

## Ante-natal Progesterone and Intelligence

By KATHARINA DALTON

### INTRODUCTION

Toxaemia of pregnancy remains the "disease of theories" both in respect of its causation and treatment. Among the many treatments suggested, although not generally accepted, is the administration of progesterone from the middle trimester for the relief of toxaemic symptoms (1, 2 and 3). An unexpected finding has been the clinical observation that children of progesterone-treated mothers appear to reach their milestones earlier and to make excellent progress at school.

#### *Pilot Study in Educational Ability*

To determine whether children whose mothers had received ante-natal progesterone (progesterone children) had thereby acquired any educational advantage over normal children, a pilot study was undertaken. Thirty-two progesterone children, aged 6 to 13 years, were matched with an equal number of controls, whose mothers had attended the practice for ante-natal care and were healthy throughout pregnancy. Controls were matched for age, social class and parity. Head teachers were given an unannotated list of 64 children and asked to grade each child's intelligence as "above average", "average" and "below average". They assessed 55 per cent. of progesterone children as being above average intelligence compared with 41 per cent. of the control children, which confirmed the clinical observation of the intellectual advantage of progesterone children.

#### *Design for follow up of Progesterone Children*

The successful pilot study was followed by a larger survey of progesterone children, with testing, (a) at the first birthday, when the milestones could most easily be determined, and (b) at the ages of 9 and 10 years, when school

tests in preparation for the Eleven Plus examinations were being made. For this survey, the names of progesterone children and controls were obtained from hospital registers; of the 262 children participating only seven were known to the author (progesterone five, control two). Assessments of development and intellectual ability were made by doctors, health visitors and head teachers, who were unaware of the category of the child. The progesterone had been administered to the mothers by intramuscular injections in dosages varying from 50 to 300 mg. daily for the relief of toxaemic symptoms.

#### *Method of Follow-up at First Birthday*

The subjects were the children of mothers included in a previous study entitled, "Controlled trials in the prophylactic use of progesterone in the treatment of pre-eclamptic toxaemia" (3). The mothers had been allocated to the progesterone or control treatment group by random envelope method between the 16th and 28th week of pregnancy. At the child's first birthday, the clinic doctor completed a prepared questionnaire, or if the child did not attend a health visitor completed the questionnaire in the home. All mothers co-operated and questionnaires were completed within three weeks of the first birthday.

Only 29 of the 64 progesterone children and 31 of the 66 control children were traced, but Table I shows that the characteristics of the two groups of children were similar in sex distribution, birth weight and immunization schedule. The traced children were a representative sample of the original 130 children in respect of sex and birthweight. The failure to trace the children appeared to be due to adoption, moving from the area without leaving an address, and residence at the local gipsy encampment.

*Method of Educational Follow-up*

Children studied were those whose mothers were included in the report "Toxaemia of pregnancy treated with progesterone during the symptomatic stage" (2). The 44 progesterone children were each matched to two controls:

- (a) The next born child in the labour ward register whose mother had a normal pregnancy and delivery (normal control);
- (b) The next child to be delivered from a mother who developed toxaemia (toxaemic control).

Toxaemia was defined as a blood pressure of 140/90 mm. Hg. or over together with either oedema or albuminuria after the 28th week and before the onset of labour, provided that prior to the 28th week the blood pressure had always been below 140/90 mm. Hg. and there had been no albuminuria.

All mothers were sent a letter asking permission for an education assessment from the child's head teacher. The head teacher was asked to complete a form stating whether the named child was "above", "average" or "below" standard in verbal reasoning, English, arithmetic, craftwork (practical ability) and physical education (co-ordination of movement and muscular control).

Of the 132 children under review educational assessments were received from 76 teachers in respect of 79 children (progesterone 29, normal controls 21, toxaemic controls 29). A further 15 children (5 from each group) were traced, but no educational assessment was possible (left U.K. 7, not registered with N.H.S. doctor so recent address unknown 3, died 2, adopted 1, permission refused 1, and 1 child remained at the named school for only three weeks). Thirty-eight children (29 per cent.) have remained untraced in spite of every effort by the General Register Office and the co-operation of the Ministry of Health. Two progesterone children had incomplete assessments, one was not graded for verbal reasoning and another for craftwork. One child (toxaemic control) is mentally retarded.

