PREGNANCY OUTCOME IN MATERNAL CRIGLER-NAJJAR SYNDROME 1 AND 2: A CASE REPORT AND SYSTEMATIC REVIEW OF LITERATURE

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ABSTRACT

Background: Crigler-najjar syndrome is a rare inherited disorder of congenital unconjugated hyperbilirubinemia and few cases of CNS with pregnancy have been reported till date.

Objective: To report a case of maternal Crigler-Najjar syndrome in pregnancy. To review all the cases of CNS 1 and 2 reported in literature till date and evaluate maternal and fetal outcome in these cases.

Materials and Methods: PubMed and Google Scholar database was searched for case reports of CNS in pregnancy using key words: Crigler-Najjar syndrome and in pregnancy, phototherapy, phenobarbital and pregnancy, till 12th November 2017.

Results: A total of 21 pregnancies were reported in 15 patients of CNS (excluding our patient). Maternal- fetal outcome was favorable in most cases with appropriate treatment with phototherapy and low dose phenobarbital.

Conclusion: CNS is a rare cause of jaundice in pregnancy. Serum bilirubin levels should be kept below 10mg/dl by judicious treatment for optimal outcome.

KEYWORDS

Crigler-Najjar syndrome with Pregnancy, Phenobarbital, Phototherapy, Uridine diphosphate glucuronosyltransferase

Introduction

Crigler Najjar Syndrome type 1 (CNS 1)(OMIM# 218800) and type 2 (CNS 2) (OMIM#606785) are rare inherited disorders of defective bilirubin conjugation in hepatocytes leading to profound unconjugated hyperbilirubinemia in presence of normal liver enzymes. These are autosomal recessive conditions caused due to complete (type 1) or incomplete (type 2) deficiency of hepatic microsomal enzyme Uridine-diphosphate-glucuronosyltransferase (UDPGT). Maternal CNS is a rare condition and very few cases have been reported till date regarding pregnancy in these patients. We report a case of pregnancy with maternal CNS 2 managed in our center, with favorable maternal and neonatal outcome followed by a systematic review of all available case reports of CNS 1 and 2 in pregnancy, till date.

Material and Methods

We searched the PubMed and Google Scholar database for case reports of CNS in pregnancy (key words: Crigler-Najjar syndrome and in pregnancy). The search was carried on till 12th November 2017. After reviewing the reported options of treatment of CNS in pregnancy, we specifically searched for phenobarbital treatment in pregnancy (keywords: phototherapy, phenobarbital and pregnancy).

Case report

The patient was 27 year old primigravida, married for nine months. She was educated till matriculation. It was a non-consanguineous marriage. The patient herself was born out of a consanguineous marriage in second degree cousins. She presented to us for the first time at eleven weeks of gestation. She had history of jaundice since birth, for which she had never consulted any specialist. The family history was not significant. There was no history of congenital anomalies, mental retardation, neonatal or infant death or jaundice in the family. There was no history of jaundice in her siblings as well. She was worked up and investigated in consultation with gastroenterologists.

Investigations revealed unconjugated hyperbilirubinemia (total bilirubin = 13mg/dl, indirect=12.2mg/dl), normal liver enzymes and negative anti-HAV, HBsAg, anti HCV, anti HEV. Complete blood count including Reticulocyte count was normal and tests for hemolysis were negative. Coagulation profile was also within normal limits. Tests for autoimmune liver disease were all negative. Hepatobiliary scan was normal. Liver biopsy was deferred due to pregnancy.

