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REVIEWS

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Gilbert's syndrome diagnosis in a pregnant woman: a case report

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary Gilbert's syndrome is a hereditary disease with raised levels of unconjugated bilirubin. The disorder is generally asymptomatic and often misdiagnosed, which can lead to unnecessary anxiety in patients, particularly during pregnancy. There is a case report of a 24-year-old pregnant woman with jaundice and elevated bilirubin levels without any history of hyperbilirubinaemia. Diagnosis of Gilbert's syndrome was made according to the patient's clinical features and laboratory results after ruling out other diseases. The patient was reassured that Gilbert's syndrome posed no significant risk to her or the foetus, and appropriate surveillance and management were provided. Accurate diagnosis is essential to alleviate worries and confirm appropriate management. Healthcare providers should consider Gilbert's syndrome as a potential cause of hyperbilirubinaemia in pregnant women and impact reassurance regarding the promising prognosis and normal life expectancy. This case emphasises the significance of considering Gilbert's syndrome in a differential diagnosis of hyperbilirubinaemia in pregnancy.
Key words: Gilbert Disease, hyperbilirubinemia, pregnancy, diagnosis.

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Background

Gilbert's syndrome is an autosomal dominant disorder with incomplete penetrance characterised primarily by mild unconjugated hyperbilirubinaemia without hepatocellular disease or haemolysis. Gilbert's syndrome was first identified in 1901 by Augustin Gilbert and Pierre Lelebre. More than 90% of the bilirubin in bile is regularly present in the form of glucuronide derivatives. The glucuronidation process that is responsible for conjugating bilirubin is regulated by uridine diphosphate glucuronosyltransferase (UGT), which is decreased to 30% of normal activity in patients with Gilbert's syndrome. As a result, patients with Gilbert's syndrome have a 70% reduction in their liver's ability to conjugate bilirubin, leading to an increase in serum levels of unconjugated bilirubin [1].

Gilbert's syndrome results from a homozygous UGT1A1 mutation and the inheritance can occur through either autosomal dominant or autosomal recessive patterns. Crigler Najjar syndrome type 2, characterized by a mutation in UGT1A1 (UGT1A1 enzyme activity < 10%), follows an autosomal recessive pattern and responds well to phenobarbital. Genetic counselling isn't typically required for Gilbert's syndrome, as it does not affect life expectancy. In cases where a missense mutation in the UGT1A1 gene causes Gilbert's syndrome, it is inherited as autosomal dominant and causes enzyme function impairment, often seen more in Asian populations. Additionally, if the gene's promoter region is affected, it is inherited as autosomal recessive, leading to altered enzyme production, which is more common in Caucasians [2, 3].

Gilbert's syndrome affects up to 10% of the population and can also result in hyperbilirubinaemia. Gilbert's syndrome, a disorder of diminished bilirubin digestion system due to a homozygous UGT1A1 mutation, can also cause mild hyperbilirubinaemia [4]. Unfortunately, Gilbert's syndrome is often ignored and misdiagnosed by physicians, which can cause anxiety among patients, especially pregnant women who may worry about the impact of the condition on their pregnancy outcomes [5].

This case presentation is being reported due to the rarity of the diagnosis and the missed diagnosis of Gilbert's syndrome during pregnancy. An accurate diagnosis could alleviate the concerns of pregnant women and save time and money for the healthcare system.

Case presentation

A 24-year-old pregnant woman was referred to a rural primary healthcare facility for routine antenatal care during her 11th week of gestation. This was her first pregnancy, and she reported no major complaints such as fever, nausea, vomiting, abdominal pain or changes in defecation habits. However, upon physical inspection, her sclera was found to be icteric. She did not have a family history of any disease. When the physician asked her, she claimed that her jaundice deteriorated sometimes, especially when fasting. Her blood pressure was within normal limits, and abdominal examination revealed no organomegaly, tenderness or rebound tenderness. Foetal heart rate was normal, and abdominopelvic sonography showed normal features. Abdominopelvic and hepatobiliary system ultrasonography did not reveal any abnormalities.

