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World Health Organization (WHO) Task Force on Oral Contraceptives, Special Programme of Research, Development, and Research Training in Human Reproduction

Breast milk volume and composition and infant growth were measured at three- and four-week intervals, up to six months, in a multicenter randomized double-blind trial comparing a low-dose combined oral contraceptive (OC) with a progestogen-only OC. A nonrandom group using nonhormonal methods was also studied in the three centers: Szeged, Hungary; Bangkok, Thailand; and Khon Kaen, Thailand. A fourth group, users of depot-medroxyprogesterone acetate (DMPA) was included in the two Thai centers. Altogether, 341 women were recruited into the study. Combined OCs caused a significant decrease in milk output and total energy content as well as widespread changes in milk constituents. In the DMPA group, no significant changes were observed in milk volume, and only minor shifts occurred in milk composition, which varied between centers. No differences were found between the progestogen-only pill and DMPA. No hormonal contraceptive was associated with any significant difference in infant weight or fat fold, nor in the rate of discontinuation for failure to gain weight. This study reiterates the need to avoid combined OCs during the first few weeks or months of lactation. Both norgestrel and DMPA appear to be safe for use in both developing and developed countries, at least when the nutritional status of the mother and infant are adequate, but further research is needed on the safety of these contraceptives in populations with malnutrition. (STUDIES IN FAMILY PLANNING 1988; 19, 6: 361–369)

Prolonged breastfeeding is common in many parts of the world, and in poorer populations many infants are totally dependent on breast milk for survival during early life (Huffman, 1984). Although lactation has an antifertility effect, this effect is temporary and variable. In many developing and developed countries, women who are still breastfeeding need effective contraception.

Contraceptive prevalence studies indicate that hormones are widely used during lactation (Strauss et al., 1981; Pebley et al., 1985). Since milk production is under hormonal control, exposure to exogenous sex hormones must lead to questions as to whether lactation is altered by such contraception. Sex hormones, furthermore, are excreted in milk, and their effect on the infant, if any, must be questioned.

Previous studies have consistently shown that combined OCs, containing estrogen and progestogen, adversely affect lactation, reducing milk volume and changing its constituents (Hull, 1981). The antilactational effect of the hormones is believed to depend on the es-

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trogen. The effects of progestogen-only contraceptives are more controversial. Most research has focused on the injectable depot-medroxyprogesterone acetate (DMPA). Some workers have found increased milk output and enhanced growth following use of DMPA; others have not (reviewed by Hull, 1981; Huber et al., 1980; Dahlberg, 1982; Jiminez et al., 1984). Progestogen-only pills have been studied less, and few effects have been found. Furthermore, relatively few studies have been conducted on milk composition, and their results are not consistent.

The Special Programme of Research, Development, and Research Training in Human Reproduction of the World Health Organization (WHO) conducted a comparative study of a low-dose combined oral contraceptive (OC) and two progestogen-only preparations, one oral and one injectable, all initiated six weeks after delivery. Findings on volume and composition of breast milk are reported here for the three hormonal contraceptive groups, and for a nonhormonal comparison group. Detailed information on infant growth has been published previously (WHO Task Force, 1984). Data on the fatty acid composition of the milk are also reported elsewhere (WHO Task Force, 1986).

Materials and Methods

Three WHO Collaborating Centres for Research in Human Reproduction participated in the study. The Department of Obstetrics and Gynecology, University Medical School, Szeged, Hungary, and Siriraj Hospital, Mahidol University, Bangkok, Thailand, recruited subjects from women attending prenatal clinics or admitted to obstetric wards in their hospitals. The Chulalongkorn Hospital, Bangkok, Thailand, recruited subjects from women attending the rural health centers in Khon Kaen, Thailand.

Preliminary contact was made during the antenatal period. A detailed explanation regarding study procedure was given soon after delivery, and after obtaining informed consent, women were enrolled in the study. Only apparently healthy women, aged 20–35 years of age, who had had two to five births and prior successful experience of breastfeeding for at least three months, were recruited for the study. All these women had hemoglobin levels of at least 10 grams per deciliter, normal uncomplicated pregnancies, and had delivered normal healthy singleton mature infants weighing between 2,700 and 3,700 grams. None had any local breast problems such as inverted nipples or breast abscesses. Women who wanted to use oral contraceptives were randomly allocated to a combined preparation containing 150 micrograms levonorgestrel and 30 micrograms ethinyl estradiol or a progestogen pill containing 75 micrograms of norgestrel. The pills were packaged identically and this component of the study was double-blind. In the Thai centers, women choosing to use the injectable contraceptive DMPA were also included. All hormonal preparations in all three centers were initiated at six weeks plus or minus three days postpartum. Women who chose to use an IUD, to undergo sterilization, or not to use any form of contraception were recruited into the control group.

