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CONTRACEPTION WITH PROGESTOGENS AND PROGESTERONE DURING LACTATION

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Summary—The growth and development of breastfed infants whose mothers used the contraceptive implants Norplant® containing levonorgestrel and the injectable containing norethisterone enanthate were studied. Each group comprised of 120 women who initiated the use during the 5th to 7th week postpartum and were compared with a similar number of IUD using mothers. The breastfeeding performance did not differ between groups. The infants of the three groups performed similarly as regards their physical growth and health as well as the time of acquisition of the various milestones of psychomental development. A vaginal ring releasing 10 mg of the "natural" progesterone per 24 h was tested in breastfeeding mothers. The continuous use of the ring produced a serum level of progesterone around 4 ng/ml. This was effective in augmenting lactational infertility even through the later phases of breastfeeding when such an effect starts to wane off. The use of the ring proved to be acceptable and had no ill-effect on breastfeeding or infant growth or health. Using the natural progesterone as a contraceptive adds a new measure of safety, since the amount of the steroid secreted in the mother's milk will not be effectively absorbed from the infant's gut. These studies suggest the possibility of using two new methods for breastfeeding mothers; Norplant and the progesterone vaginal contraceptive ring. These can be initiated early postpartum, whenever this is considered needed.

INTRODUCTION

Breastfeeding mothers form a sizable sector of the clientele of the family planning services in Egypt and many other developing countries. Consequently, every attempt should be made to broaden the contraceptive options put to these mothers. After the realization that contraceptives containing estrogens have negative effects on the quantity and possibly the quality of breast milk [1], progestogen-only preparations remained an important option for use during lactation. Several studies have demonstrated that such preparations have no adverse effect on lactation, breast milk and growth of the infant [1–4]. Some of these studies had certain shortcomings, most importantly the concentration on healthy mother/infant dyads and the small numbers of population studied. The reports concerning the new long-term levonorgestrel implants, Norplant® have been scarce and not conclusive [5, 6].

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PART I: PROGESTOGENS

The World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction (HRP) has initiated a new multi-center study of the Growth and Development of Infants Whose Mothers Use Progestogen-only Contraceptives During Lactation. The design of the later study has taken into consideration most of the lessons learnt from previous ones and allowed for inclusion of mothers or infants whose health was suboptimal. The study used Norplant® besides other older progestogen-only contraceptives.

The Assiut clinic has done the study in two phases. The first phase comprised breastfeeding mothers using Norplant® and norethisterone enanthate (NET-EN) and IUD using controls; 120 women/infant dyads in each group. All the women initiated the use of the contraceptive during the 5th to 7th week postpartum. The analysis of this phase has been completed and a brief summary of the findings will be reported here. The second, on-going phase involves lactating mothers using three other methods:

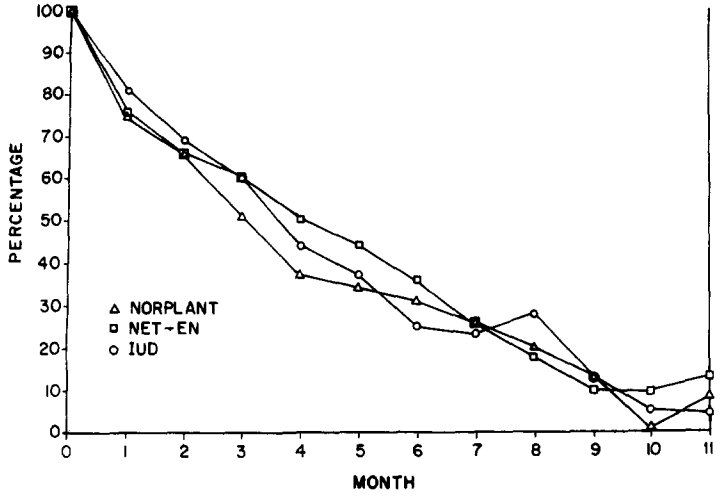

Fig. 1. Percentage of mothers who were exclusively breastfeeding their babies during the use of contraceptive methods.

depot medroxy-progesterone acetate injectable (Depo Provera), a levonorgestrel minipill and the progesterone releasing contraceptive vaginal ring, besides a control group.

RESULTS OF PART I

Effect on breastfeeding

The Norplant, NET-EN and IUD users did not differ as regards: (a) the age of beginning supplementation (Fig. 1) and (b) the age of introduction of major (starch and/or protein) supplements (Fig. 2). Complete weaning however, was earlier in the IUD group than in the NET-EN group; the Norplant group had an intermediate position (Fig. 3).