A serum test was performed on the patient, and the results are shown in Table 1. Liver function tests were normal, and tests for infections such as Hepatitis B, Hepatitis C and Human Immunodeficiency Virus were non-reactive. Fast blood sugar, Haemoglobin A_{1C}, urine analysis and renal function tests were also normal. However, the patient's total and direct bilirubin levels were increased (1.68 and 0.71 mg/dl, respectively). Repeat testing after one week showed a total bilirubin level of 2.18 mg/dl and a direct bilirubin level of 0.98 mg/dl. Based on the patient's symptoms of jaundice, deterioration by fasting and normal serum liver enzyme levels, Gilbert's syndrome was diagnosed. An

internal medicine specialist was consulted to assist the patient in reducing concerns about pregnancy outcomes and foetal health.

The patient was followed from pregnancy until childbirth. She did not have any abdominal pain or jaundice, and all prenatal ultrasonographic results were normal. She gave birth to a healthy, full-term baby without any complications. The newborn underwent a physical examination at birth and throughout the first week, which showed no abnormalities or jaundice, and was also successfully breastfeeding.

Table 1. Results of serum tests in the patient

Serum test	Patient's value	Unit	Normal range	Measurement technique	Company
White blood cell (WBC)	9.4	mg/dl	4–10	BT1500	Faramad Parsian, made in Italy
Red blood cell (RBC)	5.25	mg/dl	4–5.2	BT1500	Faramad Parsian, made in Italy
Haemoglobin (HBG)	15.8	mg/dl	11.5–16	BT1500	Faramad Parsian, made in Italy
Mean corpuscular volume (MCV)	87	mg/dl	78–100	BT1500	Faramad Parsian, made in Italy
Platelets	276 000	mg/dl	150 000–450 000	BT1500	Faramad Parsian, made in Italy
Total bilirubin	1.68 2.18	mg/dl	0.1–1.2	BT1500	Faramad Parsian, made in Italy
Direct bilirubin	0.71 0.98	mg/dl	0–0.4	BT1500	Faramad Parsian, made in Italy
Serum creatinine	0.67	mg/dl	0.6–1.3	BT1500	Faramad Parsian, made in Italy
Blood urea nitrogen (BUN)	20	mg/dl	19–44	BT1500	Faramad Parsian, made in Italy
Fasting blood sugar (FBS)	79	mg/dl	70–99	BT1500	Faramad Parsian, made in Italy
Glycated haemoglobin test (HbA_{1C})	5.4	mmol/mol	below 5.7%	BT1500	Faramad Parsian, made in Italy
AST(SGOT)	18	U/l	1–31	BT1500	Faramad Parsian, made in Italy
ALT(SGPT)	7	U/l	1–31	BT1500	Faramad Parsian, made in Italy
Alkaline phosphatase (ALP)	106	U/l	70–260	BT1500	Faramad Parsian, made in Italy
Blood group (BG & RH)	A positive			BT1500	Faramad Parsian, made in Italy
Hepatitis B surface antigen (HBsAg)	negative			ELISA reader STAT FAX 4700	USA
Human Immunodeficiency Virus Antibody (HIV Ab)	negative			ELISA reader STAT FAX 4700	USA
Hepatitis C antibodies (Anti HCV)	negative			ELISA reader STAT FAX 4700	USA
Thyroid stimulating hormone (TSH)	2.36	microIU/ml	0.39–6.1	ELISA reader STAT FAX 4700	USA
Venereal disease research laboratory test (VDRL)	negative				
Urine analysis (UA)	normal				
Urine culture (UC)	negative				

