

which would certainly have been made worse by the presence of a cardiocograph at the bedside during labour.

Congenital atrial flutter is a potentially serious arrhythmia and of the 8 reported cases which were suspected antepartum, one was associated with hydrops fetalis,⁷ and one with tetralogy of Fallot.⁸ The main risk of atrial flutter in the fetus is that of any underlying cardiac malformation plus the risk of fetal congestive cardiac failure. The associated heart block occurring *in utero* in this case was fairly constant compared with the variable block detected on neonatal ECG recordings.¹ Immediate availability of paediatric intensive care facilities is essential for appropriate management of fetal cardiac arrhythmias, but this baby showed no evidence of acidosis at delivery.

All but one of the 8 recorded cases of atrial flutter diagnosed antepartum required cardioversion, or digoxin, or a combination of both, to control the arrhythmia in the neonate.^{1 5 6 8} A regimen of cardioversion followed by digitalisation as used in this case is the accepted treatment.¹ The alternative of digoxin followed by DC cardioversion has potential drawbacks including secondary cardiac arrhythmia and aggravation of cardiac failure due to delay in version.^{1 5 6 8}

Prognosis for cardioversion of atrial flutter in the neonate is good in the absence of a cardiac lesion.

Furthermore, the prognosis is better if the diagnosis is made antepartum or at birth, than if it develops later in infancy.¹

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Received 15 July 1980

Pregnanediols and breast milk jaundice

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SUMMARY Samples of breast milk collected from mothers of infants with breast milk jaundice were analysed for 5 β -pregnane-3 α , 20 β -diol, and other pregnanediols using gas chromatography-high resolution mass spectrometry. None was detected in any of the specimens and therefore it is unlikely to be the inhibitory factor in bilirubin conjugation. The plasma osmolalities of the infants, which were determined at the onset of jaundice, were within normal limits.

Breast milk jaundice is a well-known clinical entity. Arias *et al.*¹ reported that breast milk from mothers of jaundiced infants inhibited glucuronyl transferase

activity *in vitro*. The effect was subsequently attributed to a steroid, 5 β -pregnane-3 α , 20 β -diol, isolated from the inhibitory breast milk.² The steroid was shown to inhibit glucuronyl transferase *in vitro* and to produce jaundice when given to newborn infants. Ramos *et al.*³ however, did not observe jaundice in infants given pregnanediol, nor could they identify the steroid in breast milk. Using human liver tissue, Adlard and Lathe⁴ showed that 5 β -pregnane-3 α , 20 β -diol did not inhibit bilirubin conjugation, and Hargreaves and Piper⁵ demonstrated inhibition of bilirubin glucuronide secretion from rat liver. Recent editions of standard paediatric textbooks continue to cite 5 β -pregnane-3 α , 20 β -diol as the inhibitory factor in breast milk jaundice.

In this study, the problem was re-examined by using gas chromatography-high resolution mass spectrometry to detect pregnanediols in breast milk.

Patients and methods

Breast milk samples were collected from mothers of 10 infants with breast-fed jaundice. The infants were term and were exclusively breast fed. Physical examination was normal. None had evidence of rhesus or ABO incompatibility, and routine screening for infection was negative. The peak bilirubin levels were higher than normally found in physiological jaundice and the jaundice persisted for at least 10 days and, in several cases, for many weeks. When jaundice was clinically detectable, blood was collected by venepuncture for determination of serum bilirubin concentrations and plasma osmolality. A sample of the mother's breast milk was taken and additional daily samples were collected in certain cases. Jaundice was managed by standard methods and serum bilirubin concentrations were determined daily until levels began to fall. Breast milk samples were also collected from 6 breast-feeding mothers whose infants did not develop jaundice.

Breast milk samples were stored at -20°C until analysed. Samples (1 ml) were extracted with 10 ml diethyl ether. Total extracts were purified by reverse and straight-phase chromatography on micro-columns of lipophilic Sephadex gels. Steroid-enriched fractions so obtained were converted to t-butyldimethylsilyl derivatives and analysed by combined gas chromatography-high resolution mass spectrometry.⁶ Ions of mass to charge ratio 491.3741, derived by loss of t-butyl radicals from molecular ions of pregnanediol bis-t-butyldimethylsilyl ethers, were monitored during analysis. Serum bilirubin concentrations (Pye-Unicam SP 6-200 spectrophotometer) and plasma osmolality (Advanced Digimatic Osmometer, model 3D) were determined by standard methods.