The mother–infant dyads were followed up at 3, 6, 9, 12, 16, 20, and 24 weeks after delivery. In the hormonal contraceptive groups the three- and six-week follow-ups were made prior to the initiation of hormone treatment. At each visit information was collected on infant feeding practices, morbidity due to infections, and anthropometric indexes of the infant and the mother. Standard criteria were developed, based on measurements in the infants, for exclusion from the study due to failure to gain weight (WHO Task Force, 1984). Advice on breastfeeding and supplemental feeding was given according to the usual practice in each clinic.

At each visit women were admitted to the clinic in the morning and asked to feed the infant first at the right breast. Two hours later infants were fed on the left breast. Simultaneously, the right breast milk was emptied into a sterile container using the Egnell pump for a maximum of 20 minutes. The volume of expressed milk was measured and, after mixing, a 10 milliliter aliquot was taken out for analysis of composition. The remaining expressed breast milk was offered to the baby, but the infant usually refused to drink it. Two hours later the procedure was repeated on the opposite breast. The volume of breast milk expressed was reported as an average of the volume in milliliters from both breasts obtained at two 20-minute periods of pump expression at an interval of two hours.

The two 10-milliliter aliquots taken from expressed breast milk were mixed, freeze-dried, and transported to London by air and stored at −20 degrees centigrade until analysis. The freeze-dried samples were reconstituted by adding 18 milliliters of deionized distilled water and leaving the bottle in a water bath at 37 degrees centigrade for 30 minutes and gently mixing. The following estimations were done on the reconstituted milk samples within five days after reconstitution: total fat, nitrogen, lactose, calcium, phosphorous, magnesium, sodium, potassium, and osmolality. Standard methods were used for chemical analysis, and details of these are given elsewhere (WHO Task Force, 1985).

Criteria for Withdrawal from the Study, Response Variables, and Statistical Analysis

Subjects were free to withdraw from the study at any time. In addition, they were discontinued if they encountered significant medical or health problems, changed their contraceptive method, were lost to follow-up, considered their milk supply to be inadequate, or if their infant's growth was inadequate (defined by weight gain between successive visits less than a predetermined minimum, or a weight-for-age less than the fifth percentile of the Harvard Standard). The minimum accept-

able weight gains were 325, 300, 350, 300, and 250 grams, respectively, for the 6–9, 9–12, 12–16, 16–20, and 20–24-week intervals between visits. Ethical considerations precluded imposing constraints on the use of supplements and this was not a reason for discontinuing from the study.

The main response variables considered in this report are for each of the nine constituents of breast milk indicated above, the concentration defined as the amount of the constituent by standard volume, and the total content derived from multiplying the concentration by the total volume of milk expressed. Of interest also are the corresponding average milk volume at each follow-up, the infant growth parameters, and withdrawals from the study for inadequacy of breast milk or failure of infant growth to meet predetermined criteria.

Data for each response variable were summarized as mean (or as intra-subject mean change from baseline) values for each treatment group at each visit. Data for the second visit at six weeks were taken as the pre-treatment baseline level. Comparisons were made between treatment groups using analysis of variance techniques. Withdrawals from the study due to various reasons enumerated above were analyzed by noncompeting risk life-table procedures, and rates between groups were compared using the log-rank test. The following specific contrasts of interest to the objectives of the study were tested on each occasion: the combined oral contraceptive pill group versus the progestogen-only pill group and each of the other groups versus the control group.

