Injected Progestogen and Lactation

M. KARIM, R. AMMAR, S. EL MAHGOUB, B. EL GANZOURY, F. FIKRI, I. ABDOU

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Summary

Norethisterone ethanate (200 mg every 84 days) and medroxyprogesterone acetate (150 mg every three months) were found to be completely effective in fertility control when started in the puerperium. Neither agent had any ill effect on the amount of milk or the duration of lactation. From the third month onward the three-hourly available milk and the infant weight gain per month were statistically higher in treated groups than in controls. Milk proteins showed a slight decrease in most groups, including the controls, owing to the low-protein diet.

No important side effect was produced by these agents other than amenorrhoea.

Introduction

The rapid increase in birth rate in the U.A.R. has encouraged the adoption of birth control programmes on a wide scale; all available methods of contraception are being used. In the present decade the conventional methods of contraception are being superseded by pills, intrauterine devices (I.U.D.), and more recently by the injection of contraceptives.

Contraception in the postpartum period should be an integral part of any birth control programme. Problems, however, arise when choosing an appropriate contraceptive method in the early puerperium. I.U.D.s have a high expulsion rate and a risk of perforation when applied shortly after delivery. Pills (containing oestrogens and progestogens) are claimed to affect lactation adversely (Rice-Wray, 1964; Pincus, 1965; Turabi *et al.*, 1966; Kammal *et al.*, 1968). The effect of injected progestogens on lactation, however, has had little consideration.

This paper deals with the assessment of the quantitative and qualitative effects of injected progestogens on lactation and on the breast-fed infant.

Material and Method

The trial was started in March 1969 at the birth control clinic of Ain Shams University Hospital, and many cases have been followed for more than 18 months. Our social workers contacted normally delivered patients in the obstetric wards and collected 331 cases of about the same socioeconomic standards; their average age and parity are given in Table I.

The cases were divided into three groups: group 1 consisted of 100 cases followed up from the seventh postpartum day as controls; group 2 consisted of 112 cases given the contraceptive injection 42 days after delivery—57 received norethisterone ethanate 200 mg every 84 days (group 2a) and 55 were given medroxyprogesterone acetate 150 mg every three months (group 2b); and group 3 consisted of 119 cases given the injection on the seventh postpartum day—68 received norethisterone ethanate (group 3a) and 51 medroxyprogesterone (group 3b).

All cases had a thorough clinical examination, and a full history was taken, including the menstrual history and any comments or complaints. All were asked to avoid any supplementation unless we advised them to do so. They subsequently attended our clinic once a week at 8 a.m., after feeding their children at 6 a.m.

The following methods were used to evaluate the effect of the drugs on lactation and on the breast-fed infant.

History of Present Lactation.—The impression of the mother was obtained about milk yield and the state of her infant and his bowel action. A full nutritional analysis of the cases was carried out by a nutrition expert at each visit.

Average Growth Curves.—The baby was weighed before the 9 a.m. feed and average growth curves were made.

Average weight gain per month was ascertained.

Average Three-hourly Available Milk.—The baby was fed at 9 a.m. from both breasts (10 minutes from each). The increase in weight after the feed was worked out. The residual milk was then sucked from both breasts and its amount added to that gained by the infant to obtain the three-hourly available milk.

Chemical Examination.—At noon milk was sucked from both breasts and measured, then the residual milk previously obtained was added and the whole amount was examined for proteins, fat, lactose, and total solids.

Examination of Baby.—The baby was examined clinically at each visit, particularly the breasts and the genitalia. The crown-heel length and the chest and head circumferences were measured. Dentition, sitting and walking activities were noticed, as well as mentality. *X*-ray examination of wrist and ankles was carried out at the age of 1 year to detect calcifications.

Results

Efficiency of Drugs.—These progestogens proved to have 100% contraceptive efficacy when started in the puerperium. No pregnancy occurred during the trial.

Acceptability.—This was remarkably good, only 33 cases discontinuing the trial from the third injection onward. The crude drop-out rate for all reasons did not exceed 14·2%. A total of 2,694 women-months have so far been studied.