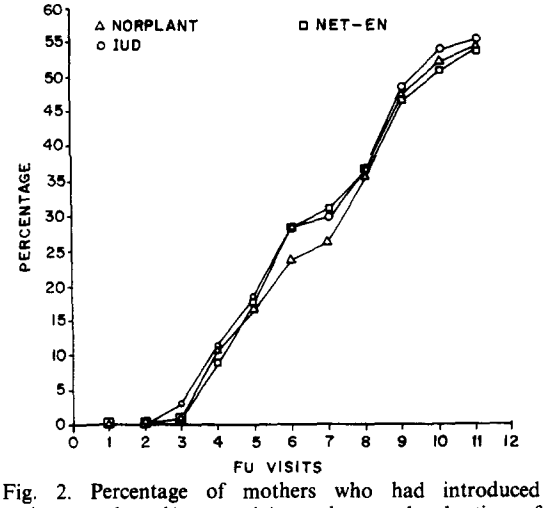

Fig. 2. Percentage of mothers who had introduced major (starch and/or protein) supplements by the time of successive follow-up visits in the three groups.

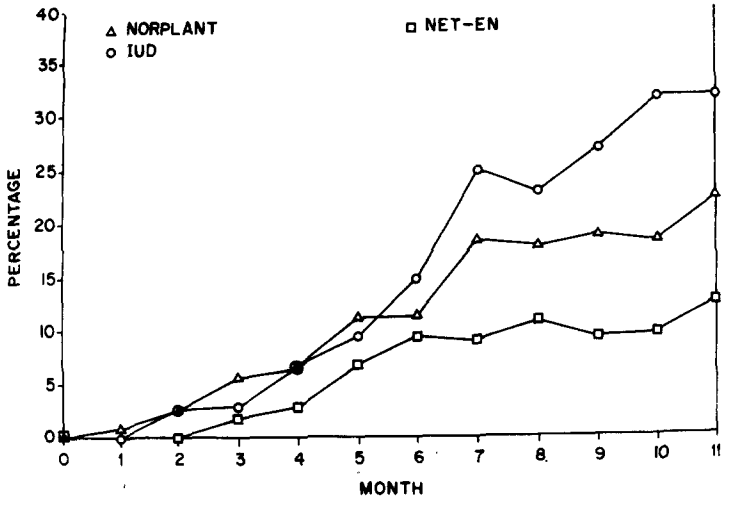

Fig. 3. Percentage of mothers who had weaned their infants by the time of successive follow-up visits in the three groups.

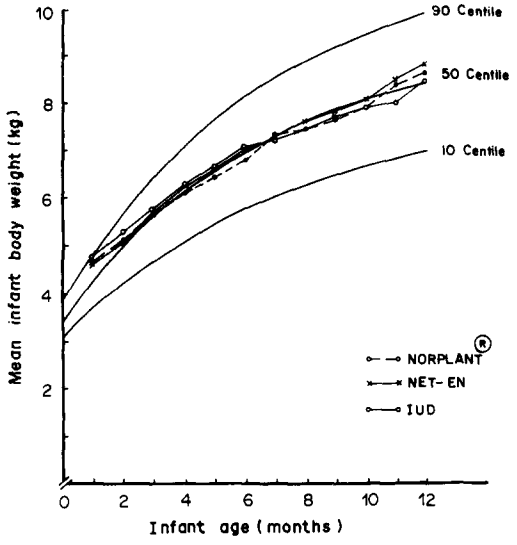

Fig. 4. Weight changes of infants whose mothers used Norplant, NET-EN and IUD during their first year of life as shown against a background of the normal Egyptian infant growth curve.

Infant physical growth

Figure 4 shows the weight increase curve of the infants in the three groups studied as shown against a background of the normal growth curve of Egyptian infants. There were no group differences; the growth curves of infants studied were around the 50th centile of the local norm.

There was no group difference in the infants mid-arm circumference or in the triceps-skin-fold thickness during the first year between the three groups.

Infant psycho-mental development

There was no group difference in the infants in attaining the various milestones of psycho-mental developments like acquiring the ability of gross movement, vision, fine movement, hearing, language and concept development, self-help skills and social skills.

CONCLUSIONS FROM PART I

The results in the Assiut clinic confirm previous reports on the safety of initiating use of NET-EN in the early postpartum periods as regards breastfeeding performance and growth and health of breastfed infants. It also demonstrates that similar conclusions as regards the contraceptive implants Norplant® are equally justifiable. If results from other centers participating in the study support this latter conclusion, this will allow early initiation of use of Norplant in the postpartum period, a time when women are more inclined to initiate contraception.

