THE EFFECT OF OXYTOCIN ON THE FOETAL SERUM BILIRUBIN

A THESIS

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Presented By
MOHAMED ALY ABD EL-ATY
M. B., B. Ch.

Supervised by
Dr. IBRAHIM SAMAHA
Ass. Prof. of Obstetrics and Gynaecology
Ain Shams Faculty of Medicine
Dr. MAHMOUD EL-SHOURBAGY
Lecturer of Obstetrics and Gynaecology
Ain Shams Faculty of Medicine

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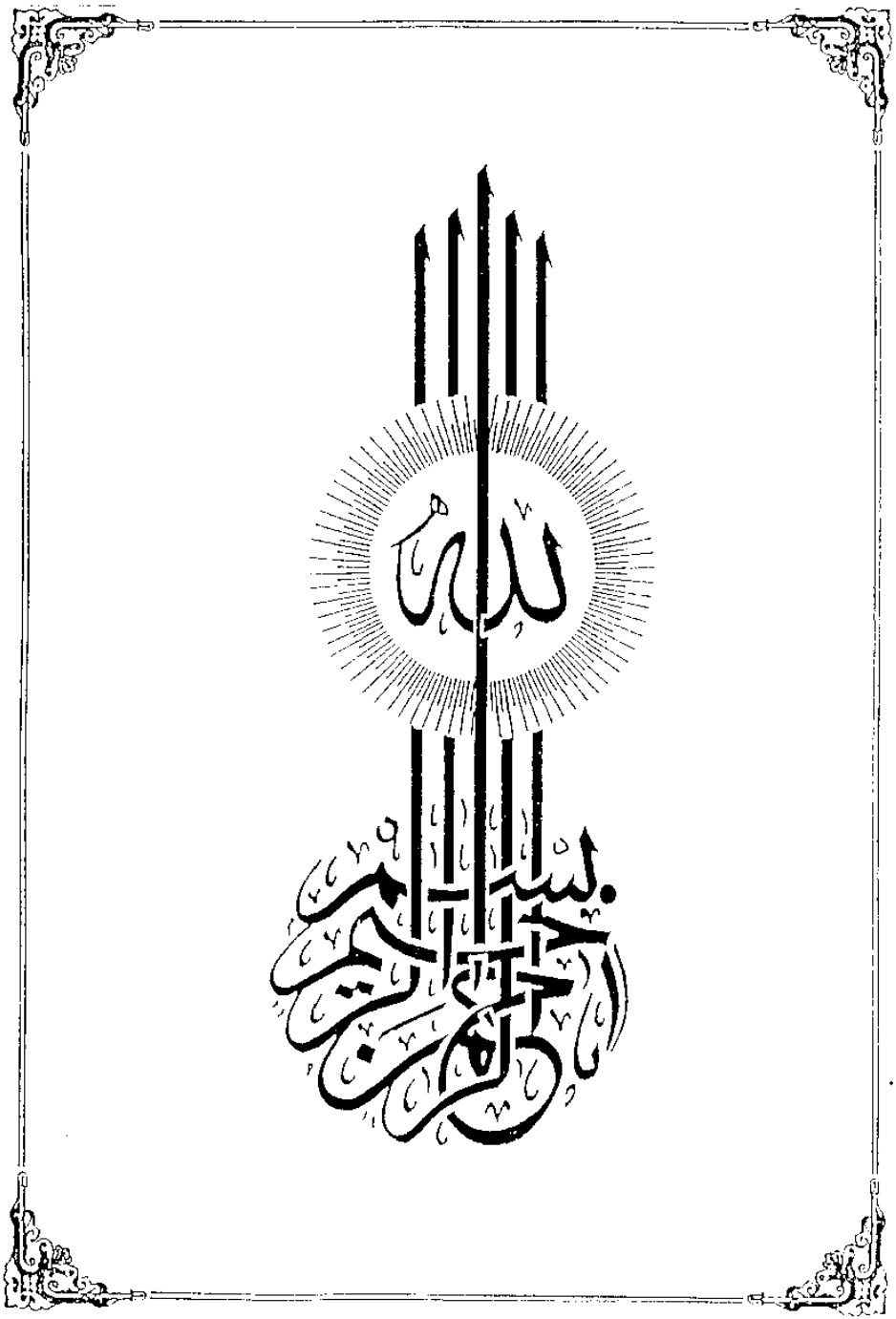