She was followed up in specialized high risk pregnancy unit along with periodic gastroenterology consultations. Early anomaly scan done at 13 weeks, detailed level 2 ultrasound at 19 weeks, fetal echocardiography at 24 weeks of gestation were all normal. She was admitted at 38 weeks in view of term rupture of membranes and labor was induced with one dose of dinoprostone gel (0.5mg) followed by oxytocin infusion for twelve hours (as per institutional protocol). Cesarean section was done under spinal anesthesia in view of failed induction. She delivered a baby boy with birth weight of 2765gm and APGAR score of 9.9.9. Maternal serum bilirubin at the time of delivery was 9.6mg/dl. The infant was jaundiced at birth, with umbilical cord total bilirubin of 8.9 mg/dl. Jaundice resolved within first week of life with phototherapy for twelve hours (as per institutional protocol). She was followed up in specialized high risk nursery unit along with periodic neonatology consultations. Evoked potentials performed at one month of age were all normal. The baby has normal developmental milestones and there are no adverse sequelae of hyperbilirubinemia so far (the child is six months old now). On follow up, maternal bilirubin levels were in the range of 6-8mg/dl.
Discussion:
Maternal jaundice during pregnancy is a well-known risk factor for fetomaternal morbidity and mortality. There are various causes of jaundice in pregnancy, which may be peculiar to pregnancy or incidental to pregnancy. Acute Fatty liver, Idiopathic cholestasis, HELLP syndrome are the conditions occurring only during pregnancy. Infective diseases including Hepatitis A,B,C, E are also seen in pregnant women, with added risks and complications. Autoimmune conditions causing jaundice include Autoimmune hepatitis and Primary biliary cirrhosis. Although rare, other conditions causing jaundice which may be seen during pregnancy are alcoholic liver disease, Wilson’s disease, hemochromatosis, neoplastic disorders etc. even rarer causes are inherited hyperbilirubinemias in pregnancy.

There are various complications which can occur in pregnancy due to jaundice. Maternal complications are hepatic decompensation and acute liver failure, hepatic encephalopathy, increased risk of life threatening varicel hemorrhage, especially during labor, post partum hemorrhage and increased maternal mortality. Fetal complications are increased risk of spontaneous abortions, preterm labor, vertical transmission (Hepatitis B and C), meconium staining of liquor, low birth weight and increased perinatal morbidity and mortality.

We have reported an extremely rare cause of jaundice in pregnancy, Crigler Najjar syndrome type 2, which is an inherited disorder of unconjugated hyperbilirubinemia.

Inherited disorders of congenital hyperbilirubinemia may be caused by increased bilirubin production or decreased bilirubin clearance. Decreased hepatic bilirubin clearance can be due to defective 1) unconjugated bilirubin uptake and intrahepatic storage, 2) conjugation of glucuronic acid to bilirubin (e.g. Gilbert syndrome, Crigler-Najjar syndrome, Lucey-Driscoll syndrome, breast milk jaundice), 3) bilirubin excretion into bile (Dubin-Johnson syndrome), or 4) conjugated bilirubin re-uptake (Rotor syndrome).

Bilirubin is converted to water soluble bilirubin mono- and diglucuronic acid in the smooth endoplasmic reticulum of the hepatocytes by the conjugating enzyme, uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1). Inherited disorders of conjugation are primarily due to alterations in the UGT1A1 gene, resulting in decreased or absent enzyme expression and function.

In 1952, Crigler and Najjar (1) described the most lethal form of unconjugated hyperbilirubinemia, CN syndrome type I, which is characterized by absent or nearly absent UGT1A1 enzyme activity (2). CN syndromes are inherited in an autosomal recessive manner and patients are either homozygotes or compound heterozygotes. Mutations in CN syndrome type I consist of either premature truncation or deletion of key amino acid sequences on any of the five exons of the UGT1A1 gene (3). CN syndrome type I typically presents immediately after birth with serum bilirubin levels greater than 20 to 50 mg/dL. Due to complete absence of enzyme activity, it is associated with bilirubin encephalopathy and death unless treated with phototherapy and exchange transfusions in the neonatal period (4). The risk for kernicterus persists into adult life (5).  Definitive diagnosis of CN 1 is by gene analysis and sequencing the coding region for known mutations in liver biopsy sample. Management in the neonatal period consists of aggressive phototherapy and frequent exchange transfusions to keep bilirubin levels below the threshold for kernicterus. Definitive treatment is liver transplantation, gene therapy may be considered as a therapeutic option for these patients in future. Crigler-Najjar syndrome type II (CN II, also called Arias syndrome) was described by Arias in 1962 (6). CN II is characterized by reduced (not absent) UGT1A1 enzyme activity (<10% of normal). The genetic defect in CN syndrome type II is usually a point mutation, hence reducing but not eliminating enzyme activity (3). The patient presents with unconjugated hyperbilirubinemia within the first few days of life, but total bilirubin levels usually do not exceed 20 mg/dL. Kernicterus is rare. In adults, intercurrent illness may lead to temporary rise in bilirubin levels. CN II can be clinically distinguished from CN I by lower levels of bilirubin (usually less than 20 mg/dL), and a decrease in serum bilirubin levels by more than 30% after treatment with phenobarbital (7). Patients respond to phototherapy in newborn period and occasionally phenobarbital therapy. Usually the prognosis remains favorable.

