PRELIMINARY COMMUNICATIONS

Breast-milk Jaundice and Oral Contraceptives

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Summary

Among breast-fed infants in the normal lying-in wards of a maternity hospital a significantly higher incidence of "idiopathic" jaundice was found in infants of mothers who had been receiving the contraceptive pill before the present pregnancy than in the infants whose mothers never had the pill. The pill became widely used in society at about the same time as breast-milk jaundice was first reported.

Introduction

Neonatal jaundice relating to breast-feeding was first recorded by Arias *et al.* (1963). Since then it has been shown that there is a higher incidence of jaundice in breast-fed than in bottle-fed infants, and that plasma bilirubin levels fell when some of the infants were taken off breast milk but rose or ceased to fall when they were returned to the breast (Newman and Gross, 1963; Arias and Gartner, 1964; Stiehm and Ryan, 1965; Arthur *et al.*, 1966; Severi *et al.*, 1970). Icterogenic milk has been shown to inhibit conjugation of bilirubin by human liver in vitro (Arias *et al.*, 1964; Arthur *et al.*, 1966; Ramos *et al.*, 1966; Adlard and Lathe, 1970). From the icterogenic milk 3a20b pregnanediol was isolated and shown to inhibit glucuronyl transferase of guinea-pig liver (Arias *et al.*, 1964). However, glucuronidation was not inhibited in human liver slices (Holton and Lathe, 1963; Adlard and Lathe, 1970) by 3a20b pregnanediol, nor was glucuronyl transferase inhibited, though in rat liver slices (Hargreaves and Piper, 1971) the secretion of bilirubin glucuronide was inhibited. It seems probable that other agents are involved but these have not yet been identified.

In the course of a study on breast-milk jaundice the impression was gained by one of us (Y.K.W.) that the condition may be related to mothers who had taken oral contraceptive pills. A prospective study was then carried out.

Patients and Methods

Unselected postnatal wards were visited at random intervals. Infants of low birth weight (less than 2·3 kg), sick infants, infants of mothers with any clinical infection or diabetes mellitus, and infants with a positive direct Coombs test were excluded. The names of breast-fed infants who were 5 days or older were obtained and their mothers were asked whether they had ever been on any oral contraceptive pills. Mothers who had received other oestrogen-progesterone preparations or had had the pill for less than one full course were excluded from the study, as were their infants. Mothers who had never been on the pill were called "No Pill." Those who had had the pill for one full course (21 days) or more were called "Pill."

The infants were classified according to the notes recorded by independent observers as follows:

Non-Jaundiced Infants.—These infants had never been jaundiced or their jaundice was slight and already fading by the fifth day of life.

Jaundiced Infants.—These infants had either an icterometer grading (Culley *et al.*, 1960; Gosset, 1960) of three or more or a plasma bilirubin level, measured by the method of Scott (1959), of 10 mg/100 ml or more on their fifth day.

Severely Jaundiced Infants.—These were infants whose plasma bilirubin levels were greater than 15 mg/100 ml on their fifth or subsequent days of life.

Results

General Data on Mothers and Infants.—A total of 116 mother-infant pairs were examined during the period of study. No significant difference was found between the jaundiced and non-jaundiced infants comparing birth weight, gestation, sex ratio, birth rank, or the age of the mothers.

Incidence of Jaundice and Maternal Pill Consumption.—There were 69 non-jaundiced and 47 jaundiced infants; 57 mothers had been on the pill and 59 had not. Of the 69 non-jaundiced infants 24 (34·8%) mothers had been on the pill; of the 47 jaundiced infants 33 (70·2%) mothers had been on the pill. Table I shows the distribution. The result strongly suggests that there is a relationship between the pill and "idiopathic" jaundice in the breast-fed infants.

Severely Jaundiced Infants.—A total of 18 infants had plasma bilirubin levels of over 15 mg/100 ml on fifth or subsequent days of life (Table II). Thus when the severely jaundiced infants are considered separately there is a similar relationship.

The mean duration of pill consumption of mothers with jaundiced infants was 24·4 months (S.D. = 21·3) and 18·6 months (S.D. = 17·1) in mothers with non-jaundiced infants. The differences are not significant. The mean interval between cessation of contraceptive pill and delivery in mothers with jaundiced infants was 18·8 months (S.D. = 11·2) and 23·7 months (S.D. = 20·4) in mothers with non-jaundiced infants. The differences are not significant.

TABLE I—*Distribution of Mothers and Infants*

Mothers	Infants		Total
	Jaundiced	Non-jaundiced	
Pill	33	24	57
No pill	14	45	59
Total ..	47	69	116

χ^2 (with Yates's correction) = 12·66; $P < 0.0005$.