Menstrual Pattern.—The average duration that elapsed between delivery and the onset of menses (bleeding) is shown in Table II. Subsequently the frequent incidence of amenorrhoea (0 days of bleeding per month) was particularly

TABLE I—*Average Age and Parity*

Group	Average Age (Years)	Average Parity
1. Controls	27·2	3·2
2a. Norethisterone ethanate (40 days)	27·1	3·3
2b. Medroxyprogesterone (40 days)	28·1	3·4
3a. Norethisterone ethanate (7 days)	26·6	3·19
3b. Medroxyprogesterone (7 days)	27·9	3·3
Total	27·3	3·29

Department of Gynaecology and Obstetrics, Ain Shams University, Cairo, U.A.R.

M. KARIM, M.CH., F.R.S.H.(HON.), Professor
R. AMMAR, M.CH.
S. EL MAHGOUB, M.CH.
B. EL GANZOURY, M.CH.
F. FIKRI, M.CH.

Nutrition Institute, U.A.R.

I. ABDOU, M.D., PH.D., Head

TABLE II—*Average Duration of Amenorrhoea after Delivery*

	Group			
	2a	2b	3a	3b
Average duration of amenorrhoea (days) ..	132	179	128	270
Range (days)	86–382	60–326	62–300	50–438

remarkable. When medroxyprogesterone acetate was started on seventh postpartum day the incidence of amenorrhoea ranged between 87% and 93% in different months compared with 73% and 81% when the same drug was started in the sixth postpartum week. The cycle control with norethisterone ethanate was better than that with medroxyprogesterone acetate. Amenorrhoea occurred in 60 to 71% of cases starting the injection on the seventh postpartum day and in 42 to 51% of those receiving the injection in the sixth postpartum week. Prolonged bleeding (more than eight days per month) occurred in only 6·4% of the cases; after the first injection it was not repeated. It was usually moderate in amount; when troublesome it was stopped by the administration of oral ethinyloestradiol 0·02 mg, two tablets a day for five days.

Effect on Uterine Involution.—Uterine involution proceeded normally in all patients who started treatment on the seventh postpartum day. The difference between the length of uterine cavity and duration of lochia in treated groups and controls was not statistically significant.

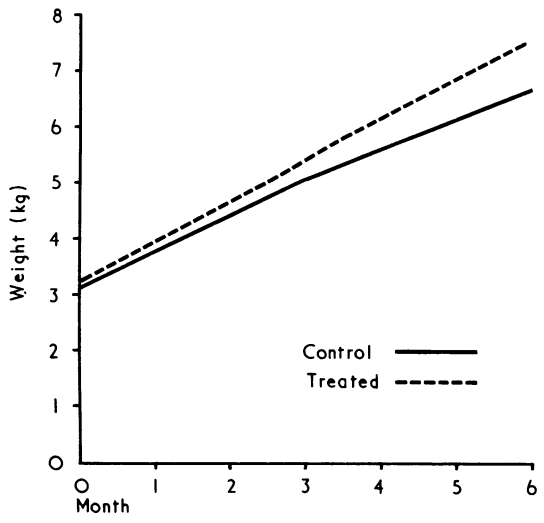
Side Effects.—There were no important side effects other than menstrual disorders.

Re-establishment of Fertility.—Among the 33 who discontinued the trial seven wanted pregnancy and did not adopt any contraceptive measures. In the three who used norethisterone acetate pregnancy occurred after five to seven months. In the four who used medroxyprogesterone acetate pregnancy did not occur until after an average of eight months.

Importance of Starting Contraception in Puerperium.—Analysis of the history showed that 20·6% of 1,440 pregnancies had occurred during previous lactations, over half of these were undesired and more than one-third of them occurred within three months of parturition.

Effect on Lactation and Breast-fed Infant.—As lactation may be affected by quality and quantity of food a nutritional analysis of all groups was performed (Table III). It showed that all groups consume a more or less comparable percentage of essential requirements of different foodstuffs. The protein intake, particularly animal protein, was rather low.

History of Previous Lactation.—The average duration of previous full lactation was statistically identical in the different groups; it ranged between 6·49 and 6·83 months.



