RESEARCH REPORT

Recommendations for Pregnancies in Patients with Crigler-Najjar Syndrome

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Abstract During pregnancy, the developing foetus in mothers with Crigler-Najjar type 1 and 2 is exposed to raised levels of unconjugated bilirubin, with the risk of neurotoxicity. We describe two pregnancies in a patient with Crigler-Najjar type 2, who was carefully monitored prior to and during pregnancy and phototherapy adjusted to maintain serum bilirubin levels below 200 μmol/l and the bilirubin/albumin molar ratio below 50%. Both pregnancies resulted in normal delivery of healthy infants who had normal neurological development. A review of all reported pregnancies in Crigler-Najjar patients and a set of recommendations are presented.

Introduction

Crigler-Najjar syndromes type 1 (OMIM # 218800) and type 2 (OMIM # 606785) are rare disorders caused by homozygous or compound heterozygous mutations in the gene UGT1A1 and characterised by markedly raised levels of unconjugated bilirubin. Before the introduction of

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phototherapy, many patients died of kernicterus in the neonatal period. Patients now can expect to survive into adulthood when treated with intensive daily phototherapy or, in the case of Crigler-Najjar type 2, with phenobarbitone with or without phototherapy. There have been very few reports of the effects of maternal unconjugated hyperbilirubinaemia on the foetus. The main concern is that the unconjugated bilirubin, which can cross the placental barrier, might cause foetal damage, especially foetal kernicterus.

In the Gunn rat, which is an animal model of the Crigler-Najjar disease, the jaundiced female rat has been reported to be less fertile than the non-jaundiced one (Davis and Yeary 1979). In addition, there seems to be an increased chance of foetal abnormalities in the jaundiced Gunn female rat (Davis et al. 1983). In humans, patients with acute and chronic liver disease also tend to be less fertile and to have an increased chance of abortion, or foetal abnormality and possibly kernicterus (Furhoff 1974; Roszkowski and Pizarek-Miedzinska 1968; Cotton et al. 1981). However, conclusions based on findings in acute and chronic hepatitis or cirrhosis cannot be extrapolated to unconjugated hyperbilirubinaemia without other features of liver disease.

At the time one of our patients expressed the desire to have children, four case reports had been published on pregnancies in patients with Crigler-Najjar disease, with five successful pregnancies (Cahill and McCarthy 1989; Taylor et al 1991; Smith and Baker 1994; Ito et al 2001). Three concerned patients with Crigler-Najjar type 2, one of whom continued to take phenobarbitone throughout the pregnancy. All were delivered of healthy infants at term. The fourth patient was diagnosed with Crigler-Najjar type 1, with total blood bilirubin levels between 357 and 458 μmol/l throughout pregnancy (1 mg/dl is 17.1 μmol/l). She underwent caesarean section. The infant had a cord total

Table 1 Recommendations for the management of pregnancy in patients with Crigler-Najjar disease types 1 and 2

1.   Discussion of potential problems and genetic counselling before becoming pregnant

2.   Administration of folic acid prior to and during pregnancy

3.   Regular assay of serum bilirubin and albumin and adjustment of phototherapy to keep the serum bilirubin $<$ 200 μmol/l and the bilirubin/albumin molar ratio $<$ 50%

4.   If the patient is on Phenobarbital, reduce dosage to 50–60 mg/day

5.   Prenatal care and delivery in a tertiary care centre, with facilities for rapid bilirubin and albumin assays and phototherapy for mother and infant

6.   Avoidance of drugs that increase unbound, unconjugated bilirubin (Robertson et al. 1991; Strauss et al. 2006)

7.   Neurological testing of the child after birth and during early childhood

bilirubin of 410 μmol/l, unconjugated 217 μmol/l. This high percentage of direct reacting bilirubin is unexpected, and as the total bilirubin level of the mother and the cord blood are so similar, it could represent an artefact. Initially there were no neurological abnormalities and the infant appeared to develop normally but he was found to have some spasticity at 9 months of age (Taylor et al. 1991). We drew up a set of recommendations (Table 1), which we presented to and discussed with the Crigler-Najjar patients and their families, emphasising the limited evidence on the effects of raised maternal bilirubin levels on the developing foetus.

We have managed two successful pregnancies in a Crigler-Najjar type 2 patient, according to our guidelines. Both children are developing normally, both physically and mentally. We reviewed all reported pregnancies in Crigler-Najjar patients discovered by searching PubMed and Embase using the terms Crigler-Najjar and pregnancy.

