Dubin Johnson Syndrome and the Enigma Surrounding Conjugated Hyperbilirubinemia in Pregnancy: A Case Report

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1. ABSTRACT

1.1. Aim and Background: Jaundice in pregnancy is an uncommon condition. The aim is to diagnose a rare congenital hepatic disorder- Dubin Johnson Syndrome and elucidate an algorithm to arrive at it thus sensitizing the readers to unconventional diagnoses encountered while dealing with a case of jaundice in pregnancy.

1.2. Case Description: We present the case of a 27-year-old antenatal patient with unexplained conjugated hyperbilirubinemia exacerbating with every pregnancy in whom a set of comprehensive albeit feasible clinical tests helped to conclusively settle at the diagnosis of DJS.

1.3. Conclusion: More often benign than not, DJS is a rare entity with no risk of fibrosis progression, cirrhosis or adverse perinatal outcomes.

1.4. Clinical Significance: It is imperative to diagnose DJS not only to differentiate it from other pre-existing or concurrent hepatic disorders in pregnancy considerably impacting management strategies and foetal-maternal outcomes but also to reassure the patient of its benign course, an essential element of good clinical practice.

1.5. Keywords: Dubin johnson syndrome; Jaundice in pregnancy; Liver disease in pregnancy; Hyperbilirubinemia; Case report

2. INTRODUCTION

Jaundice, also known as hyperbilirubinemia, is defined as a yellow discoloration of the body tissue resulting from the accumulation of excess bilirubin. Hyperemesis gravidarum, gallstones and pregnancy related diseases such as HELLP or IHCP remain the most frequently encountered causes of hyperbilirubinemia in the first,

second and third trimesters of pregnancy respectively. Adverse foetal outcomes corelate with the severity of underlying disease.

Elevation of conjugated bilirubin in a concentration higher than 20% of total bilirubin or a concentration higher than 2 mg/dL is considered pathological. In the absence of disabling symptoms, clinicians usually ignore the possibility of a rare, chronic, benign hereditary disorder unless various factors (pregnancy in this case) accentuate hyperbilirubinemia producing clinical jaundice for which medical attention is sought. We report a case of Dubin Johnson Syndrome where the diagnosis was arrived at differentially by ruling out other causes of congenital hyperbilirubinemia in the absence of more typical clinical tests.

3. CASE DESCRIPTION

Our patient was a 27-year-old, fourth gravida with three living issues referred to our hospital at 36 weeks of gestation with isolated direct hyperbilirubinemia. She reported yellowish discoloration of skin and sclera with the onset of the second trimester but seemed quite nonchalant about it as she recalled a similar onset and subsequent resolution of jaundice postpartum in all her prior pregnancies.

The patient had no complaints of nausea, vomiting, abdominal pain, recent fever or itching all over. There was no change in urine or stool colour, odour or consistency. She denied any outside food intake, habitual alcohol or other illicit drug consumption. Though unfavourable, history of any prior surgical illnesses, blood transfusions and family history of liver disorders and/or jaundice was sought after.

General examination revealed scleral icterus. She was normotensive. Systemic examination was unremarkable. Per abdomen, fundal height corresponded to 32 weeks gestation, denoting a component of foetal growth restriction.

Her total and direct bilirubin levels on admission were 4.2 mg% and 3.6 mg% respectively (lab upper limit 1 mg% and 0.5 mg%) indicating a predominantly conjugated hyperbilirubinemia. Liver transaminases and peak bile acid concentrations were normal thus ruling out intra-hepatic cholestasis of pregnancy. Absence of proteinuria, normal platelet counts, serum creatinine and uric acid along with a normal blood pressure precluded any possibility of Hypertensive disorders of pregnancy and its sequalae (HELLP). A hemogram revealed mild anaemia (Hb- 9.3 g%) and peripheral smear was unremarkable apart from mild aniso-microcytosis and hypochromia. Absence of schistocytes eliminated the possibility of haemolysis and thrombotic microangiopathies. Bearing in mind the possibility of unconjugated or mixed hyperbilirubinemias, a reticulocyte count, serum lactate dehydrogenase levels and direct and indirect coombs test were performed, all of which were negative for the same. To ascertain the etiology of direct hyperbilirubinemia, viral hepatic markers were sent. Any active focus of viral hepatitis was ruled out. Serum gamma glutamyl transferase levels were 10 IU/L (normal range: 5-27 IU/L) thus obviating any obstructive causes of jaundice. This was further backed by an abdominal ultrasound and a hepatoportal doppler which showed a normal liver echotexture, normal colour flow in hepatic veins, cholelithiasis (calculi sized 9 mm) without cholecystitis.

Perplexed with the unknown origin of elevated direct bilirubin levels, a gastroenterology consult was sought. Anti-nuclear and anti-dsDNA antibodies were negative. Levels of anti-mitochondrial and anti-smooth muscle antibody were also within the normal range thus ruling out autoimmune hepatitis (primary biliary cholangitis). A magnetic resonance cholangiopancreatography with gadolinium contrast was advised post-delivery to look for

any abnormality in the biliary tree. Meanwhile, the patient was started on tablet Ursodeoxycholic acid 300 mg thrice daily.