For each center and for each follow-up visit the study groups were compared with respect to some variables dealing with collection and analysis of milk samples. The variables are the time interval between: (a) collection and analysis of the sample, (b) despatch from field and arrival of the sample in London, (c) collection and despatch of the sample, (d) arrival at the London laboratory and analysis of the sample, and (e) beginning and end of analysis of the sample. In Szeged and Bangkok the treatment groups did not differ significantly with respect to any of the five variables. In Khon Kaen, however, the treatment groups differed during the first four visits with respect to time lag between collection and analysis and between arrival at the laboratory and analysis (these two variables are related if travel time is assumed constant). In each case the mean time lag for the DMPA samples was significantly shorter by between 30 to 60 days than for the remaining three groups. The treatment groups also differ in Khon Kaen with respect to time lag from the beginning to the end of analysis in the laboratory for samples at visit three onward. On these occasions the mean time lag for the DMPA group was significantly longer by one day than for the other groups. In order to see whether these variations affected the laboratory determinations and consequently biased the comparison between groups with respect to the chemical constituents, bivariate correlation coefficients were calculated between these time variables and each of the nine chemical constituents. The correlations, without exceptions, were generally poor and signified no need for adjustments to control for variation in the time lag variables.

Results

Each center recruited the required minimum of 25 subjects per study group, and in some centers up to 32 subjects were recruited in the treatment groups. In Khon Kaen, 58 controls were admitted because of the large number of volunteer controls available in that center.

Altogether, 341 women entered the study in the three centers. Their characteristics, by treatment group and center, have been described in detail elsewhere (WHO Task Force, 1984). The Thai women were shorter and lighter than the Hungarians, but the ponderal index (kilograms divided by centimeters squared, multiplied by 1,000) was similar in all three centers. The women in Khon Kaen had lower fat fold thickness compared to the women from the other two centers. Within the same center, however, there were no significant differences between the study groups in any of the parameters, except in Khon Kaen, where women who received combined oral contraceptives were heavier than those in the other groups.

The number of women recruited into each study group, the discontinuation rates, and the reasons for discontinuation from the study are shown in Table 1. There were significant differences between centers in discontinuation rates and reasons for discontinuation. The rates were higher in Szeged than in the two Thai centers with respect to discontinuation for all reasons combined, inadequacy of breast milk, and failure of the children to gain weight adequately. Within each center, however, no significant differences were found between the different treatment groups.

The average milk volume expressed at admission and the mean changes from the admission values at each subsequent follow-up are shown in Table 2. The volume of expressed breast milk was similar at six weeks in all centers and in all treatment groups. At subsequent follow-ups, milk volume declined over time in all treatment groups, with the exception of the progestogen-only pill and the DMPA groups in Bangkok. The decline was significantly greater in the group using combined oral contraceptives compared with the controls in each of the Thai centers. In fact, at the nine-week visit, milk volume had significantly declined from the six-week value among the combined pill users in two centers. When women using either of the progestogen-only methods were compared with the controls, no significant differences in milk volume were found at any of the follow-up visits, except for the progestogen-only pill group in Bangkok at 12 and 24 weeks.

Fat concentration (Table 3) varied between centers at the six-week baseline as well as later, being higher in

Table 1 Cumulative life-table discontinuation rates per 100 women at 24 weeks, by treatment group and center

Center	Combined pill		Progestogen-only pill		DMPA		Controls (IUD)	
	Rate	SE	Rate	SE	Rate	SE	Rate	SE
Szeged								
Number recruited	30	—	30	—	—	—	28	—
Number completed study (%)	14 (46.7)	—	14 (46.7)	—	—	—	12 (42.9)	—
Discontinuation rates:								
All reasons	53.3	9.1	50.0	9.1	—	—	53.6	9.4
Inadequacy of breast milk	45.6	9.4	32.4	9.5	—	—	37.0	9.9
Failure to gain weight	10.3	7.1	13.5	7.5	—	—	18.2	8.5
Maternal health/medical problem	0	—	3.4	3.4	—	—	4.5	4.4
Bangkok								
Number recruited	25	—	25	—	27	—	25	—
Number completed study (%)	14 (56.0)	—	16 (64.0)	—	12 (44.4)	—	9 (36.0)	—
Discontinution rates:								
All reasons	20.0	8.0	20.0	8.0	40.2	9.5	37.5	9.9
Inadequacy of breast milk	0	—	0	—	0	—	0	—
Failure to gain weight	20.0	8.0	16.7	7.6	32.4	9.5	30.0	9.8
Maternal health/medical problem	0	—	0	—	0	—	0	—
Khon Kaen								
Number recruited	31	—	30	—	32	—	58	—
Number completed study (%)	22 (71.0)	—	20 (66.7)	—	27 (84.4)	—	44 (75.9)	—
Discontinuation rates:								
All reasons	22.6	7.5	23.3	7.7	16.4	6.8	19.0	5.2
Inadequacy of breast milk	0	—	0	—	0	—	0	—
Failure to gain weight	7.3	5.0	3.7	3.6	3.3	3.3	16.1	4.9
Maternal health/medical problem	7.1	4.8	4.0	3.9	0	—	1.7	1.7

Note: SE is standard error. No statistically significant differences exist between treatment groups.

