Case report:

Crigler Najjar Syndrome [Type II] with Pregnancy: Case Report

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Abstract:
Crigler-Najjar syndromes are rare, autosomal recessive disorders caused by mutations in the genes of bilirubin metabolism. The management of these pregnancies is controversial due to paucity of literature. We discuss here a successfully managed case of pregnancy with Crigler-Najjar Syndrome.

Keywords: Crigler-Najjar syndrome, Gilbert syndrome, hyperbilirubinemia in pregnancy, phenobarbitone.

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Introduction

Crigler-Najjar syndromes are autosomal recessive disorders caused by mutations in the gene bilirubin uridine glucoronosyl transferase [UGT1A1] leading to defective conjugation of bilirubin. They are rare disorders, with an estimated incidence of less than 1 per 1000000 births. The clinical presentation varies with the type of mutation. Crigler-Najjar I [OMIM #218800] is a homozygous mutation, characterized by complete deficiency of UGT1A1 and high levels of bilirubin. Crigler-Najjar II [OMIM #606785] is a compound heterozygous mutation with partial deficiency of UGT1A1 and moderate to high levels of bilirubin.[1] Successful pregnancy in these women is rare with few cases reported in literature. Many reasons have been cited including decreased fertility, increased risk of miscarriage and poor neonatal outcome due to bilirubin encephalopathy.

The management is controversial due to paucity of literature. Many clinical approaches have been tried, ranging from conservative management to phototherapy and phenobarbitone administration. We discuss here a case of Crigler-Najjar II presenting in late pregnancy.

Case Report

History and Examination

A 25 year old lady, G2P1L0, known case of Crigler-Najjar II, reported at 33 weeks of pregnancy for her first antenatal visit. It was a spontaneous conception and hitherto an uneventful pregnancy. Her previous pregnancy had been uneventful, with term delivery at home. However, the baby had failure to thrive and succumbed to unknown illness at 6 months postnatal age. It was not known whether baby had icterus. There was no history of consanguinity. The patient and her sister had been diagnosed with Crigler-Najjar II at AIIMS, Delhi, many years back. However, most of the original documents had been lost.

On examination, she was thin built with a BMI of 22. Her pulse was 90 beats per minute, Blood pressure was 110/76 mm Hg, temperature was 98.4 degree Farenheit. She was deeply icteric. Uterus

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was corresponding to 28 weeks of gestation, which was smaller than expected. Fetal movements were normal.

Management

Investigations were done [Table 1] and the patient was started phenobarbitone. [30mg twice a day]. Within a week, her bilirubin decreased to 11mg%. She was followed up with serial fetal Dopplers as baby was SGA. She went into spontaneous labourat 37 weeks and delivered a baby boy of 2.3 kg. Baby was structurally normal and had no icterus [Figure1]. His serum bilirubin levels were normal [1mg%]. Breast feeding was initiated and sustained. The patient was advised to continue phenobarbitonein the same dosage. Both mother and baby are on regular follow up and doing well.

Discussion

Indirect hyperbilirubinemia is caused by haemolytic syndromes, Gilbert's and Crigler-Najjar syndrome. In the former two, serum bilirubin levels rarely cross 6mg%, whereas in Crigler-Najjar syndrome maternal bilirubin levels are usually more than 15 mg%.[2] Pregnancies have been reported in both Crigler-Najjar I and II; majorly in latter which is a milder form of the disorder.[3] Fetal liver is unable to conjugate bilirubin. Unconjugated bilirubin crosses placental barrier for excretion. Fetal bilirubin levels are similar to maternal levels which raises the major concern of fetal brain injury especially kernicterus. Although literature is sparse, most of these babies do well and don't sustain neurological damage. Taylor et al. (1991)[4] reported a single case of neurological damage in a baby whose mother had Crigler-Najjar I and was not taking any antenatal treatment. In our case, the patient and her sister had Crigler-Najjar II and both had carried successful pregnancies earlier.We still don't know what concentration of unconjugated bilirubin is non neurotoxic for the fetus, but most of the evidence recommends maternal unconjugated bilirubin concentrations below 200 micro mol/l [11.7 mg%] and the molar ratio between unconjugated bilirubin and serum albumin below 50%.[1]

Management options are limited in Crigler-Najjar pregnancies. Some authors have administered phototherapy to mother in order to convert bilirubin to photoisomers of bilirubin which are more water soluble and hence, do not cross placenta and blood brain barrier to the same extent as unconjugated bilirubin.

Phenobarbitone has also been tried in patients of Crigler-Najjar as it causes induction of UGT1A1 activity, which increases bilirubin conjugation and decreases bilirubin levels in Gilbert and Crigler-Najjar II. The decline is more dramatic in Gilbert with almost complete normalization of bilirubin levels. In Crigler-Najjar II, the fall is usually more than 25%, but levels almost never normalize. Doses ranging from 30-60mg per day have been suggested to reach a balance between adequate dosing and minimization of teratogenic side effects. As our patient reported at 33 weeks, this was not a concern in our case.

Adjuvant calcium supplementation has been found to increase gut excretion of bilirubin and has been suggested as beneficial. We gave calcium in a dosage of 1gm per day to our patient as is given routinely in the antenatal period.

Our pregnancy was complicated by small for gestational age [SGA] fetus. There could be a multitude of reasons and we think malnutrition and poverty were important contributors in our case. We did not find a link between Crigler-Najjar II and SGA. However, Khandelwalet al. [2018] also reported SGA in Crigler-Najjar II.[5]

Conclusion

- Pregnancy in Crigler-Najjarsyndrome is rare, high risk and requires multidisciplinary input. We need to report all cases.
- Maternal serum bilirubin levels should be kept below 11.7mg% to minimize risk of kernicterus in baby.
- Phenobarbitone 60mg per day shows good response in decreasing hyperbilirubinemia.
- Follow up of baby in post natal period is required to rule out hyperbilirubinemia, monitoring of catch up growth and any evidence of kernicterus.

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Conflict of interest: None

Figure 1: Photograph of baby

Table 1: Investigation results

Investigation	Value
Blood Group	O RhD positive
Hemoglobin	10.3gm%
Total Leukocyte Count	14,200
Platelet Count	266,000
Total Serum Bilirubin Direct Indirect	14mg% 0.5mg% 13.5mg%
Blood urea	22mg%
Serum creatinine	0.4mg%
Blood picture	Microcytic Hypochromic anemia. No evidence of hemolysis
Serum Amylase	30 U/L
Serum Lipase	10 U/L
Ultrasonography	Single, live fetus, no apparent dysmorphology, Small for gestation, Normal Dopplers.

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