The pregnancy was monitored with biweekly monitoring of liver function tests, biweekly non stress test and weekly obstetric doppler along with adequate hydration and strict temperature charting. The patient went into spontaneous labour and an emergency lower segment caesarean section was performed in view of her prior caesarean section with a short inter-conception period (13 months). She opted for a temporary method of contraception. She delivered a female child weighing 2.1 kg with an APGAR of 9/10 at 1 and 5 minutes. Intra-operatively, the liver appeared grossly black in colour and had a smooth texture. This clinched the diagnosis to a rare inherited disorder-Dubin Johnson syndrome.

The patient was counselled regarding the benign nature of this disease and cautioned about its exacerbation in her subsequent pregnancies, intervening illnesses or with the use of oral contraceptive pills.

3. DISCUSSION

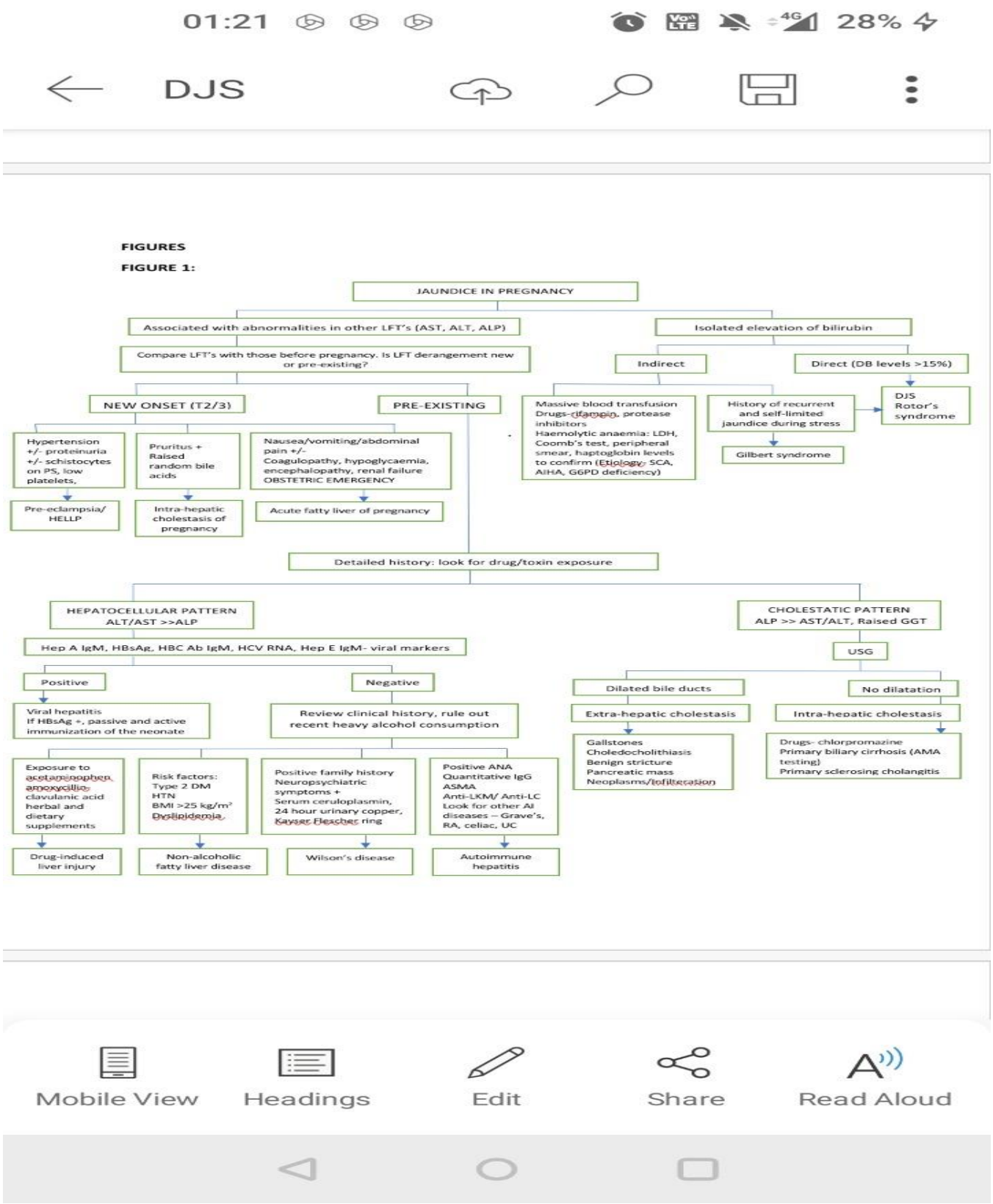
The various liver disorders transpiring in pregnancy [1] are listed in Table 1.

