Beta glucuronidase and hyperbilirubinaemia in breast fed infants of diabetic mothers

L Sirota, M Ferrera, N Lerer, F Dulitzky

Abstract

A prospective study was performed comparing bilirubin concentrations in 10 breast fed term infants of diabetic mothers (IDM) to those of 10 breast fed normal term infants. The β -glucuronidase concentrations in serum and breast milk were assayed in the respective mothers. Significantly higher bilirubin concentrations were noted in the IDM group. Serum and breast milk β -glucuronidase concentrations were significantly higher in diabetic mothers as compared with those of non-diabetic mothers. We suggest that the high concentration of β -glucuronidase in breast milk of diabetic mothers is an additional important cause leading to hyperbilirubinaemia in their breast fed infants.

Hyperbilirubinaemia is observed more frequently in infants of diabetic mothers (IDM) than those of non-diabetic mothers. Although a number of hypotheses have been suggested, the pathogenesis remains uncertain.¹ To our knowledge, there are no previous reports describing the relationship between breast feeding and hyperbilirubinaemia in IDM.

Neonatal intestinal β -glucuronidase antagonises the net clearance of bilirubin by increasing enterohepatic circulation causing increased serum bilirubin.² In 1986, Gourley and Arend reported that the β -glucuronidase present in maternal milk is an important factor in breast milk jaundice.³ In a previous report higher values of serum β -glucuronidase were found in pregnant diabetic women in comparison with non-diabetic women.⁴

In the present study we have examined the hypothesis that the increased concentration of breast milk β -glucuronidase in diabetic mothers may be an additional cause of hyperbilirubinaemia in their breast fed infants.

Patients and methods

Ten breast fed IDMs and their mothers were examined. All the diabetic mothers were insulin dependent, classes B and C, according to White's classification of maternal diabetes.

A group of 10 breast fed term infants, of appropriate weight for gestational age, and their mothers served as a control group. All the infants in the study were born by spontaneous vaginal delivery. Babies with blood incompatibilities, sepsis, birth asphyxia, bruising, cephalhaematoma, and other obvious causes of neonatal jaundice were excluded. IDMs with hypoglycaemia treated with dextrose fluids

orally or intravenously were not included in the study.

On the third postpartum day maternal serum and breast milk were collected and analysed for β -glucuronidase. Breast milk was collected with a manual pump and immediately deposited in an iced container. All serum and breast milk samples were kept at -20°C and thawed at room temperature before assaying.

The β -glucuronidase activity was assayed with phenolphthalein mono- β -glucuronic acid substrate (Sigma kit No 325) and was expressed in Sigma units at 56°C .

On the third day of life bilirubin was measured in the serum of all babies studied. This was done spectrophotometrically by the Advanced Bilirubin Stat-Analyzer Photometer model BR2.

Statistical analysis was performed using Student's *t* test.

Results

Mean (SD) serum β -glucuronidase concentration was significantly higher in diabetic mothers (71.5 (23) Sigma/units) as compared with non-diabetic mothers (30 (10) Sigma/units) ($p < 0.0005$, figure).

In both diabetic and non-diabetic mothers, breast milk β -glucuronidase concentration was significantly higher (640 (205) and 216 (70) Sigma/units, respectively) than in the serum ($p < 0.005$, figure).

Birth weight was not significantly different between the IDMs (3760 (800) g) and the control group (3400 (300) g). The packed cell volume at the age of 24 hours was not significantly different between the IDMs (54.3 (9.4)) and the controls (53.3 (6.6)).

The mean (SD) peak of serum bilirubin concentration on the third day of life was significantly higher in IDMs (210.3 (107.7) $\mu\text{mol/l}$) in comparison with controls (123.0

Mean serum and breast milk β -glucuronidase concentrations expressed in Sigma/units in diabetic and non-diabetic mothers.