Szeged than in the other two centers. In the combined OC groups, fat concentration tended to be higher than in the controls, but this effect was not consistent over time or between centers. Similarly, the DMPA groups (and to a lesser extent the norgestrel groups) tended to show lower fat concentrations than that in the controls but, again, this effect was not consistent over time or between centers.

Nitrogen concentration was consistently lower among combined oral contraceptive and DMPA groups, as compared with both the controls and the progestogen-only pills (Table 4). This was seen in all centers and

Table 2 Admission values and mean changes from admission in milk volume (ml) at each follow-up visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	Admission: 2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	72.4	8.4	30	−7.9	7.6	25	−20.9*	8.5	22	−35.5	9.4	19	−35.6	10.2	16	−41.7	13.1	13
Progestogen-only	83.0	9.3	30	−1.3	4.3	29	−13.5	5.5	28	−16.8	5.8	25	−23.9	8.2	19	−36.5	11.2	15
Controls	67.4	5.3	28	0.6	5.5	25	0.0	6.2	24	−16.6	6.8	22	−16.4	8.4	16	−20.5	11.6	14
Bangkok																		
Combined pill	71.5	5.1	25	−20.5*	4.8	25	−20.0*	5.4	25	−16.4	5.2	23	−22.9*	5.7	22	−23.1	7.3	20
Progestogen-only	73.8	5.7	25	7.3	4.1	25	13.7*	5.0	25	−0.1	6.1	24	5.8	6.7	23	7.6*	7.3	20
Controls	79.5	6.2	25	−3.1	5.6	24	−3.2	5.0	24	−6.9	5.4	21	−4.4	5.0	17	−14.7	6.7	16
DMPA	70.5	4.2	27	6.9	2.9	26	10.5	4.5	25	−3.5	4.4	23	−0.1	5.8	21	0.0	5.3	16
Khon Kaen																		
Combined pill	65.5	5.5	31	−12.8*	5.4	28	−24.1***	5.7	26	−32.2**	6.9	25	−29.0*	6.9	23	−34.3**	6.0	24
Progestogen-only	66.1	5.1	30	−1.7	4.5	29	6.3	3.9	27	−0.2	6.3	24	−14.9	4.8	23	−14.7	3.8	23
Controls	68.3	4.0	58	1.1	3.4	58	1.3	4.6	56	−12.6	4.2	54	−8.6	5.0	51	−14.0	4.5	49
DMPA	67.6	4.4	31	−1.6	4.5	30	−6.4	4.3	30	−14.1	4.6	30	−8.4	4.4	27	−3.6	7.4	26

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from the controls).

Table 3 Fat concentration (grams per liter) in milk samples at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	60	3	30	59	4	24	68	4	25	64	4	19	66	5	15	56	6	13
Progestogen-only	62	3	28	60	3	29	62	4	25	59	4	25	64	5	19	55	5	15
Controls	56	3	27	60	3	24	59	3	24	66	4	22	67	6	15	54	5	14
Bangkok																		
Combined pill	49	2	25	48	3	25	51	3	25	50	3	23	48*	3	22	48*	3	19
Progestogen-only	45	2	25	41	2	25	41	2	25	37*	3	24	39	2	23	40	3	20
Controls	50	2	25	48	2	24	49	3	24	47	3	20	39	3	17	39	3	16
DMPA	49	3	27	41	3	26	39*	3	25	40	3	23	41	3	20	35	2	16
Khon Kaen																		
Combined pill	46	2	30	48	2	28	45	2	25	46	3	25	46	2	23	54***	3	23
Progestogen-only	48	2	30	49	2	28	48	2	27	43	2	24	46	2	23	46	2	23
Controls	49	2	58	45	2	56	49	2	56	49	2	52	48	2	49	45	1	48
DMPA	47	2	30	42	2	30	41**	2	30	43	2	30	42	3	26	42	2	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from the controls).

throughout the study period, although the differences between study groups were significant only in Bangkok at 9 and 12 weeks, and in Khon Kaen at 24 weeks (combined oral contraceptives only).