Average growth curves of treated groups and controls.

History of Present Lactation.—The treated mothers pointed out that their milk yield was sufficient and their infants were usually satisfied. None of them found it necessary to supplement during the first six months of the trial. Many of those continuing stated that lactation during the trial was better than in previous deliveries.

Average Growth Curves and Weight Gain per Month.—The weight of infants of treated mothers increased significantly ($P<0.01$) after the third postpartum month (Chart, Table IV). Differences between treated groups were not significant.

Average Three-hourly Available Milk.—After the third month there was a significant increase ($P<0.05$) in the treated groups compared with the controls. From the fourth month onward the increase was highly significant ($P<0.01$).

Biochemical Results.—Milk fat, lactose, and total solids (Table VI) showed a slight increase after two, four, and six months of therapy. The variations, however, were not statistically significant ($P>0.05$). The average milk proteins, however, showed a statistically significant ($P<0.05$) decrease in most groups, including the controls (Table VII).

Effect on Breast-fed Infant.—The follow-up of babies of treated mothers and controls up to 18 months did not show

TABLE III—*Nutritional Analysis of Different Groups*

Recommended* Allowances	Percentage of Recommended Allowances of Food Taken				
	Group				
	1(30)	2a(30)	2b(30)	3a(30)	3b(30)
Calories 3,000	65	63	57·5	59	54
Proteins 100 g	53·5	60·4	50·35	57	64·5
Calcium 2 g	18	19	20	17	10
Iron 15 mg	60	69	72	66	66
Vitamin A 8,000 IU	16	22	15	33	14
Vitamin C 150 mg	29	26·5	33·5	39·5	26
Vitamin B_1 2 mg	133	110	137	127	111
Vitamin B_2 3 mg	35	36·5	66	37	37
Niacin 20 mg	90	74	88	74	80

A random sample was taken from each group.
*According to the Food and Nutrition Board, National Research Council, U.S.A.

TABLE IV—*Average Weight gain per Month in Grammes during the Period of Full Lactation*

Month	Group				
	1(100)	2a(57)	2b(55)	3a(68)	3b(51)
1	633·2	636·0*	652·6*	641·4*	643·6*
2	702·8	709·5*	714·3*	724·3*	712·0*
3	553·0	738·0†	716·9†	721·0†	736·0†
4	552·4	672·3†	730·0†	667·4†	678·3†
5	549·6	791·8†	763·0†	798·0†	801·0†
6	499·3	739·8†	748·3†	693·8†	728·6†

(1) $F=0.98$. $P>0.05$.
(2) $F=1.12$. $P>0.05$.
(3) $F=6.28$. $P<0.01$. L.S.D. 0·05 and 0·01 = 79·168 and 105·67.
(4) $F=5.93$. $P<0.01$. L.S.D. 0·05 and 0·01 = 82·90 and 109·60.
(5) $F=6.32$. $P<0.01$. L.S.D. 0·05 and 0·01 = 91·33 and 120·69.
(6) $F=5.84$. $P<0.01$. L.S.D. 0·05 and 0·01 = 93·88 and 124·60.

*$P>0.05$, not significant.
†$P<0.01$.

TABLE V—*Average Three-hourly Available Milk (ml) during Full Lactation in Controls and Treated Groups*

Month	Group				
	1(100)	2a(57)	2b(55)	3a(68)	3b(51)
1	90·8	89·2*	86·8*	91·7*	90·3*
2	122·3	126·6*	128·0*	138·0*	133·0*
3	120·6	132·3†	133·8†	138·2†	138·4†
4	116·3	138·2‡	141·3‡	151·8‡	152·0‡
5	117·6	143·0‡	142·9‡	145·0‡	149·3‡
6	116·8	141·9‡	146·3‡	152·1‡	153·6‡

(1) $F=1.09$. $P>0.05$.
(2) $F=1.62$. $P>0.05$.
(3) $F=2.64$. $0.05>P>0.01$. L.S.D. 0·05 and 0·01 = 12·56 and 16·02.
(4) $F=6.28$. $P<0.01$. L.S.D. 0·05 and 0·01 = 12·05 and 16·05.
(5) $F=11.33$. $P<0.01$. L.S.D. 0·05 and 0·01 = 10·97 and 14·5.
(6) $F=8.63$. $P<0.01$. L.S.D. 0·05 and 0·01 = 11·72 and 15·48.