Neonatology Unit,
Hasharon Hospital,
Golda Medical Centre,
Petah-Tiqva, 49372,
POB 121, Israel
L Sirota
F Dulitzky

Chemistry Laboratory,
Hasharon Hospital
M Ferrera
N Lerer

Correspondence to:
Dr Sirota.

Accepted 16 August 1991

(66.7) $\mu\text{mol/l}$ $p < 0.005$). None of the normal (control) infants was treated with phototherapy in contrast to 50% treated in the IDM group. None of the IDM group had phototherapy before bilirubin estimation on day 3.

Discussion

Hyperbilirubinaemia is frequently observed in IDM.⁵⁻⁸ Although several mechanisms have been proposed to explain this clinical finding, the pathogenesis of hyperbilirubinaemia remains uncertain. The jaundice observed in the IDM was often attributed to biochemical immaturity of the liver of the IDM. Several studies have analysed morbidity carefully, according to gestational age, and have rejected this concept.⁹⁻¹² The increased incidence of Coombs' positive ABO incompatibilities in IDMs has not been confirmed either.⁵ Polycythaemia frequently observed in IDMs may well be the most important factor associated with hyperbilirubinaemia. Venous packed cell volume above 0.65 has been observed in 20% to 40% of IDMs. Presumably the major stimulus for the enhanced red cell production is a state of relative hypoxia in utero.⁹ To our knowledge this is the first report which describes the association between breast feeding and hyperbilirubinaemia in IDMs.

The association between breast milk feeding and neonatal jaundice was first described in 1963.¹³ Recent studies have documented an increased incidence of hyperbilirubinaemia in breast fed infants during the first week of life.¹⁴⁻¹⁸ Earlier studies reported that the onset of breast feeding jaundice occurred only at the end of the first week of life.¹⁹⁻²⁰ Some studies have attributed breast milk jaundice to the inhibition of hepatic uridine diphosphate glucuronyl transferase by the steroid pregnane $3\alpha,20\beta$ -diol²¹⁻²² or to the increased concentration of lipoprotein lipase and non-esterified long chain fatty acids in human milk.²³ Recently, Gourley and Arend reported the β -glucuronidase in maternal milk is an important factor facilitating intestinal reabsorption of bilirubin in breast fed infants, thus increasing the concentration in the enterohepatic circulation.³

Previous studies reported higher values of serum β -glucuronidase in pregnant diabetic women in comparison to non-diabetic ones.²⁴ We found significantly higher concentrations of serum β -glucuronidase in diabetic mothers in comparison with non-diabetic ones, thus delivery does not have an immediate direct effect on decreasing the serum β -glucuronidase value. Our finding is in accordance with that of Gaffiney *et al* confirming that concentrations of β -glucuronidase in breast milk are much higher than those in the serum.²⁵ As the concentration of β -glucuronidase was significantly higher in the breast milk of diabetic mothers, we assume that the amount in breast milk is in direct

relationship with that in the serum. Because no significant differences were noted in the birth weight, packed cell volume, ABO and Rh incompatibility, and abnormal thyroid or liver function in IDMs compared with controls studied, we suggest that the significantly higher serum bilirubin concentration observed in the IDMs may be attributed to the higher concentrations of β -glucuronidase in maternal milk.

In conclusion we suggest that the higher concentrations of breast milk β -glucuronidase in diabetic mothers may be an additional important cause leading to hyperbilirubinaemia in the breast fed IDMs by enhancing the amount of bilirubin in the enterohepatic circulation.

