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Steroid Inhibition of Glucuronization

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Pregnanediol content was estimated in the milk of nine mothers whose babies after the 10th day of life developed a serum bilirubin level of above 15 mg per 100 ml. In four cases pregnanediol 3alpha—20alpha was detected in amounts from 89 to 141 μg per 100 ml. Epimeric pregnanediol 3alpha—20-beta was found in a single case in an amount of 105 μg per ml. 3alpha—20-alpha pregnanediol was also present in four of nine mixed early breast milk samples in amounts ranging from 11.5 to 54 μg per 100 ml. No steroid was detected in pooled milk-band samples. Clinical trials failed to support the role of steroid inhibition in our cases of protracted neonatal jaundice.

Lathe and Walker [6] were the first to observe the inhibition of bilirubin glucuronization in the serum of pregnant women and newborn infants. Arias et al. [1] then identified the inhibitor as 3alpha—20beta (20-alpha?)-pregnanediol and demonstrated its presence in the early breast milk (colostrum) ingested by hyperbilirubinaemic infants. Several authors reported a greater frequency of pathologic jaundice among breast-fed than among bottle-fed infants. In some cases the jaundice subsided soon after withdrawal of the mother's milk [8, 11, 12].

The exact mechanism of steroid inhibition is nevertheless not clear. We do not know what quantitative or qualitative differences in steroid metabolism are responsible for it and how this metabolite enters the organism of the foetus and the newborn.

Method

In the present study we estimated the pregnanediol content of the milk of mothers whose baby after the 10th day of life had a serum bilirubin level of more than 15 mg per 100 ml. Cases displaying isoimmunization or other factors responsible for the jaundice have been excluded.

Mixed early breast and mixed pooled milk-bank samples served as controls.

Pregnanediols were estimated by thin-layer chromatography and spectrophotometry [3].

Results and Discussion

Pregnanediol 3alpha—20alpha in an amount from 89 to 141 μg per 100 ml was found in the milk of four mothers with newborns suffering from icterus. The metabolite was detected also in four mixed early breast milk samples, but in a smaller amount, ranging from 11.5 to 54 μg per 100 ml.

Further samples from five mothers of jaundiced newborns and pooled milk-bank controls did not contain the pregnanediol.

Epimeric pregnanediol 3alpha—20-beta was found in a single case of protracted jaundice, where the 3-alpha—20alpha epimer was also present (105 and 130 μg per 100 ml, respectively).

The laboratory investigations were completed with clinical trials. In seven cases with prolonged jaundice the mother's milk was substituted for 4—5 days with milk obtained from other women. The rate of serum bilirubin decrease was similar as in the period when the infants had been kept on their mother's milk.

On the other hand, in one case returning to mother's milk resulted in a re-elevation of the dye level of 5.0 mg per 100 ml in three days. Strikingly, in this instance no steroid was isolated from the milk.

There are few studies on the steroid content of mother's milk in pathologic prolonged jaundice [1, 5]. STIEHM and RYAN [13] observed eight babies but in four of them the peak serum bilirubin level was below 15 mg per 100 ml, a value which we regard as a border-line of pathologic icterus in term infants. It was further remarkable that the inhibitor in the mother's milk was not found in the four cases where the withdrawal of the mother's milk was followed by a quick decrease in the serum bilirubin level.

Oral pregnanediol administration in a dose of 0.3 to 1.0 mg per kg body weight per day did not always aggravate physiologic jaundice [1, 7, 9].

ROSENFELD [10] found 3alpha—20beta pregnanediol in the urine of 7 mothers among those of 8 jaundiced newborns, and FERRIS and GREEN [4] found equal urinary steroid contents in babies with and without neonatal jaundice.

The genetic background of steroid inhibition is also obscure. The five families of ARIAS et al. [2], where the pathologic jaundice of 24 members was caused by steroid inhibition, as "familiar neonatal jaundice" must sharply be differentiated from neonatal prolonged breast milk jaundice. An earlier onset and sometimes kernicterus are characteristic of the former disease.

To summarize our present knowledge of steroid inhibition, in the serum, urine and breast milk of women during the last days of pregnancy and the first days after delivery some metabolites occur which inhibit the glucuronization of bilirubin both in vitro and probably in vivo. The quick elimination of the steroids from the mother and also from the baby excludes this mechanism as an aetiological factor except in the early physiologic and pathologic jaundice of the neonatal period.

The role of steroid inhibition in prolonged neonatal jaundice is not clear. Though in four cases we have found an elevation of the pregnanediol content of the mother's milk, some contradictory laboratory and clinical trials throw scepticism on the

hypothesis of steroid inhibition in protracted neonatal jaundice. The recently observed characteristics of the transferase system will perhaps supply some information concerning the problem.

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