PART II: PROGESTERONE

There are reports indicating that some of the progestogens used by lactating mothers are secreted in the milk and can be measured in the blood of breastfed infants [7, 8]. In spite of the fact that the levels detected are extremely low, and indeed are very near to the lower limit of the sensitivity of the methods used for measurements of such progestogens, and in spite of the assuring results as given in part I, a completely safe long-term effect cannot be fully guaranteed. The progestogens secreted in milk are absorbed by the newly born infants. The use of progesterone for augmenting and prolonging lactation infertility was suggested by Croxatto *et al.* [9] on the basis that this natural hormone is practically inactive by the oral route. Even if progesterone is ingested by the infant in the breast-milk it will not be absorbed from the gut.

An earlier formulation for administering the natural progesterone was in the form of pellets. Progesterone pellets were made by compressing the steroid in tiny cylinders which were injected subcutaneously with a trocar. Six of these subdermal pellets conjointly produced a blood level of about 3 ng/ml which persisted for about 5 months. The contraceptive efficacy was high with an overall Pearl Index of 1.8. The main problem with the method was a rather high incidence of expulsion [9].

Vaginal rings have been tested as a method of contraception by both the Population Council and the WHO, HRP. Steroids such as medroxyprogesterone acetate, norgestrel, norethisterone and progesterone were incorporated.

A Population Council's vaginal ring releasing about 10 mg of progesterone per 24 h is being evaluated in Assiut as well as in other centers in the world. The first version tried was a ring with an o.d. of 58.4 mm containing a core, 8.4 mm dia, made of 22.5% progesterone in Dowcorning Silastic 382 which is covered by a drug-free diffusion layer of the same silastic resulting in a total cross-sectional thickness of 8.8 mm. The ring is inserted in any position in the vagina and is to be continuously worn for 3 months.

In our clinic, the ring has been tried in 103 women with a control group of 83 women that were fitted with the CuT-380A IUD. Contraception was initiated during the second postpartum month; at a time when all the volunteers were

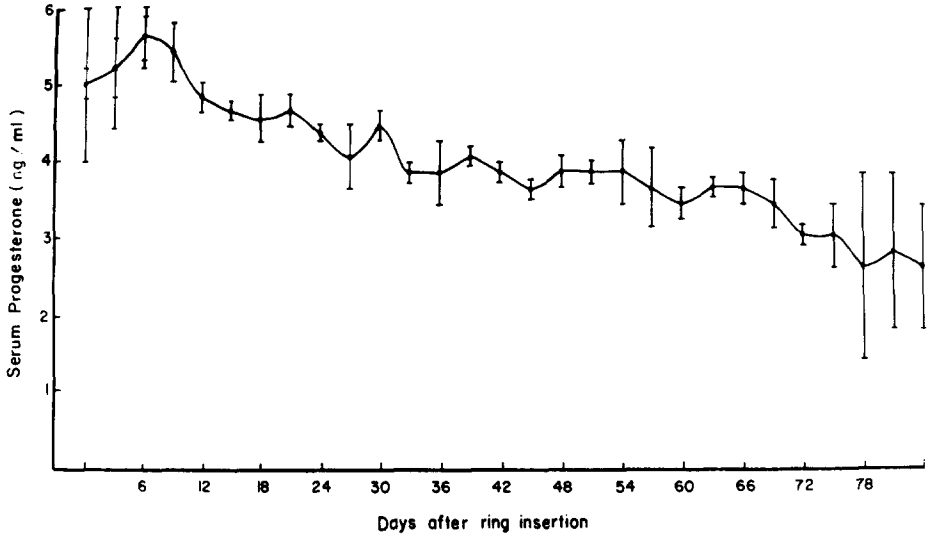

Fig. 5. Serum progesterone levels (means and SD) during the 3 month life-span of the progesterone vaginal contraceptive rings releasing 10 mg/24 h.

exclusively breastfeeding. Each study subject used four rings during the first postpartum year. In this communication we report on the pharmacokinetics of this progesterone releasing ring, its possible mechanism of action and its clinical performance during the first postpartum year.

RESULTS OF PART II

Blood level of progesterone during the effective life-span of the ring (Fig. 5)

The serum progesterone concentration reaches a mean of around 5.2 ng/ml (SD $\pm$ 0.8) during the first 2 weeks of ring use. Thereafter, the level plateaus around 4 ng/ml during most of the life-span of the ring. A drop in the levels to around 3 ng/ml occurs in the last 3 weeks.

