PAPERS AND ORIGINALS

Effect on Neonatal Jaundice of Oestrogens and Progestogens Taken before and after Conception

J. B. McCONNELL, J. F. T. GLASGOW, R. McNAIR

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Summary

Study of 182 newborn babies has shown that among bottle-fed infants the mean plasma bilirubin concentration was slightly but significantly higher ($P<0.01$) in those whose mothers had previously used steroid contraceptives. A similar finding was not noted among breast-fed infants.

A further 16 infants whose mothers had received progestogen therapy during their pregnancy had a mean plasma bilirubin concentration which was significantly higher than each of the four other groups of infants studied ($P<0.01$). Icterus occasionally reached clinically important levels in these babies.

Introduction

Experimental evidence suggests that steroid hormones exaggerate physiological jaundice in the newborn (Adlard and Lathe, 1971). Oestriol, for instance, competitively inhibits conjugation of bilirubin by human liver slices (Adlard and Lathe, 1970). High concentrations of oestrogens and certain progestogens are present in the blood and tissues at birth (Diczfalusy and Magnusson, 1958; Mitchel, 1967).

The administration of steroids to the neonate or to the mother just before delivery have been shown to increase the degree of jaundice in the newborn (Lauritzen and Lehmann, 1967; Kovisto *et al.*, 1971). Wong and Wood (1971) reported that among breast-fed infants a significantly larger number were jaundiced when their mothers had used contraceptive drugs (the pill) before conception.

We have studied the effects of these drugs on plasma bilirubin concentrations in bottle-fed and breast-fed infants during the first week of life.

The Royal Maternity Hospital, and Department of Child Health, The Queen's University of Belfast, Belfast BT12 6BJ
J. B. McCONNELL, M.B., M.R.C.P., Junior Tutor/Senior House Officer
J. F. T. GLASGOW, M.B., M.R.C.P., Senior Lecturer/Consultant Paediatrician

Department of Social and Preventive Medicine, The Queen's University of Belfast, Belfast BT12 6BJ
ROBERT McNAIR, H.N.D., Statistical Assistant

Patients and Methods

Over a five-month period we studied healthy infants in the postnatal wards of the Royal Maternity Hospital, Belfast. During this period only 8% of mothers breast-fed their infants. We studied all such, but excluded those in whom breast-feeding was stopped before the fifth day. Randomly selected bottle-fed babies were also studied. Infants of low birth weight or of mothers with diabetes mellitus or severe pre-eclampsia were excluded from the study, as were those who were sick or affected by rhesus isoimmunization. ABO incompatibility was excluded in infants whose plasma bilirubin concentration exceeded 12 mg/100 ml.

Mothers who agreed to co-operate in the study were questioned with regard to their previous use of the pill and the dose, duration of use, and the time it was stopped. Other medicines prescribed during the present pregnancy were also recorded. Hospital records supplied information regarding the present pregnancy and delivery. According to the method of feeding and the history of using the pill, infants were assigned to one of the first four groups shown in figs. 1 and 2. All were fed within six hours of delivery.

Capillary blood was obtained by heel-prick on the third and fifth days of life. Total plasma bilirubin concentration was measured by the microspectrophotometric method of O'Brien and Ibbott (1963) (reproducibility in our hands ± 0.3 mg/100 ml).

During the early part of the study a number of babies whose mothers had been given progestogen therapy during pregnancy developed hyperbilirubinaemia. Subsequently, blood was taken from 16 consecutive infants six of whose mothers had threatened to abort during the present pregnancy; the remainder had a history of repeated abortion. Thirteen mothers had received hydroxyprogesterone hexanoate (Primolut-Depot 0·25-1·0 g weekly) by injection from the eighth to the 20th weeks, while

the rest had had a 10-day course of oral dydrogesterone (Duphaston 15 mg daily) during early pregnancy. These infants were excluded from the previous groups, and constituted a fifth group. Each of these babies satisfied the above criteria; all but three were bottle-fed.

Results

Total plasma bilirubin was measured on the third day of life in 182 infants (fig. 1), but because of early discharge of some mothers and babies from hospital the numbers were slightly smaller on the fifth day (fig. 2).

Mean bilirubin concentrations were higher on the third day and decreased by the fifth day in each group. This decrease was 32% in bottle-fed as compared to 3% in breast-fed infants. The lowest mean total bilirubin concentration on both days was found in bottle-fed babies.