Table II shows the characteristics of the group, the progesterone mothers tend to be older and of higher parity, and progesterone

children tend to be heavier than controls. The greatest discrepancy is in the significantly higher proportion of previous abortions suffered by the progesterone mothers, in fact nine of the 28 mothers had experienced 15 previous abortions.

TABLE I  
*Characteristics of Groups in Follow Up at One Year*

	Progesterone	Control
Number of children	29	31
	%	%
Boys	45	45
Birth Weight		
Under 6 lb.	14	6
6-7 lb.	55	55
8 lb. and over	31	39
Immunization schedule completed	65	61

TABLE II  
*Characteristics of the Groups in the Educational Follow Up*

	Progesterone	Control
Number of children	29*	50
	%	%
Mother's Age		
Under 25 years	29	50
26-35 years	42	40
36 and over	29	10
Parity		
1	29	58
2 and 3	68	38
4 and over	3	4
Previous abortions	32	2
Birth Weight		
Less than 5 lb.	7	2
5-7 lb.	65	74
8 lb. and over	28	12
Boys	62	58

\* Including a set of twins.

*Results of Developmental and Educational Follow-Up*

The attainments of 60 children at their first birthday are shown in Fig. 1. There is a similarity in the two groups in the time of eruption of the first tooth, total number of teeth and the talking ability, but significantly more progesterone children were able to stand unaided and walk unaided than control children, and more progesterone children were breast fed until 6 months.

Analysis of the educational grading of 79

Figure 1. Attainments of 60 children at First Birthday Examination

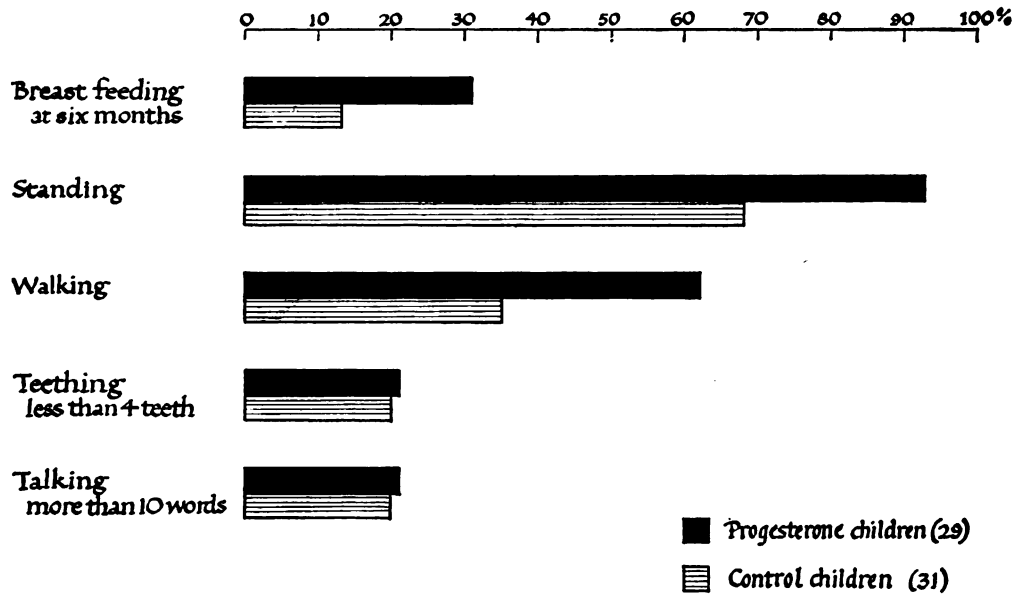
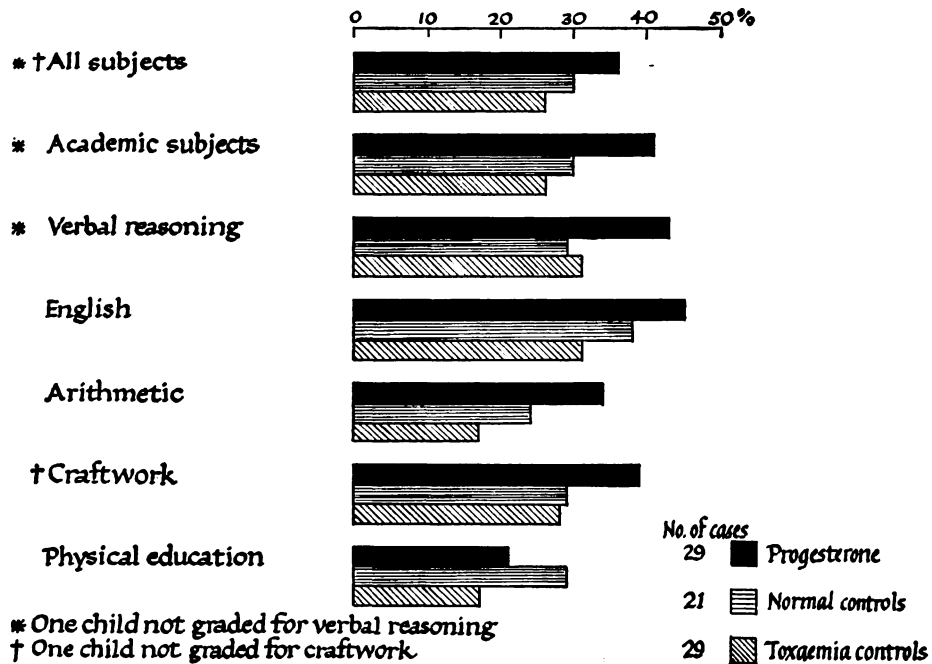