The primary goal should be to arrive at the most probable diagnosis *via* thorough history taking, physical examination, relevant biochemical, serological and radiological investigations before resorting to more invasive tests. Disorders pertinent to pregnancy might require immediate termination of pregnancy, sometimes posing a substantial risk of prematurity to the foetus. Some may be managed conservatively; others may necessitate initiation of medical therapy or require surgical interventions. A diagnostic algorithm to arrive at a diagnosis of inherited hyperbilirubinemias whilst excluding other plausible liver disorders is depicted in Figure 1.

Table 1: Spectrum of Liver Disorders in Pregnancy.

<table>
<tr><th rowspan="2">LIVER DISEASES UNIQUE TO PREGNANCY</th><th colspan="2">PREGNANCY UNRELATED LIVER DISEASES</th></tr>
<tr><th>Pre-existing/primary liver disease</th><th>Diseases co-incident with pregnancy</th></tr>
<tr><td>Hyperemesis gravidarum</td><td>Hepatitis B and C</td><td>Acute viral hepatitis (A and E)</td></tr>
<tr><td>Hypertensive disorders of pregnancy including HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets)</td><td>Non-alcoholic fatty liver disease (NAFLD)</td><td>Extra-hepatic cholestasis i.e. biliary disorders (cholelithiasis, choledocolithiasis, strictures, bile duct atresia, neoplasms)</td></tr>
<tr><td>Intra-hepatic cholestasis of pregnancy (IHCP)</td><td>Cirrhosis and portal hypertension</td><td>Drug induced/ toxin-mediated hepatitis</td></tr>
<tr><td rowspan="5">Acute fatty liver of pregnancy (AFLP)</td><td>Auto-immune liver disease</td><td>Ischaemic hepatitis</td></tr>
<tr><td>Wilson’s disease</td><td>Budd Chiari syndrome</td></tr>
<tr><td>Post liver transplantation state</td><td rowspan="3">Sepsis</td></tr>
<tr><td>Neoplasms</td></tr>
<tr><td>Inherited hyperbilirubinemias</td></tr>
</table>

FIGURE 1:



Hereditary hyperbilirubinemias are a rare group of disorders with an autosomal recessive pattern of inheritance constituting 4 main entities - Gilbert syndrome (decreased glucuronidation of bilirubin leading to a

predominantly unconjugated hyperbilirubinemia, Crigglar-Najar Syndrome (a potentially life-threatening disease in new-borns caused by absent or decreased levels of UDP-glucuronosyltransferase (UGT) enzyme), Dubin Johnson and Rotor syndromes.

DJS is characterized by a genetic mutation in the ATP Binding Cassette subfamily C (ABCC2) gene encoding the multi-drug-resistant protein-2 (MRP-2) responsible for active transport of conjugated bilirubin into the bile via the canalicular membrane [2]. Rotor syndrome typically causes mixed hyperbilirubinemia due to homozygous mutations in the SLCO1B1 and SLCO1B3 genes coding for organic anion uptake transporter proteins impairing hepatic uptake and storage of bilirubin which subsequently leaks into plasma. Genetic testing is best reserved for the purpose of large-scale scientific studies or trials. Additionally, liver biopsy would reveal an intra-cytoplasmic coarse brown pigment within the hepatocytes that stains black with Masson Fontana stain and is negative for Perl stain and Periodic acid Schiff stain [3]. However, it comes with its own set of complications including pain, intra-peritoneal bleed, intra-hepatic or subcapsular haematomas, haemobilia, bile peritonitis and cardiovascular complications in patients with pre-existing heart diseases [4].

It is pivotal to weigh the risk versus benefit ratio for any given clinical test and is best to avoid it if it does not aid in improving patient outcomes [5]. For these disorders not leading to any significant adverse perinatal outcomes, most patients in developing countries such as India, are unwilling for invasive tests and cannot afford genetic testing. Urinary coproporphyrin levels which are substantially increased in Rotors syndrome may also be used to demarcate the two, however these tests are not easily available commercially. The usual onset of disease in the second decade of life along with the classic black appearance of liver on gross examination (intra-operatively) and slightly reduced prothrombin activity tilted the diagnosis in favour of Dubin Johnson syndrome in our case.

Pre-conceptional genetic counselling and pre-implantation genetic screening could intercept and prevent spread of this inherited disorder to future off-springs however, the cost and feasibility of these tests remain questionable.

4. CONCLUSION

Patient counselling and reassurance regarding unaffected pregnancy outcomes and unwarranted drug treatment in cases of DJS is of paramount importance. A team approach often involving a gastroenterologist is crucial in managing such cases. We recommend future studies and formulation of a standardised protocol to diagnose DJS differentially based on clinical experience in a cost-effective way without resorting to more invasive testing.

5. CLINICAL SIGNIFICANCE

The essence of reporting this case lies in eliminating the various hepatobiliary disorders that may harm the mother and the foetus despite being potentially treatable to arrive at a diagnosis of other rare albeit innocuous disorders such as DJS.

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