*$P>0.05$ not significant.
†$P<0.05$.
‡$P<0.01$.

TABLE VI—*Average Milk Fat, Lactose, and Total Solids (g/100 ml) before and after Injections*

Duration	Group					F
	1	2a	2b	3a	3b	
Premedication ..	2·93	2·86	3·14	3·11	2·99	1·09*
After 2 months ..	3·2	3·18	3·26	3·13	3·32	0·96*
After 4 months ..	3·24	3·46	3·43	2·98	3·28	1·13*
After 6 months ..	3·31	3·60	3·49	3·10	3·31	
	F 1·83*	F 1·93*	F 1·03*	F 0·98*	F 1·88*	
Premedication ..	6·78	6·71	6·58	7·23	6·79	1·73*
After 2 months ..	6·84	6·86	7·03	6·82	6·84	1·21*
After 4 months ..	6·94	6·89	7·18	7·18	6·93	1·23*
After 6 months ..	6·91	6·89	7·16	7·22	6·93	1·19*
	F 1·03*	F 0·99*	F 1·62*	F 1·32*	F 1·63*	
Premedication ..	12·1	12·0	12·24	12·43	11·98	1·09*
After 2 months ..	12·23	12·4	12·31	12·13	12·21	1·12*
After 4 months ..	12·41	12·48	12·41	11·98	12·20	1·23*
After 6 months ..	12·43	12·6	12·40	12·12	12·22	1·03
	F1·86*	F1·33*	F1·83*	F1·91*	F1·38*	

F test applied to both vertical and horizontal rows.
*P > 0·05 not significant.
Results of different groups were statistically identical.

TABLE VII—*Average Milk Proteins (g/100 ml) before and after Injections*

Time of Analysis	Group					F
	1(40)	2a(40)	2b(40)	A(40)	B(40)	
Premedication	1·86	1·87	1·82	1·80	1·81	1·23*
After 2 months	1·66	1·61	1·71	1·72	1·63	1·09*
After 4 months	1·61	1·70	1·70	1·72	1·62	1·19*
After 6 months	1·60	1·63	1·68	1·70	1·60	1·08*
F	6·13†	7·09†	11·8†	1·8*	7·9†	
L.S.D 0·05	0·17	0·21	0·13		0·17	
L.S.D 0·01	0·23	0·28	0·18		0·23	

F test applied to vertical and horizontal rows.
*P > 0·05 not significant.
†P < 0·01.
Milk proteins of all groups were statistically identical at all periods of examination.
Significant drop in milk proteins (P < 0·05 or 0·01) was detected in each group (with exception of group 3a on subsequent examination.

any physical, mental or radiological abnormality. These children will be followed up for several years.

Discussion

It is essential to practise contraception in the puerperium as conception is apt to occur after the sixth postpartum week, when ovulation may be resumed (Sharman, 1951). In the present series 20·6% of previous pregnancies had occurred during previous lactations and more than one-third of them occurred before the third month after parturition.

Norethisterone ethanate and medroxyprogesterone acetate proved to be highly effective in controlling fertility when started in the puerperium. In order to evaluate their effects on lactation other factors, such as age-parity, previous full lactations, socioeconomic and nutritional standards, that may influence physiology of lactation were comparable in the different groups of the trial. Our results indicate that these pure progestogens produced no ill effect on lactation. They may, however, maintain a good milk supply after the third postpartum month, and probably they delayed involutionary changes that were found to occur in the breast in control cases about this time.

The average three-hourly available milk was therefore higher in the treated groups than in controls after the third postpartum month. The significant increase in average growth curves and weight gain per month of infants of treated mothers over those of controls reflect to a fair extent the available milk yield, as supplementation was avoided during the first six months of the trial.