Figure 2. Above Average School Grades of 79 children at 9-10 years



children aged 9 to 10 years revealed that the progesterone children received significantly more "above average" grades than either the normal or toxæmic controls (Fig. 2). The better grades obtained by progesterone children exceeded that of the controls by 10 per cent. in all subjects, 14 per cent. in academic subjects, 13 per cent. verbal reasoning, 11 per cent. English, 14 per cent. arithmetic and 10 per cent. craftwork, and it is only in physical education that the progesterone children are similar to controls. These results are significant as shown by the chi-square test with one degree of freedom on two-tailed tests in respect of all subjects, academic subjects and arithmetic.

To determine whether progesterone could account for the advantages observed at the first birthday follow up and in the educational follow up, the progesterone children were divided into a "high dosage" group, whose mothers received 8 g. or over during pregnancy (e.g. 100 mg. from 24th week to delivery), and "low dosage" group, whose mothers received less than 8 g. progesterone. Fig. 3 shows a progressive decrease in attainments, from the "high dosage" group through the "low dosage" group to the controls whose attainments were lowest. This decrease was observed in respect of (a) breast feeding at 6 months, (b) standing and (c) walking at the first birthday, and in the "above average" grades of (d) all school subjects, (e) in academic subjects, (f) verbal reasoning, (g) English and (h) arithmetic.

In the educational follow-up an analysis was made of the time in pregnancy when progesterone was first administered. A significant improvement in educational performance was demonstrated among children who received progesterone before the 16th week (Fig. 4). In respect of children studied at the first birthday a similar comparison was not possible as the mothers were not entered into the controlled trials until after the 16th week.

The questionnaire completed at the first birthday asked for information about genital development. No case of masculinization of the girls was noticed, but one boy in the progesterone group had small testes and in the control group two boys had undescended testes and three had neonatal breast engorgement.

#### DISCUSSION

Mammary development is dependent on endogenous progesterone. The exogenous progesterone administered to these mothers during pregnancy would be expected to further increase this development. This could account for more progesterone mothers breast-feeding at six months, and for the success at breast-feeding to be related to the dosage of progesterone administered.

Reifstein (4) analysed 82 pregnancies treated with 17- $\alpha$ -hydroxy-progesterone caproate for habitual abortion and described the babies as "tending to reach maturity more rapidly". The progesterone children in this study are only ahead in standing and walking, but not in the other milestones of teething and talking, suggesting a selective rather than general maturation. The educational follow up suggests an intellectual advantage as opposed to increased physical ability.

No cases of masculinization occurred among the girls. Wilkins (5) reviewed 101 cases of masculinization but found only two girls who had received progesterone (as opposed to progestogens) whereas ten had received no hormone therapy at all.

Ehrhardt and Money (6) have described ten girls aged 3-14 years whose mothers had been treated with synthetic progestogens for the prevention of threatened abortion, in whom nine had evidence of hermaphroditism. They found a high IQ in six of them and a marked tendency to be tomboys. Gronroos *et al.* (7) and more recently Barker and Edwards (8) have shown that toxæmia in the mother is often associated with diminished intelligence in the child.