- Cowett RM, Schwartz R. The infant of diabetic mother. *Pediatr Clin North Am* 1982;29:1213-31.
- Poland RL, Odell GB. Physiologic jaundice: the enterohepatic circulation of bilirubin. *N Engl J Med* 1971;284:1-6.
- Gourley GR, Arend RA. β -glucuronidase and hyperbilirubinaemia in breast fed and formula fed babies. *Lancet* 1986;i:644-6.
- Ferrara M, Mizrahy O, Saposhnik A, Feinstein G. Serum β -glucuronidase activity during pregnancy in gestational diabetes. *Isr J Med Sci* 1973;15:746-8.
- Zetterstrom R, Strindberg B, Arnold RG. Hyperbilirubinaemia and ABO haemolytic disease in newborn infants of diabetic mothers. *Acta Paediatr Scand* 1958;47:238-42.
- Taylor P, Wolfson J, Bright N. Hyperbilirubinaemia in infants of diabetic mothers. *Biol Neonate* 1963;5:289-94.
- Olson B, Osler M, Pedersen J. Neonatal jaundice in infants born to diabetic mothers. *Danish Med Bull* 1963;10:18-23.
- Peevy KJ, Landaw SA, Gross SR. Hyperbilirubinaemia in infants of diabetic mothers. *Pediatrics* 1980;66:417-9.
- Landon MB, Gabbe SG. Diabetes and pregnancy. *Med Clin North Am* 1988;72:1493-511.
- Gabbe SG, Lowensohn RI, Wu PY, Guerra G. Current patterns of neonatal morbidity and mortality in infants of diabetic mothers. *Diabetes Care* 1978;1:335-9.
- Lemons JA, Vargas P, Delaney JJ. Infant of the diabetic mother: review of 225 cases. *Obstet Gynecol* 1981;57:187-92.
- Stevenson DK, Bartoletti AL, Ostrander CR, Johnson JD. Pulmonary excretion of carbon monoxide in the human infant as an index of bilirubin production. II. Infants of diabetic mothers. *J Pediatr* 1979;94:956-8.
- Nowman AJ, Gross S. Hyperbilirubinaemia in breast fed infants. *Pediatrics* 1963;32:995-1001.
- Adams JA, Hey DJ, Hall RT. Incidence of hyperbilirubinaemia in breast vs. formula fed infants. *Clin Pediatr (Phila)* 1985;24:69-73.
- Saigal S, Lunyk O, Bennett KJ, Patterson MC. Serum bilirubin levels in breast fed and formula fed infants in the first 5 days of life. *Can Med Assoc J* 1982;127:985-9.
- De Carvalho M, Klaus MH, Merkat RB. Frequency of breast-feeding and serum bilirubin concentration. *Am J Dis Child* 1982;136:737-8.
- Lascari AD. 'Early' breast-feeding jaundice: clinical significance. *J Pediatr* 1986;108:156-8.
- Maisels MJ, Gifford K. Neonatal jaundice in full-term infants. Role of breast-feeding and other causes. *Am J Dis Child* 1983;137:561-2.
- Dahms BB, Krauss AN, Gartner LM, Klain DB, Soodalter J, Auld PAM. Breast-feeding and serum bilirubin values during the first 4 days of life. *J Pediatr* 1973;83:1049-54.
- Maisels MJ. Neonatal jaundice. In: Avery GB, ed. *Neonatology: pathophysiology and management of the newborn*. Hagerstown, Md: Harper and Row, 1981:473-544.
- Arias IM, Gartner LM, Seifter S, Furman M. Prolonged neonatal unconjugated hyperbilirubinaemia associated with breast feeding and a steroid, pregnane-3(alpha), 20(beta)-diol, in maternal milk that inhibits glucuronide formation in vitro. *J Clin Invest* 1964;43:2037-47.
- Murphy JF, Hughes I, Verrier Jones ER, Gaskell S, Pike AW. Pregnandiol and breast milk jaundice. *Arch Dis Child* 1981;56:474-6.
- Poland KL, Schultz GE, Garg G. High milk lipase activity associated with breast milk jaundice. *Pediatr Res* 1980;14:1328-31.
- Plaice CHJ. A note on the determination of serum β -glucuronidase activity. *J Clin Pathol* 1961;14:661-5.
- Gaffiney PT, Shepherd RW, Todehope DI, Ward M. Enzymes in human colostrum and milk-sequential changes in concentration. *Aust Pediatr J* 1983;19:196-201.