The possibility, however, of secretion of progesterone in breast milk and its effect on infant growth cannot be excluded. Dalton (1968) reported that children of mothers who were treated with progesterone for toxaemia during pregnancy were found to be heavier than those of controls and stressed that more progesterone children were breast-fed until six months. Gómez-Rogers *et al.* (1967) reported that the use of 500 mg of medroxyprogesterone acetate as a six-monthly contraceptive did not affect lactation. These progestogens did not affect the milk constituents. The decrease in milk protein reported in most groups is believed to be due to low protein intake in this class of women, as proved by nutritional analysis. They have therefore to call on body proteins for synthesis of milk proteins.

There is a distinct divergence of opinion regarding the effect of oestrogen and progesterone on lactation. Several authors (Nelson, 1934, 1936; Ansilmino and Hoffman, 1936) have pointed out that oestrogen and progesterone inhibit lactation in animals; others (Seyle, 1940; Mayer and Klein, 1949; Meites and Turner, 1961) believe that progesterone is the predominant factor. Folley (1956) concluded that oestrogen in small doses stimulates and in large doses inhibits the mammary gland. The addition of progesterone renders the stimulating dose inhibitory. Joshi and Rao (1968) pointed out that different animal species differed in their response to oestrogen and progesterone. Chinnatamby (1967) stressed that higher doses of progesterone significantly reduced the duration of lactation in women. Satterthwaite and Gambel (1962) reported a diminished flow of milk after the first or second cycle on using 5 and 10 mg of norethynodrel. Rudel *et al* (1965), on the other hand, using continuous treatment with oral progesterone chlormadinone, found that it had no inhibitory effect on lactation. Kammal *et al.* (1968) reported a decrease in milk fat and proteins in those receiving Lyndiol 2·5 and 1, continuous lynoestrenol (0·5 mg), or long-acting injectable steroid Deladroxate (150 mg dihydroxyprogesterone acetaphenide + 10 mg oestradiol ethanate). Ferin *et al.* (1964), however, reported no effect on quality or quantity of milk in lactating women taking 2·5 and 5 mg lynoestrenol.

When started during the puerperium the progestogens we used did not produce any significant side effects except frequent amenorrhoea. As amenorrhoea occurs normally during this period it was not troublesome to the users. This is certainly shown by the acceptability of this method, which reached more than 85%. We believe that the seventh postpartum day may represent an optimum date for starting contraceptive injection, as women are easily motivated after delivery, and they can be included in the contraception programme before they are discharged from hospital. If the drug action requires a lag period to be fully established it will coincide with that of physiological sterility. On the other hand, the injection may be given in the sixth postpartum week, when women came for postnatal examination.

Many patients, fearing the effect of pills on lactation, start taking the pills too late; injectable drugs (single six-monthly or two three-monthly injections) could safely tide them over this critical period. Such a regimen will protect the patient for an average of at least 11 months from pregnancy as it tends to occur after a lag of at least five months following the last injection.

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Insulin Antagonist of Pituitary Origin in Plasma of Normal and Diabetic Subjects

P. ZIMMET, F. M. NG, J. BORNSTEIN, J. McD. ARMSTRONG, H. P. TAFT

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Summary

Studies on ultrafiltrates of the plasma of normal and diabetic subjects have shown that a polypeptide of similar characteristics to the growth-hormone-derived polypeptide In-G is present in higher concentrations in diabetic subjects, thus indicating a possible role in the pathogenesis of diabetes mellitus. The polypeptide is absent from the plasma of hypophysectomized diabetic patients.

Introduction

It has been previously shown that a polypeptide obtained by hydrolysis of ovine growth hormone is capable of inducing a fall in blood glucose in patients suffering from diabetes mellitus and potentiating insulin hypoglycaemia in normal subjects (Armstrong *et al.*, 1969; Bornstein *et al.*, 1969a). Other studies (Bornstein *et al.*, 1968a, 1968b, 1969b, 1969c) have shown that the action of this polypeptide (Ac-G) is limited to the reversal of the specific inhibition of glyceraldehyde-3-phosphate dehydrogenase, α-glycerophosphate dehydrogenase, and acetyl-CoA-carboxylase by a polypeptide (In-G) corresponding to another part of the growth hormone sequence. Thus it appeared important to demonstrate the presence of In-G in normal human plasma and to determine whether raised levels of this polypeptide were present in the plasma of diabetic patients.