Table 1: Review of case reports of CNS1 and 2 with maternal and fetal outcome

<table>
<thead>
<tr>
<th>Reference</th>
<th>CN type</th>
<th>Maternal age (years)</th>
<th>Maternal bilirubin during pregnancy (mg/dl)</th>
<th>Maternal bilirubin at delivery (mg/dl)</th>
<th>Cord bilirubin (CB) or D1 bilirubin (mg/dl)</th>
<th>Maternal treatment (Phototherapy(Pb),Photorheolytic therapy (PT))</th>
<th>Mode of delivery</th>
<th>Maternal Complications</th>
<th>Gestational delivery</th>
<th>Birth weight (grams)</th>
<th>Sex of baby</th>
<th>Newborn treatment</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cahill 1989(11)</td>
<td>2</td>
<td>23</td>
<td>10.4-10.7</td>
<td>6.1</td>
<td>7.1 D1</td>
<td>Pb</td>
<td>Induced</td>
<td>None</td>
<td>Term</td>
<td>3900</td>
<td>Female</td>
<td>PT</td>
<td>Healthy</td>
</tr>
<tr>
<td>Taylor 1991(12)</td>
<td>1</td>
<td>21</td>
<td>21.27</td>
<td>25</td>
<td>24CB</td>
<td>None</td>
<td>CS</td>
<td>None</td>
<td>Term</td>
<td>4130</td>
<td>NA</td>
<td>PT</td>
<td>Quadruplegic at 18 months</td>
</tr>
<tr>
<td>Smith 1994(13)</td>
<td>2</td>
<td>23</td>
<td>5.3-9.6</td>
<td>8.8</td>
<td>7.6 CB</td>
<td>None</td>
<td>Spontaneous</td>
<td>None</td>
<td>Term</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>Bo 2000(14)</td>
<td>2</td>
<td>30</td>
<td>7.0</td>
<td>3.2-6.8</td>
<td>4.4-6.8</td>
<td>NA</td>
<td>NA</td>
<td>3.8-5.5</td>
<td>NA</td>
<td>none</td>
<td>PT + Pb</td>
<td>PT + Pb</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Holstom 2005(15)</td>
<td>2</td>
<td>28</td>
<td>4.2-5.4</td>
<td>4.2-5.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.2-5.4</td>
<td>NA</td>
<td>PT + Pb</td>
<td>Pb</td>
<td>Pb</td>
<td>None</td>
</tr>
<tr>
<td>Saxena 2005(17)</td>
<td>2</td>
<td>24</td>
<td>7.6</td>
<td>8.1</td>
<td>10.2 D1</td>
<td>NA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Spontaneous</td>
<td>None</td>
<td>None</td>
<td>Term</td>
</tr>
<tr>
<td>Gagdos 2006(18)</td>
<td>1</td>
<td>28</td>
<td>13.5-16.4</td>
<td>14.2</td>
<td>13CB</td>
<td>PT and albumin</td>
<td>CS</td>
<td>None</td>
<td>Term</td>
<td>5760</td>
<td>Female</td>
<td>PT</td>
<td>Healthy</td>
</tr>
</tbody>
</table>
CNS I and II are rare diseases with only few hundred cases described in the literature. The incidence is estimated to be 1 in 1,000,000 births. There is no particular racial or gender predisposition (8). As such, the exact prevalence in pregnancy is not known. We searched the PubMed and Google Scholar databases using the above mentioned keywords, and we found a total of twenty one pregnancies reported in fifteen patients of CNS (excluding our patient) (11-25) (Table 1). Out of these, there are four pregnancies in four patients of CNS 1 and seventeen pregnancies in eleven patients of CNS 2. Due to severity of the disease and the risk of congenital malformations, the only definite therapy, early death is almost inevitable with CNS I, as such, very few patients reach the reproductive age and to date, only four cases of pregnancy in CNS 1 patients have been reported.

The main fetal risk during pregnancy in CNS patients is the risk of fetal kernicterus and the maternal risk is that of rising bilirubin levels due to stress of pregnancy. Raised levels of unconjugated bilirubin cross the placental barrier by passive diffusion, hence the developing fetus is at increased risk of bilirubin-induced neuronal degeneration leading to permanent neurologic damage leading to ataxia, deafness, spasticity, mental retardation, choreoathetosis, seizure and even death (9).