Case Report

A woman with Crigler-Najjar disease type 2, who had been followed since childhood in our hospital, had maintained her bilirubin levels between 200 and 250 μmol/l with 1–2 h of phototherapy (10 lamps of 100 W) per day. She did not use Phenobarbital because of the side effects. She was compound heterozygote for the mutations L15R and S191F in the UDT1A1 gene.

At the age of 27 years, she became pregnant. At 9 weeks gestation her serum bilirubin was 234 μmol/l and albumin 43 g/l. Total bilirubin and direct bilirubin were determined using commercially available diazo-based colorimetric assays on a Roche Modular Analytics P 800-Module (Roche Diagnostics Nederland, Almere, The Netherlands). As during the course of her disease less than5% of the total bilirubin was direct reacting, in the later phases of the pregnancy, only total bilirubin was measured. The phototherapy was increased to 3 h/day resulting in bilirubin levels between 165 and 205 μmol/l. Her serum albumin

dropped to 34 g/l. Delivery was forceps-assisted after induction because of mild proteinuria at 39 weeks. At delivery, her bilirubin was 239 μmol/l. The healthy boy weighed 3440 g and had an Apgar score of 9 at 5 min. Cord blood bilirubin levels were the same as the mother's. The mother's bilirubin rose after delivery to 278 μmol/l and her albumin dropped to 30 g/l (Fig. 1). Directly after birth, her son's bilirubin was 177 μmol/l with albumin 35 g/l; phototherapy was given to the child for 3 days, bilirubin dropped to 10 μmol/l with unchanged albumin.

Two years later, she gave birth to a healthy girl at 39 weeks, weighing 3,150 g with an Apgar score of 10 at 5 min. Bilirubin and albumin levels were similar to the first pregnancy. Both children have developed normally without hyperbilirubinaemia or neurological abnormalities during a follow up of 11 and 9 years, respectively.

Discussion

Since the second pregnancy of our patient, there have been five more case reports on the outcome of pregnancy in patients with Crigler-Najjar type 1 and 2, giving a total of four Crigler-Najjar type 1 patients and eight Crigler-Najjar type 2, and 17 deliveries. The reports are summarised in Table 2. As can be seen, no neurological damage has been detected in the offspring, with one exception. The one exception was a Crigler-Najjar type 1 patient reported by Taylor et al. (1991) who had previously had three first trimester therapeutic abortions performed for social reasons and a prior miscarriage at which time she had a bilirubin level of 460 μmol/l. This patient is not reported to have been treated for the hyperbilirubinaemia. In all the other patients it has been possible to reduce maternal unconjugated bilirubin levels by increasing the intensity or duration of the phototherapy, in two instances in combination with fortnightly albumin infusions to increase bilirubin binding capacity or and in some Crigler-Najjar type 2 patients by continuing low dose phenobarbital treatment. As expected, maternal bilirubin levels were higher in Crigler-Najjar type 1, who also required much longer daily exposure to blue light – from 12 to 16 h.
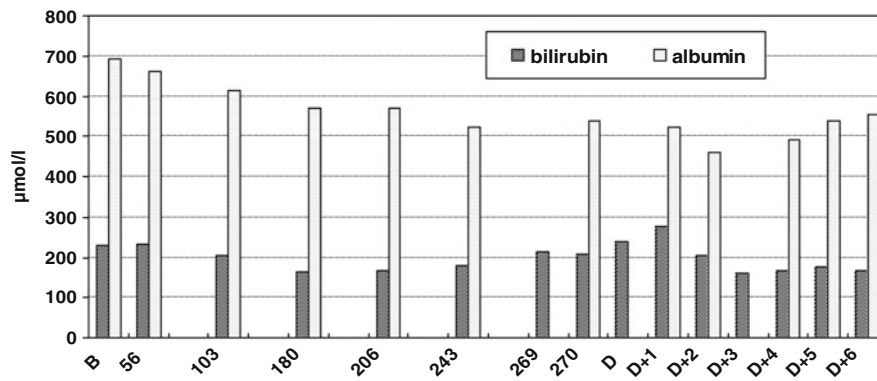
Fig. 1 Maternal serum bilirubin and albumin in μmol/l during pregnancy and after delivery. B = mean values in the 2-year period prior to pregnancy; numbers = duration of pregnancy in days; D = delivery; D + number = day after delivery