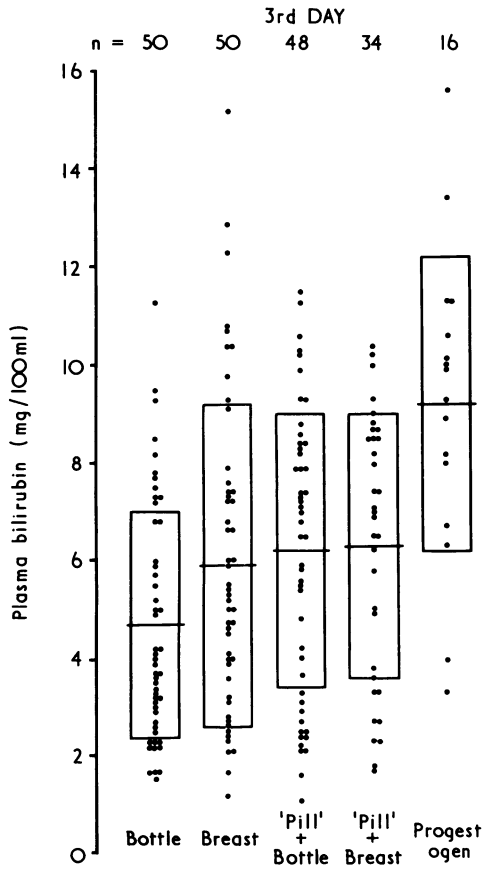

FIG. 1—Total plasma bilirubin concentrations (mg/100 ml) on third day in five groups of infants studied (182+16). Boxes represent means ±S.D.

Comparison of the mean total bilirubin concentrations of each of the groups is shown in fig. 3. Despite an apparent skewed distribution of data in at least one of the groups the *t* test remains a valid means of statistical analysis (Ratcliffe, 1968). The 1% level was thought to be a more acceptable criterion of significance in view of the confidence we had that the null hypothesis was true—that is, that previous maternal use of the pill does not increase the neonatal bilirubin concentration.

In infants whose mothers had not taken the pill breast-feeding was associated with a higher mean bilirubin concentration compared to bottle-fed infants on both days. The difference, however, was significant only on the fifth day. Infants of mothers who had used the pill had significantly higher mean bilirubin concentrations in bottle-fed but not breast-fed infants on both the third and fifth days of life (fig. 3).

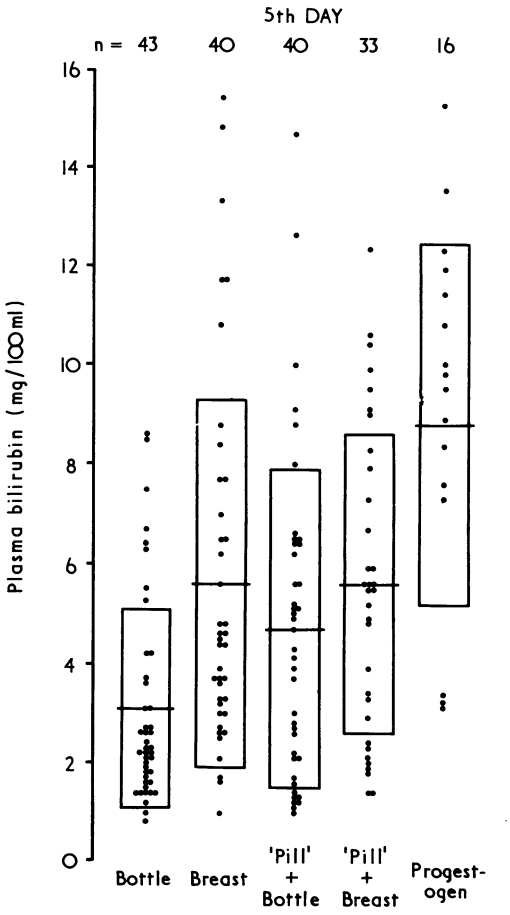

FIG. 2—Total plasma bilirubin concentrations (mg/100 ml) on fifth day in five groups of infants studied (156+16).

DAY 5 \ DAY 3	Bottle	Breast	Pill + Bottle	Pill + Breast	Progest-ogen
Bottle		N.S.	P<0·01	P<0·01	P<0·001
Breast	P<0·001		N.S.	N.S.	P<0·001
Pill + Bottle	P<0·01	N.S.		N.S.	P<0·001
Pill + Breast	P<0·001	N.S.	N.S.		P<0·01
Progest-ogen	P<0·001	P<0·01	P<0·001	P<0·01	

FIG. 3—Comparison of mean plasma bilirubin concentrations in five groups of infants on third day (above) and on fifth day of life (below). N.S. = Not significant at 1% level.