There was no difference in the blood levels of progesterone attained during the use of successive rings (Fig. 6) denoting no alteration of absorptive capability of the vaginal skin with passage of time or prolonged release of the steroid in the vagina.

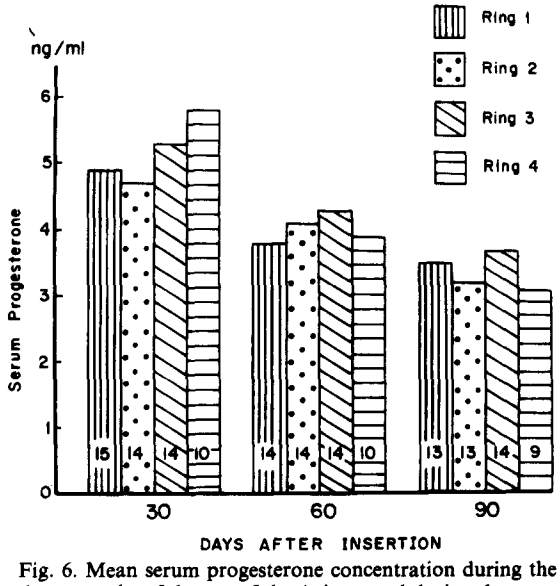

Fig. 6. Mean serum progesterone concentration during the three months of the use of the 4 rings used during the year.

Mechanism of action of the progesterone ring

The ovarian activity was monitored by both closely repeating ultrasonographic examination using a vaginal probe (VUSG) as well as by repeated measurement of serum estradiol and progesterone. This part of the study was done during the second half of the first postpartum year, a time when lactational infertility is waning i.e. during the use of the third or fourth ring. A control group of non-contracepting breastfeeding mothers were studied in parallel. Evidence of ovulation was seen more commonly in the control (66 out of 118 subjects; 55.9%) than in ring users (25 out of 100 subjects); (Table 1). It has to be noted, however, that the majority of these ovulatory incidences were followed by evidence of inadequate luteal function.

Resumption of menstruation was definitely delayed in ring users relative to IUD users (Fig. 7).

Clinical performance of the 10 mg/24 h progesterone ring

The continuation/discontinuation rates. The continuation/discontinuation rates are given as

Table 1. Types of ovarian activity in CVR users and breastfeeding controls during the second half of the postpartum year

Types of ovarian activity	CVR	Controls	χ^2 Test
Quiescent (flat) ovaries[a]	(39)/100	(16)/118	18.57**
Partial ovarian activity[b]	(31)/100	(20)/118	5.96*
Luteinized unruptured follicle[c]	(8)/100	(8)/118	0.12
Follicular cystic enlargement[d]	(7)/100	(8)/118	0.004
Ovulation[e]	(25)/100	(66)/118	
with normal luteal phase[f]	(10)/100	(18)/118	1.33
with deficient luteal phase[g]	(15)/100	(48)/118	37.44**
Total	100	118	

[a]No ovarian follicle reaching 10 mm dia during 1 menstrual cycle (or month) of observation.
[b]One or more follicle reaching 10–15 mm dia without subsequent ovulation.
[c]A leading follicle does not disappear but, instead loses its demarcation and gets filled by internal echoes.
[d]One or more follicle of 30 mm dia or more.
[e]A leading follicle of 18–28 mm dia which changes to or disappears and gets replaced by a corpus luteum; free fluid may be detected in the pouche of Douglas.
[f]A normal corpus luteum is visualized for at least 6 days or more and is associated with a serum progesterone of 5 ng/ml in one or more of the blood samples during its life-span.
[g]One or more of the following features (i) time from ovulation to beginning of subsequent menstruation < 12 days and (ii) short lived CL, a serum progesterone not attaining 5 ng/ml in any of the samples.
*Significant difference ($P < 0.05$); **highly significant difference ($P < 0.01$).

calculated by the life-table method and compared with IUD users (Table 2). One pregnancy occurred in a total of 1007 months of ring use. Unfamiliarity with the ring or logistical problems were the main reasons for discontinuation.

Effect on breastfeeding. There was no difference in the time of introduction of supplements between ring users and IUD controls (Fig. 8) or in the number or type of supplementary feeds used.

