

# Cholestasis of pregnancy, Is it due to biliary gene mutation? Case Report

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## Background

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestatic liver disease of undefined aetiology and pathogenesis. It is characterised by pruritus and raised serum bile acid levels ( $\geq 10 \mu\text{mol/l}$ ), which usually appear in the second half of pregnancy and persist until delivery. ICP is associated with increased fetal risks, such as preterm delivery, fetal distress and intrauterine fetal death.

ICP is thought to be caused by abnormal biliary transport, which may result from a number of factors, including hormonal, environmental and genetic. The hypothesis that genetically determined dysfunction of hepatocanalicular lipid transporters contributes to ICP was first supported by Jacquemin et al.

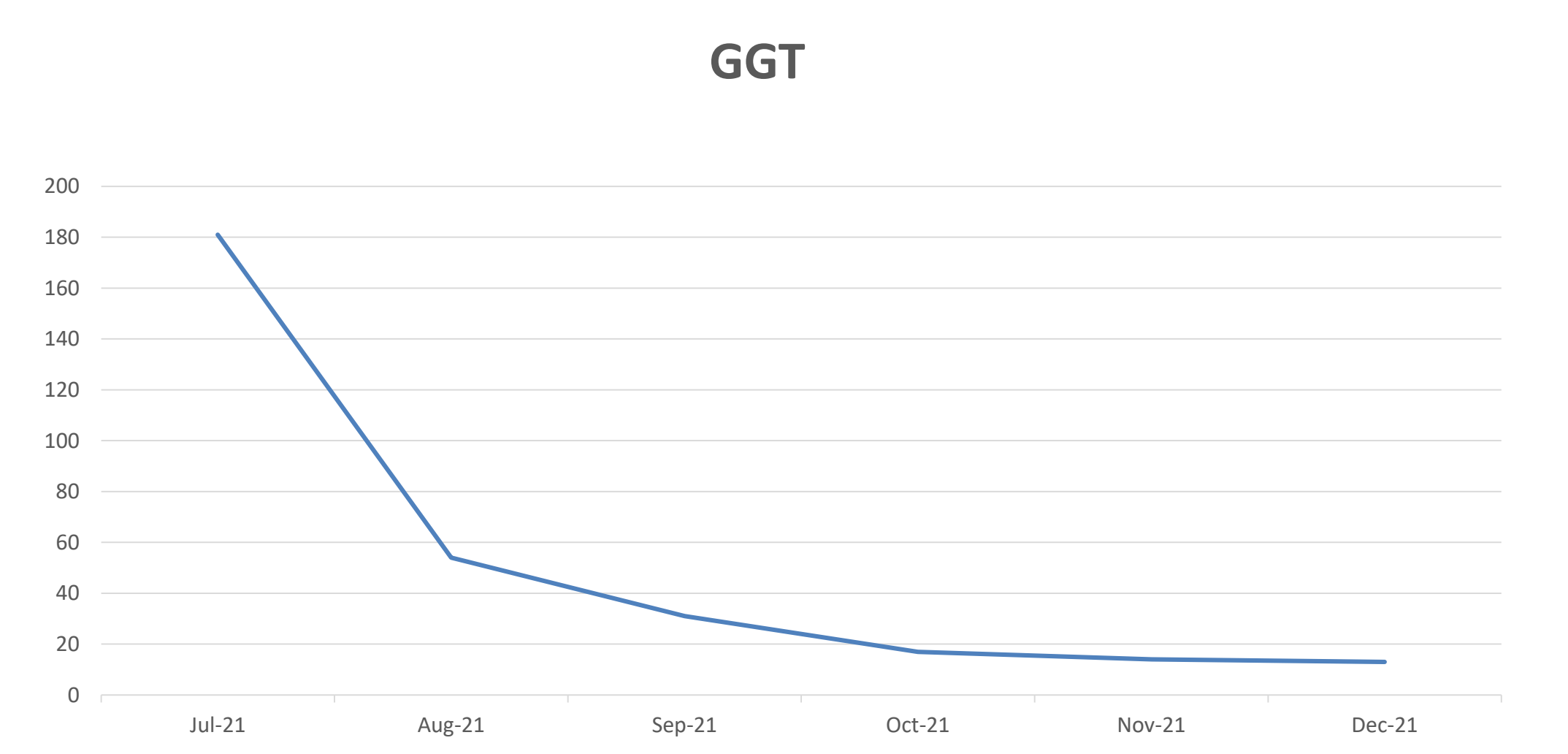