Table 2. Differential diagnosis of hyperbilirubinaemia in pregnancy

Condition	Diagnostic tests	Prognosis	Management
Gilbert's syndrome	Clinical evaluation, serum bilirubin levels, genetic testing (optional)	excellent, benign	Supportive care
Early-onset intrahepatic cholestasis of pregnancy (ICP)	Serum bile acid levels, liver function tests, exclude other causes, ultrasound of liver and gallbladder (optional), genetic testing (optional)	Variable, risk to the foetus, depends on gestational age and severity of ICP	Ursodeoxycholic acid (UDCA), monitoring foetal wellbeing
Crigler-Najjar syndrome	Serum bilirubin levels, genetic testing	Requires lifelong management, may lead to kernicterus	Phototherapy, liver transplantation
Haemolysis disorders	Haemolysis markers, blood smear, genetic testing	Variable depends on underlying condition	Treatment of underlying cause
Hepatitis	Serology tests, liver biopsy, Polymerase Chain Reaction (PCR) for viral RNA	Variable, risk to foetus and mother	Monitoring, antiviral therapy
Cholestasis of pregnancy	Liver function tests, serum bile acid levels, exclude other causes, ultrasound of liver and gallbladder (optional), genetic testing (optional)	Variable, risk to the foetus, improves after delivery	Ursodeoxycholic acid (UDCA), Monitoring foetal wellbeing

Discussion

Gilbert's syndrome is a disorder that affects 5% to 10% of adults and is typically harmless. Individuals affected by this syndrome have mild indirect bilirubinaemia, which can be exacerbated by fasting despite liver function tests remaining normal. The condition is caused by decreased activity of glucuronosyltransferase 1A1 (UGT 1A1). Gilbert's syndrome is associated with a missense mutation in the coding area of the UGT 1A1 gene, causing a G71R mutation that replaces glycine with arginine at position 71 of the corresponding protein product [6]. These mutations result in elevated serum bilirubin levels without causing any other significant symptoms. In Caucasians and Africans, most individuals are homozygous for UGT1A128, while in Japanese, Chinese and Korean populations, UGT1A16 mutation in a homozygous state causes Gilbert's syndrome [7].

Although Gilbert's syndrome is present in 7% of the general population and is more commonly seen in men than women at a ratio of 2–7:1. It is rarely diagnosed before puberty, and birth defects and hormonal changes during puberty have been proposed as possible explanations for this. Dehydration, fasting or stress can cause episodes of Gilbert's syndrome. Bilirubin is an endogenous antioxidant, and hyperbilirubinaemia associated with this condition is typically mild and less than 6 mg/dl [8].

Research by Hemmati et al. has shown that the ratio of males to females with Gilbert's syndrome in Fars province, Iran, was 2:1, Gilbert's syndrome is prevalent in Iran likely due to higher rate of consanguineous marriage, screening method (rifampin test), and increased genetic susceptibility in the Iranian population [9].

Around 30% of patients with Gilbert's syndrome do not exhibit any symptoms. Others may experience fatigue, nausea, loss of appetite, jaundice, vomiting, hypoglycaemia, itching and stomach pain. These symptoms are often triggered by an infection, dehydration or stress. In Gilbert's syndrome, patients experience recurrent mild jaundice. To diagnose Gilbert's syndrome, other genetic causes of hyperbilirubinaemia, such as Criggler-Najjar syndrome, must be ruled out [8]. The diagnosis of Gilbert's syndrome can be made using various methods, such as the alkaline methanol method, thin layer chromatography and High-Performance Liquid Chromatography (HPLC), which allow for the precise separation and measurement of bilirubin in its conjugated and unconjugated forms [10]. Polymerase Chain Reaction (PCR) is a newer method that can rapidly identify genetic polymorphisms in the UDPGT1 gene's TATA box using fluorescence resonance energy conversion. Once diagnosed, patients should be assured of its benign nature, good prognosis and normal life expectancy, with no special treatment required other than supportive care. While patients may sometimes report vague symptoms, such as abdominal discomfort and general fatigue, unnecessary investigations can be avoided by using appropriate diagnostic tests [8].

Gilbert's syndrome can lead to delayed diagnosis and challenging symptomatic interaction. To diagnose Gilbert's syndrome with certainty, clinical suspicion and information about the disease are required. A study conducted by Felsher et al. in 1970 found a direct relationship between calorie consumption and bilirubin levels among patients. They observed that an unexpected increase in unconjugated bilirubin typically occurred within 24 hours of fasting, while the level decreased significantly within 12 to 48 hours after increasing calorie intake. A family history of similar issues may suggest the possibility of an inherited disorder, but an autosomal passive legacy cannot be inferred from the limited family history obtained. Despite mildly elevated total bilirubin levels with prevalent unconjugated hyperbilirubinaemia, typical outcomes from other investigational modalities also support the finding of Gilbert's syndrome [5].