Results and discussion

Pregnanediols could not be detected in any of the milk samples collected from mothers of jaundiced infants (Table). In order to test the sensitivity of the analytical technique, each analytical series included a milk sample (1 ml) supplemented with 5β -pregnane- 3α , 20β -diol (1 ng). In each instance, the steroid was detected by gas chromatography-mass spectrometry. The breast milk from one of the mothers of an unaffected infant contained small amounts (about 1 ng/ml) of 5α - or 5β -pregnane- 3α , 20β -diol together

Table Analyses of infant blood and maternal milk in cases of breast fed jaundice

Case	Infant blood		Maternal milk	
	Peak serum bilirubin ($\mu\text{mol/l}$)	Plasma osmolality (mmol/kg)	No of samples analysed	Pregnanediols
1	321	281	4	ND
2	260	280	1	ND
3	216	288	4	ND
4	331	286	4	ND
5	294	284	1	ND
6	305	—	1	ND
7	251	297	2	ND
8	265	281	5	ND
9	191	276	2	ND
10	189	271	4	ND

Conversion: SI to traditional units: bilirubin—1 $\mu\text{mol/l} \approx 0.058$ mg/100 ml.

Serial daily breast milk samples were analysed in association with Cases 1, 3, 4, 8, and 10.

ND = not detected.

with isomeric components. The significance of this finding is not clear. Measurements of plasma osmolalities in infants were within normal limits (Table).

The technique of gas chromatography-high resolution mass spectrometry was used as it gives analyses of unparalleled specificity and sensitivity. Despite the great sensitivity, pregnanediols were not detected in breast milk collected from mothers of jaundiced infants. Analysis of serial daily samples of breast milk showed no intermittent secretion of pregnanediols into breast milk. The results indicate that pregnanediol is unlikely to be the inhibiting factor in bilirubin conjugation. We specifically analysed unconjugated pregnanediols in this study; the presence of other steroids in breast milk contributing to the aetiology of the jaundice cannot be excluded.

Possibilities other than steroid inhibition have been suggested. Free fatty acids inhibit bilirubin conjugation by rat liver slices,⁷ and human milk contains lipases which liberate free fatty acids from triglycerides.⁸ Luzeau *et al.*⁹ found that lipoprotein lipase activity was increased in inhibitory milk. Thus an excess of fatty acids may be a factor in the aetiology of breast-fed jaundice. The mechanism of absorption of the fatty acids is unknown however, because fats are normally converted to triglycerides in the intestinal mucosa before absorption.¹⁰ The findings may only be an *in vitro* phenomenon since fatty acids are known to accumulate in stored milk.¹⁰

A relation has been suggested between breast-fed jaundice and a low intake of fluid in the first few days after birth. None of the jaundiced infants in this study was clinically dehydrated, and their normal

plasma osmolalities suggested that hydration was adequate.

A rapid decrease in jaundice when breast feeding is stopped and a recurrence with the reintroduction of breast milk certainly suggests that at least one inhibitor is present in breast milk. Its nature, however remains unknown.

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Received 26 June 1980

Alpha-thalassaemic hydrops fetalis

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SUMMARY Concentrations of total protein, albumin, colloid osmotic pressure, and immunoglobulins G and M were measured in the umbilical venous plasma of 4 infants with α -thalassaemic hydrops fetalis. Total protein, albumin, and colloid osmotic pressure concentrations were low, and these are likely to be contributory factors in the formation of fetal oedema. Immunoglobulin G levels were low suggesting a reduction in placental transfer probably due to placental oedema.

Infants affected with the homozygous form of α -thalassaemia are invariably hydropic at birth. The mechanisms for the formation of this intrauterine oedema are still poorly understood and chronic anaemia, congestive cardiac failure, and hypoproteinaemia have all been suggested as factors; it is unlikely that any one of these alone is responsible.

Such infants suffer from severe anaemia due to the chronic haemolysis associated with the abnormal haemoglobin resulting from defective alpha chain synthesis.^{1,2} It is thought that this may lead to high

output cardiac failure as well as causing anoxic damage to the capillary walls thereby increasing their permeability to plasma proteins. In other conditions however, equally low levels of haemoglobin do not cause hydrops³ nor is there any clear evidence that tissue oxygenation is disturbed *in utero*. Indeed a normal acid-base balance was reported in one newborn infant.⁴ A third possible factor, that of hypoproteinaemia, has not previously been studied in cases of α -thalassaemia, although it is known that both plasma proteins³ and colloid osmotic pressure⁵ may be reduced in hydrops fetalis associated with rhesus isoimmunisation.

We now report a study of plasma proteins in 4 infants with α -thalassaemic hydrops fetalis.

Materials and methods

Blood was collected from the umbilical vein of 4 infants with hydrops fetalis immediately after birth. In each case the diagnosis of α -thalassaemia was confirmed by haemoglobin electrophoresis. Clinical data were available for the 3 infants (Cases 1-3) born