The 16 infants whose mothers had been given progestogen therapy during early pregnancy had a mean bilirubin concentration on the third day of 9·1 mg/100 ml (fig. 1). By the fifth day (at which time seven of the 16 had concentrations greater than 10 mg/100 ml) the mean concentration had decreased by 3% to 8·8 mg/100 ml. There was a highly significant difference on both days between the mean bilirubin concentrations of this and each of the other four groups. Those infants whose mothers had received a total dose of more than 3 g of hydroxyprogesterone hexanoate had mean plasma bilirubin values (±S.D.) of 10·3 ± 1·2 mg/100 ml compared to 7·7±2·2 mg/100 ml when the total

dose was less than 3 g. The difference here was not statistically significant, though the numbers in each group were small.

Further statistical analysis of the first four groups of data suggested that social class, age or parity of the mother, duration of labour, or sex of the infant did not influence neonatal bilirubin concentrations. Unlike a group of low birth weight babies recently reported (Crawford, 1973), we were unable to show a significant sex differential among the infants of mothers previously using the pill. The ratio of males:females in this group was 42:39 as compared to 48:53 among those who had not used the pill. There was no difference between the mean bilirubin concentrations in infants of blood group O mothers compared to the rest. Neither the length of time the mother had used the pill nor the interval which had elapsed between discontinuing its use and conception significantly influenced the results. It was noted, however, that within the group whose mothers had taken the pill 13 infants conceived within one month of stopping it had mean bilirubin levels on the third day of $7{\cdot}6 \pm 2{\cdot}4$ mg/100 ml compared to $5{\cdot}8 \pm 2{\cdot}8$ mg/100 ml in the remainder ($0{\cdot}02 < P < 0{\cdot}05$). Finally, we found no support for the notion that oxytocic drugs given during delivery significantly influenced the babies' bilirubin concentrations, as some have speculated (Ghosh and Hudson, 1972).

Discussion

Many factors, both prenatal and postnatal have been reported to play a part in the aetiology of physiological jaundice of the newborn (Wood *et al.*, 1962; Odell, 1967). We report the influence which two types of "steroid therapy" appear to have on bilirubin concentrations in the newborn.

Firstly, previous maternal use of the pill is associated with a small but statistically significant increase in the bilirubin concentration in bottle-fed babies during the first week of life. This lends support to the recent suggestion (Wong and Wood, 1971) that previous maternal use of the pill was associated with higher bilirubin values, though their report only concerned breast-fed infants. Our results obviously could not be explained by their idea that this increase was related to substances contained in mother's milk. Together these findings suggest that some subtle, preconception influence alters the infant's capacity to metabolize bilirubin. Credence for this idea may be strengthened by the recent report that low birth weight infants whose mothers had previously used the pill were less likely to develop respiratory distress syndrome (Crawford, 1973). However, the pathogenesis of both findings is not known at present.

The fact that a similar association was not noted among breast-fed infants may be related to a "masking effect" of other "inhibitors" in breast milk. Indeed we confirmed the studies of Arthur *et al.* (1966) that breast-feeding (per se) was associated with a higher mean bilirubin concentration than was artificial feeding. Our findings suggest that breast-feeding and prior maternal use of the pill each have an icterogenic effect in the newborn. The net result on bilirubin concentrations when both factors operate together is, however, only minimally greater than if either operates singly. This might suggest that the two factors are acting at different points in bilirubin metabolism or competing for one site of limited capacity.

There was a second and perhaps more important observation from the point of view of clinical management. The group of infants whose mothers had been given progestogen in early pregnancy had a very significantly higher mean bilirubin concentration than was present in each of the other groups of newborns tested. It is known that small amounts of progesterone, or its metabolites, may be recovered from human fetal tissues after a single intramuscular injection of radioactive progesterone to the mother between the 11th and 17th weeks of pregnancy (Plotz and Davis, 1957). It would seem reasonable to suppose that hydroxyprogesterone hexanoate administered regularly throughout a 12-week period might similarly cross the placenta and remain in small amounts within the fetus, thus augmenting the concentration of steroids to be excreted after birth. In view of the inefficiency of the glucuronyl transferase enzyme system at that time a minimal increase of steroidal "inhibitors" might exaggerate neonatal jaundice, as has already been suggested by Lauritzen and Lehmann (1967). Certainly the fact that all but three of the infants in this group were bottle-fed would suggest that the inhibitor properties of the progestogens were superior, quantitatively if not qualitatively, to those of breast milk.

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Requests for reprints should be addressed to: Dr. J. F. T. Glasgow, The Nuffield Department of Child Health, The Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ.

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