I N T R O D U C T I O N

Bilirubin Metabolism

Vaughan, Mckay and Behrman 1979[2] reviewed the bilirubin metabolism in the newly born infants. Bilirubin is derived principally from the degradation of haemoglobin of red blood cells trapped by the spleen and reticulo-endothelial system. The newly formed unconjugated bilirubin is bound to plasma albumin and transported prenataly to the placenta, where it is cleared and subsequently metabolized by the maternal liver. Postnataly it is transported to the liver where it is taken into the hepatocytes. The bilirubin and other organic anions are bound to the Y (ligandin) and Z proteins within the cytoplasm. Concentrations of Y protein are low in the foetus and newly born infants, and this may reduce the intracellular binding and transport of bilirubin. Unconjugated bilirubin cannot be excreted in the urine or in the bile. Normally the liver conjugates bilirubin with glucouronic acid. The glucuronide is water soluble and is normally excreted into the bile by the liver predominantly, but when the plasma level is elevated, it is excreted by the kidney. Glucuronic acid is made available for this conjugation by transfer from

uridine diphosphoglucuronic acid ctalyzed by the enzyme glucuronyl transferase.

Since many other biologic substances also are conjugated with glucuronic acid, such as steroids, phenolic compounds, carboxylic acids, and sulfonamides, they may compete with bilirubin for conjugation and lead to elevation of unconjugated bilirubin level. Sulfonamides and salicylates compete with unconjugated bilirubin for protein-binding sites. Sodium benzoate in injectable diazepam, as well as furosmide and gentamycin, also uncouple bilirubin from albumin(1).

Hypoxia and acidosis reduce the bound fraction of free bilirubin. Hypothermia and hypoglycaemia increase the level of non esterified fatty acids, which also compete with bilirubin for the binding sites of albumin. Sepsis contributes in the occurance of kernicterus but the mechanism of action is not clear.

Physiological jaundice

Under normal circumstances, the level of unconjugated bilirubin in umbilical cord serum is I to 3 mg./100 ml.

and rises at a rate of less than 5 mg./100 ml./24 hours, thus jaundice becomes visible on the second day or third day, usually peaking between the second and fourth days at 5 or 6 mg./100 ml., and decreasing to below 2 mg./100ml, between the fifth and seventh days of life. This type of jaundice is believed to be the result of breakdown of foetal red cells combined with transient limitation in the conjugation and excretion of bilirubin by the liver.

Among premature infants the rise in the serum bilirubin level tends to be the same or little slower than in term infants, but longer duration, generally resulting in higher levels, the peak being reached between the fourth and seventh days, the pattern depends upon the time required for the preterm infant to achieve mature mechanisms for metabolism and excretion of bilirubin.

The diagnosis of physiological jaundice can be established only by excluding known causes of jaundice on the basis of history, clinical and laboratory findings.

Pathological jaundice:

The deposition of unconjugated bilirubin in brain cells results in the neurologic syndrome, kernicterus. The precise blood level above which unconjugated bilirubin will be toxic for an individual infant is unpredictable, but kernicterus is rare with serum levels under 18 to 20 mg/100 ml. The duration of exposure necessary to produce toxic effects is also unknown. The less mature the infant, the greater the susceptibility to kernicterus. In full term infants it usually occurs when the bilirubin level exceeds 20 mg./100 ml., however it may occur at lesser concentrations, 15 mg./100 ml. or even less in cases of prematurity (Boggs et al., 1967, Carswell et al., 1972 and Thomas et al.,1976)(7-11-41).

Breast feeding and hyperbilirubinaemia:

Arias, Gartner, Seifter and Furman 1964 (3) described a syndrome of severe and prolonged hyperbilirubinaemia due to elevation of the neonatal serum unconjugated bilirubin level in seven breast fed newborns.

They observed that cessation of breast feeding lead to disappearance of the hyperbilirubinaemia, while, reinstitution of breast feeding lead to its appearance again. They found a substance in the milk of the seven mothers of those newborns which can competetively inhibit the glucuronyl transferase enzyme in vitro, an enzyme which is essential for bilirubin conjugation in the liver. This substance was identified as pregnane-3(alpha); 20 (beta)-diol, a steroid which is secreted in the milk of some women.

Smallpiece and Davies 1964 (39) observed that the mean serum bilirubin level of the newborns who were fed by their mothers adequately and early in their neonatal life was lower than the mean serum bilirubin level of newborns who were not fed adequately and early in their neonatal life by their mothers.

Gould, Mountrose, Whitehouse and Barnardo 1974 (24) in a prospective study found no difference in the mean

serum bilirubin level between the breast fed and the bottle fed infants.

Makhlouf and Samaha 1976 [28] detected the steroid pregnane- 3(alpha), 20 (beta)-diol in breast milk in 20 out of 25 mothers whose newborns developed neonatal hyperbilirubinaemia. They suggested that it had an important role in prolonged neonatal hyperbilirubinaemia, but other factors might contribute for this prolonged hyperbilirubinaemia.

Chew and Swann 1977 [15] in a prospective study found no significant difference between the mean serum bilirubin level in breast-fed infants and that of artificially fed infants.