As is well known, chronic liver disease in women is associated with poorer reproductive outcome in terms of infertility and adverse pregnancy outcomes, including stillbirth, miscarriage, fewer live births, and gestational diabetes(10). But, conclusions based on findings in acute and chronic liver disease cannot be extrapolated to unconjugated hyperbilirubinaemia without other features of liver disease. As mentioned in Table 1, in most of the cases reported in CNS in pregnancy, there was no mention of difficult or assisted conception or subfertility. In fact, few authors have reported two or more pregnancies in their patients(14,15,17,22).

As expected, maternal serum bilirubin levels are much higher in patients with CNS 1 and there is no benefit of phenobarbital therapy. These patients have been treated with phototherapy, the intensity and duration of which was increased during pregnancy. Phototherapy acts by converting a portion of bilirubin to a water soluble isomer, which is then excreted in bile. Usually CNS 1 patients need 12-16hrs per day of phototherapy for lowering serum bilirubin levels(22). Albumin infusions have been used during pregnancy to keep the free unconjugated fraction of serum bilirubin as low as possible. Gajdos et al (18) performed albumin infusions every 2 weeks (1 g/kg body weight in 3 h) along with phototherapy to lower prepregnancy serum bilirubin levels of 23.5mg/dl to 15.3-16.5mg/dl. However, Hannam et al (19) reported no fall in bilirubin levels in their patient with fortnightly albumin infusions.

On the other hand, patients with CNS 2 respond to the low dose phototherapy. Most patients use daily phototherapy (for 1-3hrs/day) alone or in combination with photobarbital (25-100mg/day)(22). The concern with photobarbital use in pregnancy is the risk of congenital malformations. A recent Cochrane review(26) concluded higher risk of malformation in children born to women taking phenobarbital for epilepsy than children born to women without epilepsy (N = 345 vs 1591, RR 2.84, 95% CI 1.57 to 5.13), but the dose used for treatment of epilepsy is much higher (750-1500 mg/day). None of the authors have reported any malformation in the babies born to women with CNS 2 using phenobarbital in lower doses (usually 30-60mg/day).

Jaundice in pregnancy is associated with preterm labour and low birth weight. However, all the reported cases of CNS 1 and CNS 2 delivered at term (more than 36weeks). In fact, some of the patients presented at term, having received no treatment for CNS during pregnancy and some patients had induction of labor due to postdated pregnancy. All the patients delivered uneventfully, caesarean section being done for obstetric indications. There was no reported antepartum, intrapartum or postpartum complication, including PPH. The birth weights were within normal limits with no evidence of fetal growth restriction except in one of the women with CNS I(19).

The high levels of unconjugated bilirubin in patients with CNS can cross the placenta. As such, fetal unconjugated bilirubin levels at birth (reflected by cord blood bilirubin and day 1 serum bilirubin) are roughly equivalent to those found in their mothers at time of delivery. These levels fell with time, either without any treatment, or phototherapy alone or in combination with phenobarbital. In few instances, exchange transfusion was needed to reduce the toxic levels of unconjugated bilirubin. As can be seen, no neurological damage was detected in the neonate, neither at birth, nor during follow up except one patient. The one exception was a CNS 1 patient reported by Taylor et al (12). The woman previously had three first trimester MTPs for social reasons and a spontaneous abortion at 8weeks when she had a bilirubin level of 27mg/dl. This patient never received any treatment for hyperbilirubinemia and the high serum levels of unconjugated bilirubin led to quadriplegia of the neonate.

At present, since there are no studies to determine exactly what level of unconjugated bilirubin is non-neurotoxic for the developing fetus, but it seems reasonable to try to keep the maternal (and hence, fetal) unconjugated bilirubin concentrations below 10mg/dl, as we see from the review of literature, there was no fetal affection in the patients with bilirubin levels less than 15mg/dl. The standard guidelines for management of neonatal hyperbilirubinemia recommend initiation of phototherapy at total serum bilirubin level more than 9mg/dl and exchange transfusion above 19mg/dl in low risk term neonates. The corresponding bilirubin levels for high risk and preterm neonates are 5mg/dl and 15mg/dl for phototherapy and exchange transfusion respectively (27).