Lactose concentrations (Table 5) were unaltered by combined oral contraceptives. In contrast, DMPA was associated with highly significant increases in this component of milk in Bangkok. In Khon Kaen, no contraceptive altered lactose. In the Bangkok center, also, the progestogen-only pill group tended to show higher levels of lactose than the controls, but the difference was significant only at the 16-week visit.

Tables 6 and 7 show data on calorie concentrations and total calories supplied by the milk (concentration multiplied by volume). Concentrations tended to be lowest in the DMPA groups; a similar lowering in the progestogen-only pill groups in the Thai centers was not seen in Szeged. Although the combined OC did not consistently change calorie concentrations, it did markedly reduce the total calorie content of milk (Table 7) because it caused a reduction in milk volume. Even in Szeged, where the differences were not statistically significant, combined pills were associated with a 12–25 percent reduction in total calories available around 16 to 24 weeks. The deficit was even greater (37–40 percent) in Khon Kaen. There were no consistent changes in total calorie content of milk in the DMPA or progestogen pill groups, compared with the controls. Total values for fat, nitrogen, and lactose (nutrient multipled by volume) were not affected by the contraceptives (data not shown).

Previous researchers, observing increases in milk volume in DMPA users and decreases in combined OC users, with reciprocal changes in various constituents, have questioned whether these two contraceptives merely alter the dilution of the milk *vis à vis* its water content. An answer to this is found in Table 8, which records osmolality. There are no differences between any of the treatment groups at any age. Therefore, the milk of mothers using DMPA or estrogen-containing pills cannot merely be considered more dilute or less dilute, respectively.

In the two Thai centers, combined pills were asso-

Table 4 Nitrogen concentration (mmols/liter) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	154	4	30	134	3	24	135	4	22	127	5	19	121	4	15	138	5	13
Progestogen-only	155	3	28	141	2	29	141	4	28	135	5	25	135	5	19	145	13	15
Controls	164	5	27	145	4	25	149	5	24	143	6	22	138	7	15	139	8	14
Bangkok																		
Combined pill	152	5	25	135*	4	25	129*	3	25	124	5	23	130	5	22	123	4	19
Progestogen-only	147	5	25	144	5	25	140	6	25	137	7	24	133	4	23	134	12	20
Controls	157	4	25	148	4	24	142	4	24	134	4	20	133	4	17	133	4	16
DMPA	154	4	27	129**	3	26	128	5	25	127	3	23	122	4	20	131	7	16
Khon Kaen																		
Combined pill	152	4	30	136	7	28	127	4	25	125	5	25	126	7	22	117*	7	23
Progestogen-only	148	4	30	133	5	29	132	4	27	126	4	24	128	5	23	124	3	23
Controls	148	3	58	139	3	56	138	3	56	133	3	52	134	4	49	132	4	48
DMPA	149	3	30	130	3	30	129	3	30	128	2	30	126	3	26	123	3	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$ (significantly different from the controls).

Table 5 Lactose concentration (mmols/liter) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	195	3	30	194	3	24	190	3	22	192	3	19	186	3	15	188	4	13
Progestogen-only	191	2	28	194	3	29	195	2	28	193	4	25	187	4	19	184	4	15
Controls	190	4	27	191	5	25	188	3	24	186	3	22	184	4	15	190	3	14
Bangkok																		
Combined pill	194	2	25	191	4	25	196	3	25	194	3	23	193	4	22	189	4	19
Progestogen-only	192	3	25	198	3	25	199	2	25	202*	3	24	204	3	23	199	5	20
Controls	190	4	25	192	4	24	194	2	24	193	2	20	199	4	17	194	3	16
DMPA	193	3	27	207**	3	26	202	3	25	202*	2	23	197	6	20	202	4	16
Khon Kaen																		
Combined pill	190	3	30	195	4	28	193	2	25	199	3	25	194	5	22	191	3	23
Progestogen-only	190	3	30	197	3	29	195	3	27	197	3	24	192	3	23	199	3	23
Controls	189	2	58	193	2	56	193	2	56	193	2	52	192	2	49	193	2	48
DMPA	191	3	30	193	2	30	197	2	30	198	2	30	198	4	26	195	3	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$ (significantly different from the controls).

