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Hyperbilirubinaemia in the neonate and associated implications for the late preterm neonate (part two): A review of the background literature and critical review of the current research papers findings on the topic

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Introduction

Neonatal jaundice is a clinical manifestation of hyperbilirubinaemia (Watson, 1999). It presents as a yellow discolouration of the skin that reflects increased levels of bilirubin (Beachy, 2007; Truman, 2006,). Physiologic jaundice is a common problem faced by neonates, approximately 60% full term and 80% preterm infants develop visible jaundice (Beachy, 2007; Truman, 2006). If left untreated and levels continue to rise it can lead to acute bilirubin encephalopathy and kernicterus (Bhutani et al., 2004; Blackburn, 2007; Raju et al., 2006).

Production and clearance of bilirubin

Bilirubin is produced when red blood cells are destroyed and accounts for 75% of bilirubin

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production in the term infant. The red cells are removed from the circulation by the liver and spleen and broken down into globin, a reusable protein, and haem. Haem oxygenase then breaks down the haem into biliverdin and carbon monoxide. The lungs remove the carbon monoxide and biliverdin is further reduced by biliverdin reductase into bilirubin (Blackburn, 2007; Dent, 2000). In this form bilirubin is known as unconjugated or fat-soluble. Before excretion can occur bilirubin needs to become conjugated, this occurs in the liver but free bilirubin cannot enter the liver unaided. Unconjugated bilirubin binds to albumin for transportation to the liver (Beachy, 2007; Dent, 2000; Watson, 1999).

Once bilirubin reaches the liver it is released from albumin and bound to Y and Z proteins that aid entry into the liver and the process of conjugation then occurs (Beachy, 2007). The enzyme uridine diphosphate glucuronyl transferase (UDPGT) catalyses a series of reactions and the bilirubin becomes joined to two glucuronic acid molecules. In this form bilirubin is known as conjugated or water-soluble and is available for excretion. Conjugated bilirubin enters the small intestine and is either further reduced by bacterial flora to urobilinogen and excreted in the stool or reabsorbed across the intestinal mucosa in a process known as enterohepatic circulation (Beachy, 2007; Dent, 2000).

However this process of bilirubin production and clearance may be altered in the newborn infant predisposing then to physiological jaundice. This is in part due to the fact that a newborn infant has a higher haemoglobin level and a shorter red blood cell life span than adults. This combination of high haemoglobin and shorter life span produces a high rate of haemolysis and in turn a higher production of bilirubin (Dent, 2000; Watson, 1999). Higher levels of bilirubin put extra pressure on the metabolic processes involved in excretion that may already not be working as efficiently as required, particularly in the preterm infant. It is thought the transport of bilirubin to the liver may be hindered in the newborn by decreased levels of Y and Z proteins, limiting binding for clearance. It is also believed that newborns have decreased levels of the UDPGT enzyme causing the liver to be overloaded with bilirubin. UDPGT activity begins to increase rapidly after 24 h post birth but does not reach adult levels until 6—14 weeks (Blackburn, 2007; Dent, 2000).

The gastrointestinal tract also plays a role in bilirubin metabolism. Newborns have a higher level of bilirubin reabsorbed from the intestine due to the decreased levels of bacterial flora required to metabolise bilirubin for excretion and also have a high level of B-glucuronidase activity in the gut mucosa that acts on the conjugated bilirubin causing it to become unconjugated, thus allowing it to be reabsorbed through enterohepatic circulation (Beachy, 2007; Blackburn, 2007). All of these factors increase the newborn's risk of developing hyperbilirubinaemia.

As would be expected all factors that contribute to physiological jaundice in the term infant are even more significant in the preterm infant further increasing their risk of hyperbilirubinaemia. For example the life span of red blood cells is even shorter in the preterm infant creating a further increase in bilirubin production. The extremely low birth weight infant's lower serum albumin levels severely limit the binding of bilirubin especially when levels are high due to the very short life span of the red cells (Beachy, 2007; Blackburn, 2007).). Finally, excretion of bilirubin may be decreased in the preterm infant due to slower gut motility than term infants. Introduction of enteral feeds may be delayed in preterm infants causing delay in bacterial colonisation and delayed stooling, which may increase enterohepatic circulation (Beachy, 2007; Watchko and Maisels, 2003). All these factors together will increase the amount of unconjugated bilirubin and therefore increase the risk for jaundice and toxicity.

Bilirubin toxicity

In certain circumstances bilirubin can become toxic to the central nervous system causing neurological impairment. Factors influencing bilirubin toxicity are incompletely understood and it is not known at what bilirubin concentration the infant is at significant risk of brain damage (AmericanAcademyof Pediatrics, 1994; Hansen, 2001). This is because the blood brain barrier consists of endothelial cells that remain permeable to fat-soluble substances whilst excluding water soluble and large molecules (Ives, 2005). Unconjugated bilirubin is fat-soluble and can therefore freely cross the blood brain barrier entering the basal ganglia and cerebellum, staining the nuclei of the cells yellow. Cellular metabolism is disrupted and this may lead to acute bilirubin encephalopathy or kernicterus (Dent, 2000).

It is important for healthcare practitioners to understand that acute bilirubin encephalopathy is potentially a reversible brain injury (Beachy, 2007); classic signs include lethargy, poor feeding and hypotonia. However intervention at this point