Difficult labour and hyperbilirubinaemia:

Miller and Read 1958 [32], and Zuelzer and Brown 1961 [51] reported that prolonged and difficult

labour is commonly associated with delayed onset of respiration, respiratory distress syndrome, and neonatal hyperbilirubinaemia. They suggested that neonatal hyperbilirubinaemia might be due to disturbance of hepatic enzyme system essential for bilirubin conjugation as a result of neonatal hypoxia.

Weiland and Langer 1965 [49] reported that vacuum extraction delivery is commonly associated with neonatal hyperbilirubinaemia.

Chalmers, Campbell and Turnbull 1975 [12] found no significant correlation between neonatal hyperbilirubinaemia and the duration of labour.

Campbell, Harvey and Norman 1975 [10] in a retrospective study found that in infants with neonatal hyperbilirubinaemia, abnormal delivery as breech, forceps or vacuum occured in 42%, but occured in only 33% of infants without neonatal hyperbilirubinaemia. They also observed that vacuum extraction

deliveries were three times commoner among infants with neonatal hyperbilirubinaemia.

Friedman and Sachtleben 1976 (21) suggested that operative instrumental delivery might cause focal haemorrhages not readily detectable in the infant, but might nevertheless subsequently be manifisted by the occurence of neonatal hyperbilirubinaemia.

The effect of epidural anaesthesia:

Davies Gomersall, Robertson, Gray and Turnbull 1973 (18) suggested an association between epidural anaesthesia, given during labour, and the increased incidence of neonatal hyperbilirubinaemia.

Campbell, Harvey and Norman 1975 (10) got the same result in a prospective study. They thought initially that the high instrumental delivery rate resulting from the use of epidural anaesthesia might

have caused more soft tissue trauma, which contribute to the development of significant hyperbilirubinaemia. They found, however, that instrumental deliveries associated with epidural anaesthesia were not more frequent in the jaundiced group.

Friedman, Lewis, Clifton and Bulpitt 1978 (22) in a retrospective study found that 15% of the newborns delivered with the use of epidural anaesthesia developed hyperbilirubinaemia, while, 10% only of those delivered without the use of epidural anaesthesia developed hyperbilirubinaemia.

Gould, Mountrose, Brown, Whitehouse, and Barnardo 1974 (24) in a prospective study observed that epidural anaesthesia had no effect on the neonatal serum bilirubin levels.

The role of the previous use of contraceptive pills:

Wong and Wood 1971 (50) were the first to observe

an increase in the incidence of neonatal hyperbilirubinaemia among newborns who had been born to mothers who were pill users.

McConnel, Glasgow and McNair 1973 (30) observed that there is a relation between previous maternal pill use and the increased incidence of neonatal hyperbilirubinaemia.

Gould, Mountrose, Whitehouse, Brown and Barnardo 1974 (24) in a prospective study, failed to find a relation between neonatal hyperbilirubinaemia and the maternal use of oral contraceptive pills before pregnancy. Also they found no relation between the duration of discontinuation of pill use before pregnancy and neonatal hyperbilirubinaemia.

Role of prostaglandins :

Karim, Trussell, Patel and Hillier 1968 (26) were the first to use prostaglandin $F_{2\alpha}$ for induction of labour by the intravenous route.

Embrey 1969 (19) used prostaglandin E_2 for induction of labour by the intravenous route. He observed that prostaglandin is more effective than oxytocin for induction of labour particularly when the cervix is unripe.

Calder, Moar, Ounsted and Turnbull 1974 (9) carried out a prospective study to find the relation between the method of delivery and neonatal hyperbilirubinaemia. Four groups of thirty primigravidae and their infants were selected. In group A labour was induced by intravenous oxytocin, in group B by intravenous prostaglandin E_2, in group C by extra-amniotic prostaglandin E_2 and in the fourth group D labour was spontaneous throughout its course.

The mean serum bilirubin levels in the neonates were significantly higher in group A and B than in group D. The mean serum bilirubin level in group C did not differ significantly from group D. They suggested that the neonatal hyperbilirubinaemia

might be due to artificial interruption of pregnancy, drug administration and the route of its administration.

Chew 1977 [14] carried out a prospective study in which he selected three groups of patients. In the first group labour was induced by amniotomy and prostaglandin E_2 by mouth. In the second group, labour was induced by amniotomy and intravenous oxytocin infusion. In the third group labour was spontaneous throughout its course. Significant difference was found between the mean serum bilirubin level of the first group and that of the third group. This difference was not found between the second and the third groups.

Oxytocin and obstetrics:

Blair Bell in 1909 [6] was the first to use oxytocin in obstetric practice.

Watson 1920 [48] was the first to use oxytocin systemically for the induction of labour.