Table 6 Calorie concentration (Kcal/liter) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	847	24	30	834	30	24	911	34	22	875	38	19	880	44	15	800	53	13
Progestogen-only	864	22	28	846	23	29	859	34	28	827	33	25	844	49	19	806	42	15
Controls	810	24	27	839	22	24	830	22	24	885	31	22	894	52	15	782	43	14
Bangkok																		
Combined pill	747	19	25	728	26	25	761	24	25	742	25	23	734	23	22	731	27	19
Progestogen-only	707	19	25	679	19	25	683	19	25	650*	23	24	659	19	23	671	27	20
Controls	749	20	25	734	21	24	740	25	24	723	24	20	675	25	17	674	26	16
DMPA	745	20	27	684	22	26	662*	29	25	675	28	23	659	32	20	633	25	16
Khon Kaen																		
Combined pill	718	15	30	734	17	28	704	20	25	720	22	25	733	26	22	771*	26	23
Progestogen-only	733	18	30	741	20	28	733	17	27	693	18	24	709	18	23	711	21	23
Controls	739	14	58	710	18	56	739	14	56	742	16	52	724	15	49	708	12	48
DMPA	719	22	30	676	18	30	671**	15	30	696	20	30	679	23	25	683	22	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$ (significantly different from the controls).

Table 7 Total calorie content (Kcal) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	116	10	30	116	12	24	105	9	22	87	7	19	84	7	15	71	12	13
Progestogen-only	141	15	28	135	15	29	118	15	28	119	18	25	120	22	19	106	19	15
Controls	111	10	27	115	11	24	115	12	24	99	10	22	112	14	15	92	16	14
Bangkok																		
Combined pill	106	8	25	72***	4	25	77**	4	25	80*	6	23	72**	4	22	72	10	19
Progestogen-only	104	9	25	108	7	25	117	8	25	95	8	24	105	10	23	102	9	20
Controls	117	8	25	107	7	24	105	8	24	101	8	20	97	8	17	87	7	16
DMPA	105	7	27	105	5	26	106	6	25	93	6	23	94	3	20	90	8	16
Khon Kaen																		
Combined pill	96	8	30	76*	9	28	61***	7	25	51***	5	25	52***	4	22	50**	6	23
Progestogen-only	98	8	30	96	8	28	87	8	27	89	9	24	72	7	23	75	8	23
Controls	101	6	58	99	6	56	103	6	56	83	5	52	86	6	49	79	7	48
DMPA	97	7	30	88	7	30	81*	6	30	73	6	30	78	7	25	85	9	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from the controls).

Table 8 Osmolality (milliosmols/kg. water) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	299	2	30	295	2	24	290	2	22	291	2	19	284	2	15	289	3	13
Progestogen-only	296	2	28	293	2	29	296	2	28	294	2	25	289	3	19	294	3	15
Controls	297	2	27	294	1	25	292	2	24	288	3	22	290	3	15	291	2	14
Bangkok																		
Combined pill	284	2	25	283	2	25	284	2	25	284	2	23	288	2	22	282	3	19
Progestogen-only	286	2	25	288	2	25	290	2	25	292	2	24	291	2	23	288	2	20
Controls	284	2	25	284	2	23	285	1	24	287	2	20	290	2	16	288	2	16
DMPA	286	2	27	289	2	25	288	2	24	286	2	23	287	2	19	291	2	16
Khon Kaen																		
Combined pill	278	1	30	284	2	28	278	2	25	276	2	25	273	6	22	277	3	23
Progestogen-only	279	2	30	279	2	29	278	2	27	279	2	24	281	2	23	280	2	23
Controls	281	1	58	279	2	56	280	1	56	280	1	52	279	1	49	279	1	48
DMPA	277	3	30	281	2	30	277	1	30	280	2	30	280	2	26	274	4	25

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.

ciated with consistent and significantly lower sodium, potassium, calcium, magnesium, and phosphate, compared with either the progestogen-only pill or with the controls (data not shown). The effect was seen at all treatment visits (that is, from nine weeks onward). In Szeged, the difference, while also consistent, was much less and it was rarely statistically significant. Occasional changes in the progestogen-only group, compared with controls, were consistent with chance, after taking into account the effects of multiple observations. DMPA had no effect on these minerals. Generally, these results of the analysis of total value of these minerals mirrored the decline found in the milk volume. The concentration of each of the minerals, except calcium, did not differ significantly between the treatment groups at any visit and were not affected by treatment. For calcium, however, the concentration for the combined pill group declined steadily throughout in all centers. At all follow-up visits, its mean value was significantly lower than at admission; they were also lower than those of the other groups who did not differ among themselves and were at approximately the same level throughout the study.