TABLE II—*Severely Jaundiced Infants*

	Mothers	
	Pill	No Pill
All infants with plasma bilirubin level above 15 mg/100 ml	14	4
All infants with plasma bilirubin level above 15 mg/100 ml, excluding possible ABO blood group incompatibility and those less than 3 kg birth weight ..	11	3

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Discussion

Oestriol given to neonates have been shown to increase plasma bilirubin levels (Lauritzen and Lehmann, 1967). When oestradiol was given to mothers 24 hours before delivery, the incidence and level of subsequent jaundice of the breast-fed neonate were found to be increased over the controls (Koivisto *et al.*, 1971). It is, however, difficult to understand that maternal consumption of oral contraceptive pills for a varying duration and after a varying interval since cessation could have any effect on the breast-fed infant's liability to jaundice. The figures, however, speak for themselves.

It should be noted that the oral contraceptive pill came into increasingly widespread use in the U.S.A. from 1958 and in the U.K. from 1960 onwards and that breast-milk jaundice was first recorded in 1963.

It would be interesting to know if these results could be confirmed in other centres.

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MEDICAL MEMORANDA

Nephrotic Syndrome: A Complication of Secondary Syphilis

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The association between secondary syphilis and the nephrotic syndrome is well recognized but very uncommon. Since Herrmann and Marr classified the renal complications of syphilis in 1935 about 30 cases have been recorded in the world literature. To our knowledge no case has been reported in the British literature during this time. As detailed histological appearances have been described on only three occasions (Brophy *et al.*, 1964; Falls *et al.*, 1965; Robins and Ladd, 1962) we feel it worth while reporting the following case.

Case Report

A 22-year-old woman was admitted to the Royal South Hants Hospital on 17 January 1969 for investigation of generalized oedema. Her initial complaint, two weeks previously, was of early-morning facial swelling. During the following two weeks her arms and legs also became oedematous and her weight increased by 25 kg. In association with these symptoms an irritant rash appeared on her body. She had been well before this episode and, in particular, there was no evidence of previous renal disease or of recent streptococcal infection. No medication of any kind had been given in the preceding few months. She was married with two children but was separated from her husband. Her two pregnancies, six and three years previously, had been uneventful and Wassermann reactions on both occasions were negative.

On admission she appeared pale and unwell, with a pyrexia of 100°F (37·8°C), pronounced periorbital oedema, and extensive pitting oedema from the waist downwards. There was no lymphadenopathy. The pulse was regular, 80/min, and the blood pressure was 105/70 mm Hg. The jugular venous pressure was not raised. Fine crepitations were heard at both lung bases. A red scaly macular rash covered the trunk but not the limbs. No abnormalities were found on neurological examination.

Laboratory investigations were: haemoglobin 10·5 g/100 ml; W.B.C. 5,100/mm³ (36% segmented neutrophils, 52% lymphocytes, 8% eosinophils); erythrocyte sedimentation rate 110 mm/hr (Westergren); total serum protein 3·9 g/100 ml (albumin 0·8 g/ globulin 3·1 g); serum protein electrophoresis, diffuse increase in α2-globulin; serum cholesterol 325 mg/100 ml; serum creatinine 1·25 mg/100 ml; blood urea 54 mg/100 ml; serum electrolytes normal; antinuclear factor and L.E. cells not found. The urine deposit contained two red blood cells and four white cells per high-power field and some hyaline casts.

She was treated initially with frusemide but despite increasing doses continued to deteriorate. Three days after admission she developed bilateral pleural effusions with evidence of pneumonia. Treatment was supplemented with ampicillin and spironolactone. On 24 January positive serological results for syphilis were received and a course of procaine penicillin was started. Within three days she began to make a rapid recovery, and during the subsequent three weeks she lost 20 kg in weight and became oedema-free. The macular rash disappeared in a matter of days. Further serological examination confirmed syphilitic infection by showng a positive Venereal Disease Research Laboratory slide test, treponemal immobilization test, and fluorescent treponemal antibody test.

Despite the satisfactory clinical response gross proteinuria and hypoalbuminaemia persisted. In view of this a renal biopsy was performed early in April. A detailed report of the light and electron microscopical findings is given below. She was seen regularly as an outpatient after her discharge from hospital. Her clinical improvement continued and diuretics were stopped by the end of May. Since this time there has been no recurrence of oedema. On 29 July proteinuria persisted, with a serum albumin of 1·9 g/ 100 ml. By October the serum albumin had returned to normal at

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