to the study group she belonged to. The women were then instructed not to feed their babies for the next 2-2½ hours. About 2-2½ hours after the contraceptive drug administration, 5 ml of the maternal blood and breast milk sample (fore milk) was collected from both breasts. The women were then requested to feed their babies. After the feed, 5 ml of milk was again collected from both breasts (hind milk). The women were taught to collect their own milk samples manually by self-expression. The two milk samples were pooled together, well mixed and snap frozen before storing at -20°C. 1½-2 hours after their breast-feed, 1-3 ml of the infant's blood sample was collected from infants belonging to Gr.I and II, whereas 4-5 ml of blood was collected from infants in Gr.III. The infants' blood samples were collected from the peripheral blood vessels with the help of a scalp vein needle. The sera from the maternal and infant's blood samples

were separated, immediately frozen and stored at -20°C till they were assayed.

About 1.0 ml of maternal serum samples, and 2.0 ml (Gr.I), 4.0 ml (Gr.II) and 8.0 ml (Gr.III) of the milk samples were processed according to the method of Saxena *et al.* (4) for NET and LNG levels. Each sample was monitored for recovery. The mean percent recovery ranged from 80-90% for serum and 70-80% for milk. The entire quantity of the infant's sera was used for the analysis. Thus for Gr.I & II, 1.0 - 1.5 ml of the infant's sample was taken for the assay, and for Gr.III 3.0 - 3.5 ml of sera was taken for the assay. The samples of each individual baby from Gr.III were taken in aliquots of 0.5 ml each. These samples were pipetted into 6 or 7 different extraction tubes. Each sample was further extracted twice with diethyl ether. At each time, the ether extract was poured into one assay tube and evaporated under nitrogen. Thus a single assay tube contained the ether extracted steroids from 3.0 - 3.5 ml of infant sera. The sensitivity of our assay system for both LNG and NET was 62.5 fmols per tube for both serum and milk samples. The serum and milk blanks never exceeded 62.5 fmols per tube. The samples of maternal sera, breast milk and infant's sera of all the volunteers belonging to each study group, were assayed at the same time in a single assay. The radioimmunoassay reagents for both NET and LNG were kindly gifted to us by Schering A.G., Berlin, West Germany.

RESULTS

The individual levels of NET and LNG in maternal serum and breast milk samples at 2 hours and infant's serum at 4 hours after the respective pill ingestion by the mother are shown in Table I. The detection of NET and LNG levels in the infant's serum samples indicates that the gestagens are transferred into infant's circulation through the breast milk. The transfer ratios seen in Table I were all calculated with the group mean levels. The transfer ratio of NET or LNG for the combination pills is approximately the same, *viz.* 10 percent (both for Gynovlar and Ovral) from the maternal sera to breast milk and 8 percent (Gynovlar) and 12 percent (Ovral) from breast milk to infant's sera (Table I). However, the percent transfer for norgestrel only pill (Minipill) is quite different, 6 percent from maternal sera to milk and 38 percent from milk to infant's sera (Table I).

TABLE I**TRANSFER OF GESTAGENS (n.MOLES/L) INTO INFANT'S SERA
FROM MATERNAL SERA VIA BREAST MILK**

GESTAGENS	NET/LNG LEVELS (n.MOLES/L)	MATERNAL SERA	BREAST MILK	INFANT'S SERA
	NET Levels±SD	78.08±27.69	7.99±4.71	0.65±0.39
	Range	18.7 -119.5	3.1 -18.5	0.22-1.4
GYNOVLAR n = 15	% NET Transfer	100	→ 10%	100 → 8.1%
	Range		6-34%	3-23%
	LNG Levels±SD	24.38±10.35	2.04±0.98	0.25±0.15
	Range	10.3 -44.7	1.0 -4.3	0.12-0.66
OVRAL n = 15	% LNG Transfer	100	→ 10%	100 → 12.2%
	Range		5-18%	8-42%
	LNG Levels±SD	2.92±2.37	0.16±0.04	0.06±0.04
	Range	0.7 -8.4	0.096-0.242	0.021-0.170
MINIPILL n = 10	% LNG Transfer	100	→ 6%	100 → 38%
	Range		2-34%	13-92%

DISCUSSION

Earlier studies have shown a lot of discrepancy in the transfer of contraceptive steroids from maternal circulation into breast milk (2,3,4,5). This is mainly because different investigators have used different types of contraceptive steroids, different types of drug delivery system and different types of sampling schedules. In our present study, we have attempted to minimize these variables as far as possible by using only the oral route of drug administration, by using 19-nor-testosterone series of contraceptive steroids (NET or LNG) and "Peak" time sampling schedules for collection of maternal sera, breast milk and infant's sera. The maternal sera and breast milk samples were collected about two hours after the ingestion of the contraceptive steroids by the mother and the infant's sera samples collected about 1½ to 2 hours after breast-feed by the infant, when the highest concentration of the contraceptive steroids are expected in these body fluids (4,5,6,7).

The data of the present study indicates that in women using NET- or LNG-containing combination pills having same amount of EE_2 - 50 ug, the transfer of NET or LNG from maternal serum to breast milk is around 10 percent and a similar range, i.e. 8 to 12 percent transfer, was observed from the breast milk to the infant's circulation (Table I). Although the combination pills belonged to the same 19-nor-testosterone series of steroids, the total amounts of progestogenic components (either NET or LNG) and their ratios to the estrogenic (EE_2) component in the pill were different from each other. The biological progestogenic potency of LNG and NET are known to be different. The only common factor was the total amount of estrogenic component EE_2 , which was identical, i.e. 50 ug in both types of combination pills.

In the minipill (30 ug LNG only) users, the transfer of steroid from maternal circulation to breast milk was somewhat lower, about 6 percent. However, it was surprising to find that the transfer of LNG from breast milk to infant's circulation was 38 percent which is significantly higher than that observed in the other two study groups (Table I). Whether this discrepant finding is due to the lack of estrogenic component in minipills or due to some other reason, cannot be further commented upon by the present study.

How much of gestagen ingested through the breast milk is actually absorbed by the infant is not known. Nilsson et al. (8) have calculated from their study on two infants only, that in 250 ug LNG combination pill users, a daily dose of 0.3 ug LNG is received by the infant through the milk, assuming that the infant consumes 600 ml of breast milk. Our present study of 40 infants conclusively shows that gestagens present in maternal circulation pass into the breast milk and are absorbed by the infant's gastrointestinal system and reach its circulation. Though the transfer percentage with minipills is much higher the quantity of LNG per se received by the infant is much smaller considering the amount of drug in the minipill. For contraceptive purposes, combination pills are not recommended for lactating women and progestogen only minipills are commonly used. Further indepth studies are required to study the pharmacodynamic effects of LNG present in the infant's circulation.

CONTRACEPTION

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