In principle, the effects of Gilbert's syndrome on pregnancy are minimal and conditional for mild hyperbilirubinaemia, which is associated with the disease. Stress, infections and dehydration can exacerbate symptoms, so pregnancy, which is a state of physiological immune deficiency and stress, can indirectly cause symptoms of hyperbilirubinaemia [11]. Limited research is available on the impact of pregnancy on patients with Gilbert's syndrome. Just a single case report by Mohan et al. detailed a positive obstetric result. Another study by Alder et al. found anxiety during pregnancy was associated with poor obstetric and neonatal outcomes. Therefore, it is important to reassure the patient regarding the benign nature of Gilbert's syndrome to reduce anxiety levels. Several studies have shown that encouragement from the physician during the diagnostic period reduces anxiety levels and lessens symptom awareness and patients' beliefs about the seriousness of their condition [5, 8].

However, when Gilbert's syndrome is combined with other prevailing conditions, such as lactation, G-6-PD deficiency, thalassemia, spherocytosis or cystic fibrosis, it can potentiate severe hyperbilirubinaemia and cholelithiasis [12]. In a study by Kamal et al., pregnancy was identified as a significant risk factor for clinical jaundice episodes. The study found that pregnancy was a significant risk factor for worsening indirect hyperbilirubinaemia, starting from the first trimester and lasting throughout pregnancy and part of the postpartum period. If a pregnant woman is diagnosed with Gilbert's syndrome, other diseases should be ruled out first, and attention should be paid to nausea, vomiting, yellowing of the skin and sclera, systemic itching and other manifestations [13]. Foetal complications are the most worrying as they are related to cholestasis in pregnancy and foetal death. The association between high bile acid levels and stillbirths was reported systematically in literature; however, most studies to date have not robust to report stillbirth [14].

For the differential diagnosis of a patient's condition, the possible diseases listed in the Table 2 must be taken into account.

Gilbert's syndrome is often underdiagnosed or misdiagnosed, which can lead to unnecessary worry for patients. This is especially true for pregnant women, who may be concerned about the impact of the condition on their pregnancy outcomes.

This issue is reported to occur infrequently during pregnancy, and the patient does not have typical clinical features except jaundice. In summary, Gilbert's syndrome should be ruled out if patients present with unconjugated hyperbilirubinaemia due to stress, infection or dehydration. This unique diagnosis must reassure the patient of its benignity, favourable prognosis and a normal life expectancy. The patient's bilirubin level was only 2 mg/dl, whereas in Crigler-Najjar syndrome, it is up to 20 mg/dl. Other causes of haemolysis and infectious jaundice were also ruled out. Eventually, the diagnosis of Gilbert's syndrome is made by ruling out other diseases. Accurate diagnosis and disease referral not only reduced patient anxiety but also helped avoid additional diagnostic and treatment healthcare system costs.

The diagnosis of Gilbert's syndrome in pregnant women is important because it can help alleviate concerns and ensure appropriate monitoring and management of the condition. In most cases, Gilbert's syndrome does not pose a significant risk to the mother or foetus, and patients can be reassured that their pregnancy outcomes are likely to be favourable.

Conclusions

Diagnosis of Gilbert's syndrome is often delayed or missed and causes anxiety in patients, especially pregnant women, who are concerned about the outcome of their childbirth. Delayed diagnosis can increase patient anxiety. The use of medical sedation is beneficial to reduce concerns in pregnant patients with Gilbert's syndrome and may influence disease outcomes [2].

In conclusion, this case report highlights the importance of considering Gilbert's syndrome as a potential cause of hyperbilirubinaemia in pregnant women. By raising awareness of this disorder and ensuring prompt and accurate diagnosis, healthcare providers can help to reduce unnecessary worry and ensure appropriate management of the condition.

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