Data on mean weight at each visit are shown in Table 9. There were no differences in weight or length (data not shown) between the treatment groups at any visit in the three centers, indicating that in each of these populations nutrition was adequate to support growth of lean tissue. Both absolute levels and inter-visit changes in tricep fat-fold thickness, ponderal index, arm circumference, and head circumference were similar among treatment groups at each follow-up visit (data not shown).

Considering illness episodes (data not shown), no significant or consistent differences were found between the contraceptive groups in the proportion of infants episode-free, in the mean number of episodes per child, or in the number of days of sickness. The background levels of morbidity, as reported by mothers, were very different in the three centers: in Szeged, illness episodes were very rare in the first six months of life; in Bangkok, under 15

Table 9 Infant weight (grams) at each visit, by center and treatment group

Center and treatment group	Visit number (weeks)																	
	2 (6 wks.)			3 (9 wks.)			4 (12 wks.)			5 (16 wks.)			6 (20 wks.)			7 (24 wks.)		
	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N	$\bar{X}$	SE	N
Szeged																		
Combined pill	4,490	79	30	5,078	75	25	5,563	110	22	6,170	126	19	6,719	172	16	7,179	216	13
Progestogen-only	4,387	65	30	4,939	70	29	5,440	78	28	6,083	90	25	6,685	99	19	7,188	128	15
Controls	4,342	78	29	4,925	98	25	5,373	95	24	5,987	109	22	6,311	145	16	6,699	183	14
Bangkok																		
Combined pill	4,666	91	25	5,285	104	25	5,836	111	25	6,430	132	23	6,949	175	22	7,440	168	20
Progestogen-only	4,717	89	25	5,401	115	25	5,969	132	25	6,562	160	24	7,170	180	23	7,719	187	20
Controls	4,552	99	25	5,155	134	24	5,628	164	24	6,243	188	21	6,811	239	17	7,214	267	16
DMPA	4,463	74	27	5,078	92	26	5,582	107	25	6,189	125	23	6,677	145	21	7,134	168	16
Khon Kaen																		
Combined pill	4,564	66	31	5,147	81	28	5,667	98	26	6,237	120	26	6,749	131	24	7,092	142	24
Progestogen-only	4,444	65	30	5,041	90	29	5,571	113	27	6,180	142	24	6,652	154	23	6,988	163	23
Controls	4,485	48	59	5,121	67	58	5,666	65	57	6,233	80	53	6,712	92	51	7,082	96	49
DMPA	4,432	56	31	4,981	73	30	5,526	75	29	6,030	78	30	6,544	92	27	6,965	106	26

Note: $\bar{X}$ = mean; SE = standard error; N = number of subjects.

percent of infants had been ill between any two visits; while in Khon Kaen, 50–75 percent of them were reported to have been ill at each visit.

Discussion

This study supports the findings of previous ones indicating that combined oral contraceptives, containing estrogen and progestogen, disturb the physiology of lactation (Hull, 1981). Other studies are consistent with the findings presented here, and point to a reduction in milk volume, a deficit in calories, and widespread changes in minerals.

Although combined OCs altered the milk in this study, no harm to the infants was detected. To some extent, this is surprising, when viewed against the magnitude of the changes in milk. It underlines the need, in studies of nutrition of breastfed infants, to take into account other aspects of the maternal–infant interaction, such as the duration and frequency of suckling and the content and frequency of supplementation.

There are a number of possible explanations for the absence of a relationship between contraceptive use and infant growth in this study. The first concerns the capacity of women to produce milk, which in well nourished women probably exceeds the needs of most infants (Hartmann et al., 1985). Recent research has shown that human milk output has a wide margin of variation, within which infants seem able to grow satisfactorily. Furthermore, milk yield appears not to be affected greatly by marked differences in level of living and diet, above a certain threshold.

Infant demand and maternal supply are dynamically interrelated in a way that is not well understood but that certainly changes from day to day and from feed to feed. Our method of measuring milk output, by extraction with a breast pump, should reflect the maximum capacity at the time of examination, but may have little relationship to the amount actually ingested by the baby during that or any other 24-hour period. This problem highlights the difficulty with researching the relationship of milk output to infant growth.