Experimental

Blood was obtained, after 10 hours' fasting, from 58 volunteers comprising 16 normal subjects, 9 juvenile onset diabetics, 26 maturity onset diabetics, 3 cases of pancreatic diabetes, and 4 hypophysectomized diabetics. If patients were receiving treatment it was stopped 24 hours before the taking of blood.

The red cells were removed by centrifuging, 10 ml of plasma was acidified to pH 2·3 and ultrafiltered through Cellophane at 80 lb/in² (5·62 kg./cm²) and 4°C. The ultrafiltration generally took about four hours to complete. The ultrafiltrate, which contains blood electrolytes and all components of molecular weight less than 8000, was freeze-dried, yielding 25-30 mg/ml, and tested in the standard assay for In-G with glyceraldehyde-3-phosphate dehydrogenase (G.P.D.) at a concentration of 2 mg dry material/3 ml, as previously described by Bornstein *et al.* (1968b). The results, expressed as percentage inhibition of a standard amount of enzyme, are shown in Table 1.

It is seen that extracts of plasma of both juvenile and maturity onset diabetics inhibit the enzyme more than extracts of normal plasma, whereas those of pancreatic diabetics are in the low normal range, and, most significantly, extracts derived from the plasma of hypophysectomized diabetics are virtually devoid of activity.

In order to test the specificity of the inhibition a number of procedures were carried out.

(1) *Chromatographic Behaviour of Inhibitory Fraction.*—Pooled plasma fractions were chromatographed on Dowex 50-H⁺ and CG50-H⁺ and the inhibitory activity was shown to lie in a fraction corresponding to In-G prepared from human growth hormone (Fig. 1).

(2) *Enzymic Specificity.*—Previous work (Bornstein *et al.*, 1968b, 1969c) had shown that In-G inhibition was confined to glyceraldehyde-3-phosphate dehydrogenase, α-glycerophosphate dehydrogenase, and acetyl-CoA-carboxylase, all other enzymes tested not being inhibited. The purified fractions from pooled plasma were tested on a number of enzymes and the results in Table II show that, for the enzymes tested, only the relevant ones were inhibited.

(3) *Reversal of Inhibition by an Authentic Sample of Ac-G.*—The results of the effect of a sample of ovine Ac-G on the inhibition of glyceraldehyde-3-phosphate dehydrogenase produced by the crude plasma extracts are given in Table III, and it is seen that partial reversal was obtained.

TABLE I—*Effect of an Ultrafilterable Plasma Fraction on Glyceraldehyde-3-phosphate Dehydrogenase*

Source of Plasma	No. of Subjects Treated	Percentage Inhibition	S.E. of Mean	P*
Normal subjects	16	23·3	1·41	
Diabetic subjects:				
Juvenile onset (insulin therapy)	9	52·4	7·34	<0·001
Mature onset: Untreated	7	41·7	6·76	<0·01
Mature onset: Diet control	4	31·8	4·64	<0·05
Mature onset: Oral therapy	8	40·1	6·91	<0·01
Mature onset: Insulin therapy	7	60·9	10·02	<0·001
Mature onset: All cases	26	44·8	4·26	<0·001
Pancreatic diabetes	3	15·0	2·31	<0·05
Hypophysectomized diabetes	4	2·1	1·41	<0·001

*Compared with extracts of normal plasma.
For extracts of hypophysectomized diabetic plasma and any of the diabetic plasma extracts P<0·001.

Monash University, Clayton, Victoria 3168, Australia
P. ZIMMET, M.B., B.S., M.R.A.C.P., Research Scholar
F. M. NG, PH.D., Lecturer in Biochemistry
J. BORNSTEIN, M.D., D.SC., Professor of Biochemistry
J. McD. ARMSTRONG, PH.D., Senior Lecturer in Biochemistry
H. P. TAFT, M.D., F.R.A.C.P., Associate Professor of Biochemistry and Medicine