Table 2 Reports of Crigler-Najjar and pregnancy in the literature

Reference	CN type	Maternal age (years)	Maternal bilirubin during pregnancy (μmol/l)/	Maternal bilirubin at delivery (μmol/l)/	Cord blood or 1st day bilirubin (μmol/l)	Maternal treatment	Mode of delivery	Newborn treatment	Foetal outcome
Taylor 1991	NA/ 1	21	363–458	420	410 CB	None	CS	PT	Quadriplegic at 18 months
Gajdos 2006	1	28	230–280 (400 before PT)	242	222 CB	PT albumin	CS	PT	Healthy
Hannam 2009	1	26	200–380 (526 before PT)	317	323 D1	PT	CS	PT + Phb	Healthy
Hannam 2009	1	22	399–510	480	420 CB	PT albumin	Spontaneous	PT + exchange transfusion	Healthy
Cahill 1989	2	22	178–183	104	121 D1	Phb	Induced	PT	Healthy
Smith 1994	2	24	91–164	150	130 CB	None	Spontaneous	None	Healthy
Ito 2001	2	< 34	55–116			PT + Phb	CS	None	Healthy
			75–173	65–94	87 CB	PT + Phb	CS	None	Healthy
Holstein 2005 Holstein 2011	2	36	72–94	NA	NA	PT + Phb	CS	None	Healthy
		38	72–94	NA	NA	Phb	CS	None	Healthy
		41	72–94	NA	NA	Phb	CS	None	None
Saxena 2005	2	24	NA	139	174 D1	None	Spontaneous	None	Healthy
		25	130			None	Spontaneous	Blood transfusion, PT + Phb	Healthy
Passuello 2009	2	37	68–154	67	94 D1	Phb	Spontaneous	None	Healthy
Arora 2009	2	26	137–144	144	227 D1	None	Spontaneous	PT	Healthy
Current case	2	27	165–205	239	187 D1	PT	Induced	PT	Healthy
		29	168–256	195	146 D1	PT	Spontaneous	None	Healthy

Features of pregnancies in patients with Crigler-Najjar reported in the literature, *PT* phototherapy, *Phb* phenobarbital, *CS* caesarean sections, *NA* not available, *CB* cord blood, *D1* blood taken on first day after delivery. Bilirubin levels reported in mg/dl were converted to μmol/l by multiplying by 17.1. Note that in the report by Saxena (2005) cord blood levels showed a surprisingly high level of conjugated bilirubin, which might be an artefact

In general, low doses of phenobarbital have been given (25–100 mg/day).

Unconjugated bilirubin can cross the placenta, and this is indeed the normal route for excretion during pregnancy as the foetal liver is unable to conjugate or excrete bilirubin (Macias et al. 2009; Gajdos et al. 2006; McDonagh 2007; 2010). It is conceivable that phototherapy of the mother might reduce exposure of the foetal brain to a greater extent than reflected by serum bilirubin levels as the photoisomers of bilirubin are more water soluble and do not cross the blood–brain barrier or presumably the placenta to the same extent as unconjugated bilirubin (Mreihil 2010). At birth, foetal unconjugated bilirubin levels are in most reports roughly equivalent to those found in their mothers with Crigler-Najjar disease; however, phototherapy is usually stopped several hours before delivery, and circulating levels of photoisomers would be expected to be decreasing. However, serum levels were lower than the mother's in both infants reported here, which is compatible with a reduced clearance of photoisomers by the placenta.

At present it is impossible to state what concentration of unconjugated bilirubin is non-neurotoxic for the developing foetus, but it seems reasonable to try to keep the maternal (and therefore the foetal) unconjugated bilirubin concentrations below 200 μmol/l and the molar ratio between unconjugated bilirubin and serum albumin below 50% (Gajdos et al. 2006; Strauss et al. 2006). Current national guidelines state that a bilirubin over 170 μmol/l is an indication for phototherapy in term infants without risk factors for kernicterus and 70 μmol/l in high-risk infants.

In most patients with Crigler-Najjar who attended antenatal clinics, it has been possible to achieve these levels by increasing phototherapy, and, if needed, by infusions of human albumin.

Admission to hospital to facilitate monitoring and treatment of both mother and infant is necessary – as can be seen by the frequent need for phototherapy of the neonate. Careful planning of the admission, including use of a written protocol and frequent visits by the metabolic diseases team to monitor and educate the medical and nursing staff of the obstetrics unit, is essential.

Conclusions

Regular monitoring and adjustment of treatment to keep bilirubin levels below 200 μmol/l and bilirubin/albumin molar ratios below 50% during pregnancy in patients with Crigler-Najjar syndrome can result in good foetal outcome.

Conflict of Interest Statement

None.

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