Second, while this study showed no apparent variation in suckling frequency between the various treatment groups, no information is available on its duration or intensity. Longer suckling would result in the infant's receiving more lipid-rich (and consequently energy-rich) hind milk (milk at the end of a feed). More intense suckling would stimulate future milk production (Huffman, 1984).

Third, although the proportion of infants receiving supplementation was not increased in the OC group, no information was obtained on the number of supplementary feeds, or on the amount of energy and other nutrients supplied by them. It is possible that the supplemented infants in the combined OC group ate more when not at the breast.

Fourth, the lack of significant differences observed may have resulted from the size of the study. Small differences in growth may result from the use of different contraceptives, which could not be detected in a study of this size. With the numbers available, we have statistical power of about 80 percent to detect as significant a minimum difference of 400–500 grams in weight at 24 weeks, depending on the contraceptive group. Even with all centers combined, the study showed only a 290–350 gram difference in weight increment.

Any substance leading to a reduction in the duration of lactation or in the amount of milk supplied to infants could be harmful, especially in settings where infants are totally dependent on breast milk for nutrition. Besides the calories and protein, essential lipids, amino acids, and minerals necessary for growth, human milk supplies a number of other substances that protect the infant from pathogenic microorganisms, including immunoglobulins and lactoferrin (Hartmann et al., 1985).

The protective effects of human milk are likely to be even more relevant in those developing countries where the probability of infant diarrhea is high and/or supplementation inadequate. In addition, the nutritional deficits in the milk of estrogen-containing OC users would be likely to assume importance in malnourished women, or in the populations of many developing countries where birth weights are low and infant growth starts to falter from the third to the sixth month of life.

Thus, combined oral contraceptives containing estrogen cannot be recommended for use during early lactation. The age at which it seems safe to recommend them will be a subject for debate and controversy, but is expected to vary in different countries according to the population's mean duration of lactation, the usual time of return of fecundability or return of menses, and the normal pattern of infant supplementation (Hull, 1981; Laukaran, 1981).

This study involves a double-blind randomized trial of two oral contraceptives containing the same progestogen, one containing estrogen. The trial supports the hypothesis that it is the estrogenic component of combined pills that causes their antilactation effect. The biologic rationale for this stems from the knowledge that estrogen and prolactin, the main hormone responsible for milk production, antagonize each other (Cowie, 1984). Estrogen decreases the sensitivity of the nipple to tactile stimulation, and thus may reduce the neurogenic response to suckling that leads to the reflex release of prolactin. It may also directly affect milk synthesis. Although the effect of estrogen is probably dose-related, this study also shows a clear antilactational effect for a modern pill containing a low dose of estrogen. It should be noted, however, that since the estrogen-containing pill contains substantially more progestogen than the progestogen-only pill, a dose-related effect of progestogen, rather than only an effect of the estrogen, cannot be ruled out by this comparison.

This study has also found no important adverse ef-

fects from the use of the two progestogen-only contraceptives. The milk of the women using the progestogen pill are remarkably similar to those of the nonhormonal controls. The small differences observed are consistent, with the multiple observations of this study, with chance. The significance of the findings for DMPA—small alterations in milk composition—are more difficult to evaluate. They may be explained by suppression of endogenous estrogen production or enhanced prolactin output by the DMPA (Chaudhury et al., 1977), and if so, may even be beneficial. We conclude that either of these contraceptives is preferable to estrogen-containing contraceptives during lactation.

The safety of these compounds in the presence of infant or maternal malnutrition still needs to be established. The subjects in this study were selected to exclude mothers and babies with any hint of nutritional compromise. One of the criteria for inclusion (birth weight 2,700–3,700 grams) may have resulted in a greater degree of selection in the Thai centers, where birth weights are lower, than in the Hungarian one, and may explain the greater length of the babies in Khon Kaen. This study population may, therefore, be considered "nutritionally elite," and the results may not apply to populations of less than optimal nutritional status.

Since DMPA does alter milk constituents in well nourished women, albeit minimally, we do not know what effect it would have during the seasonal changes in nutritional status experienced in some countries, in the presence of severe maternal calorie deficit, or if the nutritional demands of the infant were increased—for example, following an attack of diarrhea.

While it seems unlikely that DMPA will prove harmful in populations with marginal or frank malnutrition, and it may even prove beneficial to lactation, further research on it and other progestogen-only contraceptives is needed.

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