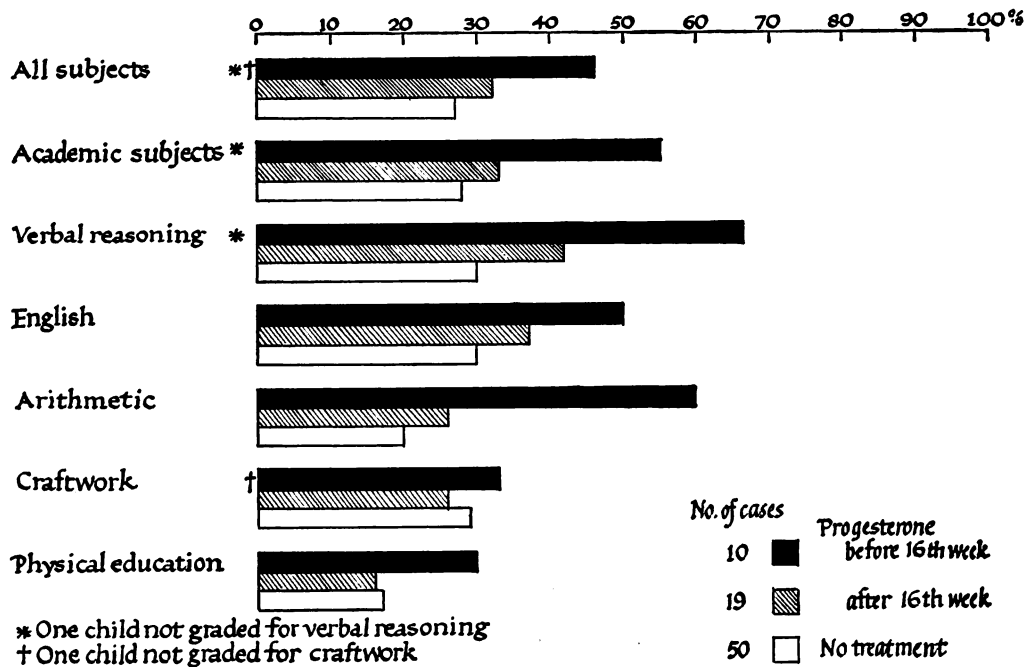
The first child's intelligence score may be expected to be the highest, with a progressive decline in subsequent children (8). This educational survey included considerably less first children among the progesterone group (29 per cent.) compared with control children (58 per cent.), but nevertheless the intellectual advantage of the progesterone group was significant.

The progesterone mothers had a high incidence of previous abortions and it may be that more intense maternal care given to a much

Figure 3. Effect of High Dosage Progesterone on Attainments



Figure 4. Above Average School Grades and Time of Progesterone administration.



wanted child could account for the high incidence of breast-feeding and even the earlier development of activities (standing and walking) as opposed to teething and talking, but this would not account for better developmental and educational attainments being related to dosage or to the time of administration. The developmental attainments were further analysed for a relationship between breast and bottle feeding. The method of feeding could not account for the observed differences as 45 per cent. of the 22 breast-fed children were walking compared with 46 per cent. of the 37 bottle-fed; and again 86 per cent. of breast-fed children were standing compared with 75 per cent. of bottle fed.

It may be argued that this survey is incomplete. It is based on a clinician's observation of bright school children whose mothers had received progesterone during pregnancy. It is hoped that this paper will stimulate others to make a closer examination of the intelligence of further groups of progesterone children.

#### SUMMARY

A study has been made of 90 children whose mothers received ante-natal progesterone, compared with matched controls. More progesterone children were breast-fed at six months, more were standing and walking at one year, and at the age of 9-10 years the progesterone children received significantly better gradings than controls in academic subjects, verbal reasoning, English, arithmetic, craftwork, but showed only average gradings in physical education.

The developmental and intellectual advantages were all related to the dose of progesterone received by the mothers, those receiving over 8 g. being related to earlier walking and standing and also better school gradings. The intellectual advantage was greatest in children

whose mothers received progesterone before the 16th week of pregnancy.

#### ACKNOWLEDGMENTS

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