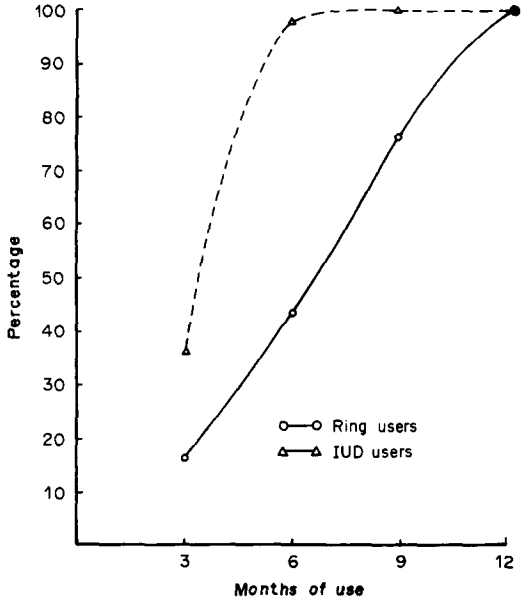

Fig. 7. Percentage of women who had resumed menstruation by successive postpartum months in the progesterone CVR and IUD groups.

Table 2. Net cumulative continuation/discontinuation rates in the first year of use per 100 women CVR vs IUD groups

	CVR		IUD	
Reasons	Events	Rate	Events	Rate
Pregnancy	1	0.98	0	1.00
Menstrual problems	0	0.00	2	2.42
Complete weaning (one or no breast feed per 24 h)	5	4.97	4	4.83
Severe infant illness	3	2.96	2	2.42
Use related problems				
Failure to obtain a ring	3	2.93	0	0.00
Loss of ring	10	9.71	0	0.00
Unpleasant vaginal effects	2	1.98	0	0.00
Expulsion	0	0.00	1	1.21
Other use problem	0	0.00	1	1.21
Planning pregnancy	1	1.01	0	0.00
Separation from husband	1	0.99	0	0.00
Other personal reasons	7	6.85	0	0.00
Lost to follow-up	4	3.99	0	0.00
Continuation rate		66.59		85.54
Total subjects enrolled		103		83
Total months of use		1007		958

Infant weight increment and health. Table 3 shows that there was no difference in the weight gain of infants during their mothers use of successive rings when compared with infants whose mothers used the IUD.

CONCLUSIONS FROM PART II

1. The progesterone vaginal contraceptive ring showing an *in vitro* release rate of 10 mg/24 h maintains a blood level of about 4 ng/ml of this steroid throughout most of the life-span of the ring (3 months).
2. This level of progesterone produces effective contraception during lactation, even after resumption of menstruation.
3. This contraceptive effect depends in part on the delay in resumption of ovulation. Other mechanisms with a similar effect on cervical mucus should be operating since in at least 10% of users ovulation followed by adequate corpus luteum were observed.
4. A 1 year net cumulative continuation rate of 67 per 100 indicates a reasonable degree of acceptability that can be further improved by improving the logistics and by improving the familiarity of the community with ring use.
5. The use of progesterone CVR did not alter the breastfeeding performance or influence the growth of the infant.

Table 3. The mean infant daily increment (g/day) in the two groups in the successive study intervals

1st	3 Months (ring)	18.25 ± 7.54	19.94 ± 8.57
		$t = 1.39$	(insignificant)
2nd	3 Months (ring)	14.31 ± 8.75	9.77 ± 7.60
		$t = 3.46$	(highly significant)
3rd	3 Months (ring)	7.76 ± 6.90	8.04 ± 6.34
		$t = 0.25$	(insignificant)
4th	3 Months (ring)	5.97 ± 6.75	7.34 ± 5.26
		$t = 1.35$	(insignificant)

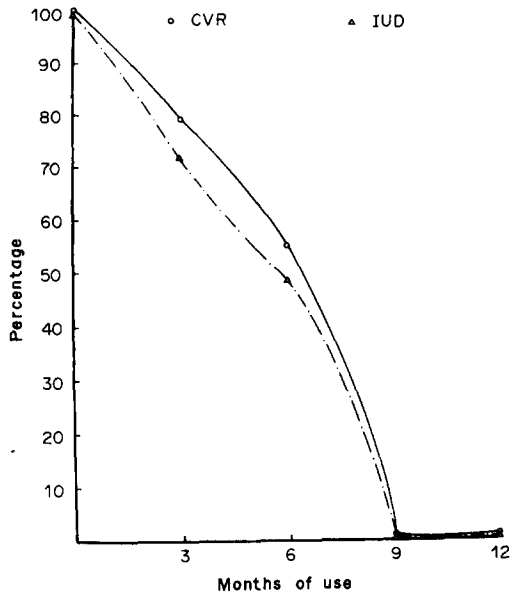

Fig. 8. Percentage of mothers who were exclusively breast-feeding the infants during the successive months in the progesterone CVR and IUD groups.

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