As discussed above, treatment of CNS 1 comprises primarily of daily phototherapy. In case of acute hyperbilirubinemia, exchange transfusion may be needed. Definitive therapy is liver transplantation. Phenobarbital in enzyme inducing dose is beneficial in CNS 2 patients. The dose of phenobarbital in non pregnant patients is 3-5 mg/kg/day titrated preferably to 60-180 mg/ day in single or divided doses. The dose is reduced further (30-60 mg/ day) in pregnancy to avoid its teratogenic side effects. The response to phenobarbital therapy is usually seen within two to three weeks. It is advised to avoid drugs that displace bilirubin from albumin like penicillin, sulphonamides, salicylates, ceftriaxone and furosemide (28). Another drug which is beneficial in CNS 2 with similar efficacy and fewer adverse effects is clofibrate (2 g/ day), but it is contraindicated in pregnancy (28). Adjuvant daily oral calcium supplementation has been found to increase the enteric excretion of bilirubin (29). Recently, a patient with

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### Table 1

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Case(s)</th>
<th>Gestation</th>
<th>Birth Weight</th>
<th>Mode of Delivery</th>
<th>Maternal Serum Bilirubin (mg/dl)</th>
<th>Neonatal Serum Bilirubin (mg/dl)</th>
<th>Neonatal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannam et al (19)</td>
<td>2009</td>
<td>1</td>
<td>Term</td>
<td>Term</td>
<td>CS</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>Passuello et al (20)</td>
<td>2009</td>
<td>2</td>
<td>Term</td>
<td>Term</td>
<td>PT</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>Azor et al (21)</td>
<td>2009</td>
<td>2</td>
<td>Term</td>
<td>Term</td>
<td>PT and albumin</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>Wilson (22)</td>
<td>2012</td>
<td>2</td>
<td>Term</td>
<td>Term</td>
<td>PT</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
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<tr>
<td>Hansel et al (23)</td>
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<td>1</td>
<td>Term</td>
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<td>PT</td>
<td>None</td>
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<tr>
<td>Chaudhary et al (24)</td>
<td>2014</td>
<td>2</td>
<td>Term</td>
<td>Term</td>
<td>PT</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>Chauabal (25)</td>
<td>2016</td>
<td>2</td>
<td>Term</td>
<td>Term</td>
<td>PT</td>
<td>None</td>
<td>None</td>
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</table>

---

### Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Neonatal Serum Bilirubin (mg/dl)</th>
<th>Neonatal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>Healthy</td>
</tr>
</tbody>
</table>

---

### Table 3

<table>
<thead>
<tr>
<th>CNS 1</th>
<th>CNS 2</th>
<th>Bilirubin Levels</th>
<th>Neonatal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Healthy</td>
</tr>
</tbody>
</table>
CNS 1 was successfully treated with hepatic progenitor cell transplantation (30).

Regarding the prenatal diagnosis, it is not possible to do enzymatic diagnosis in chorionic villi or amniocytes as UGT is not active in these tissues. The cloning of the UGT1 gene and the identification of disease-causing mutations has led to the possibility of performing DNA based diagnosis. Prenatal diagnosis of CNS 1 in two Tunisian families has been reported in literature in which mutations in families were known (31).

Conclusion

Since there are few reports of pregnancy in CNS patients, Wilson et al (22) in 2013 had formulated some recommendations for pregnancy in CNS based on then available literature. Keeping in view these recommendations, newer case reports and our analysis of available literature, we conclude that:

• CNS is a rare cause of jaundice in pregnancy. CNS 1 is the more severe form; hence these patients are rarely seen till reproductive age. CNS 2 is less severe and responsive to medical therapy, hence the patients are seen to attain reproductive age and there are more case reports of pregnancy in CNS 2 patients.

• Unlike other causes of liver disease, CNS does not appear to cause subfertility or increased risk of abortions.

• If the patient presents before pregnancy, genetic and preconception counseling should be done. Phototherapy and phenobarbital therapy should be adjusted to lower the serum bilirubin levels.

• Usually the pregnancy is uncomplicated with no increased risk of maternal complications.

• There is no increase in incidence of preterm labor and low birth weight infants.

• Pregnancy should be managed in high risk pregnancy unit of a well-equipped tertiary care center with frequent gastroenterology consultations.

• Prenatal diagnosis may be offered if the mutation in parents is known.

• Serum bilirubin levels should be kept below 10 mg/dl by judicious use of phototherapy and low dose phenobarbital.

• The neonate should be examined for bilirubin encephalopathy and phototherapy and exchange transfusions may be needed.

• The infant should be monitored carefully for development milestones and tests for brainstem function especially for hearing must be done.

• The maternal and fetal outcome is usually favorable if the bilirubin levels are kept below the toxic levels.

REFERENCES