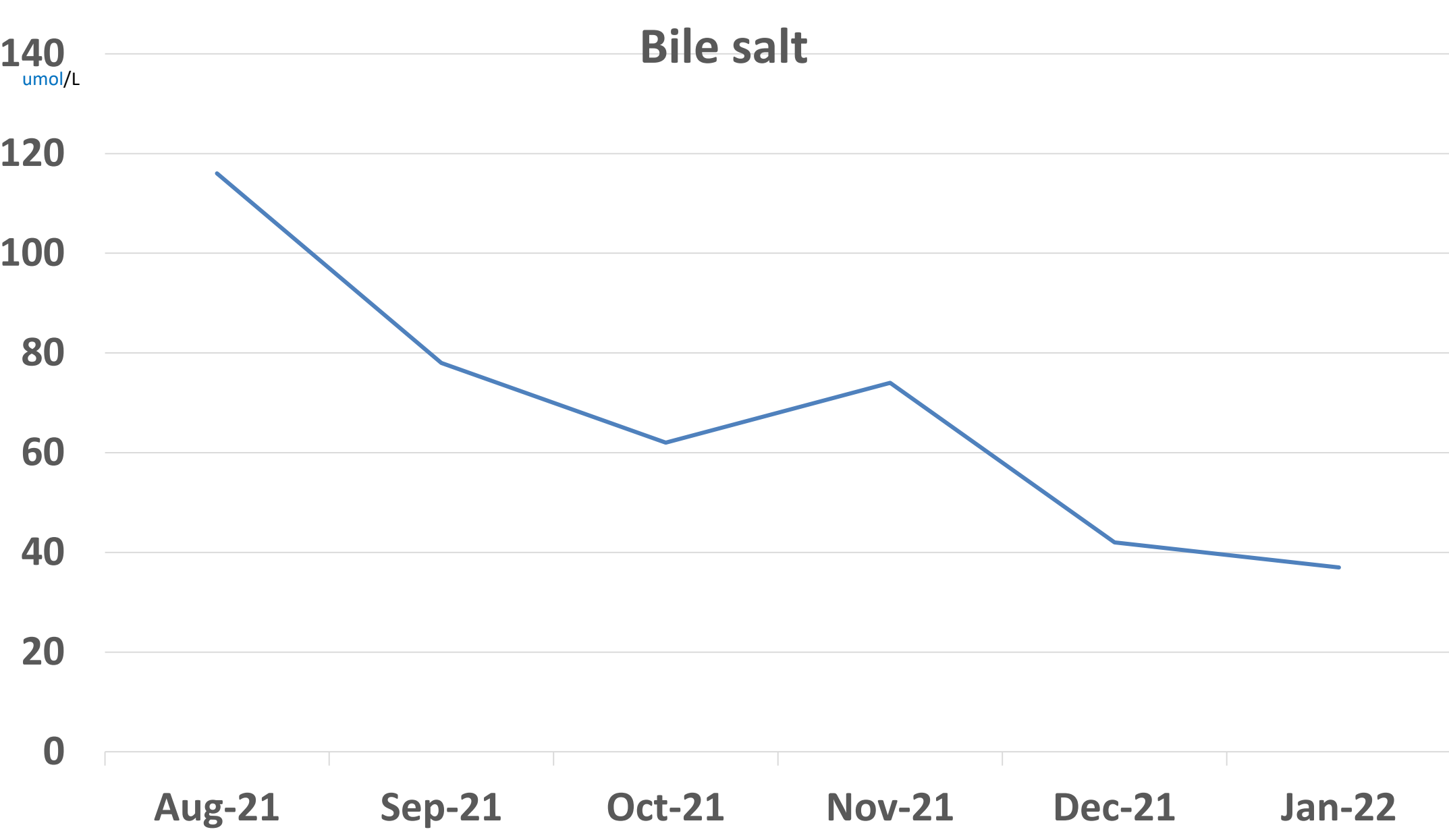
Women with early onset ICP especially with raised bile acids  $>40 \mu\text{mol/L}$  have 20% chance of biliary transporters mutations, 3-5 folds increase in gall stones and cirrhosis. In our case the patient presented with recurrent significant obstetric cholestasis with raised gamma glutamyl transferase (GGT) on a background history of gall bladder stones. This raised the suspicion of underlying genetic susceptibility to Multiple Drug Resistance Protein 3 (MDR3), the canalicular protein involved in the transport of phosphatidylcholine to bile.

## Case Presentation

26 year-old pregnant woman had liver function tests (LFT) by her GP following her recurrent vomiting and itching at 8 weeks. Results showed elevated ALT 1461 Int Unit/L, elevated GGT 181 Int Unit/L, bilirubin 40  $\mu\text{mol/L}$  and raised bile acid level at 117  $\mu\text{mol/L}$ . She had no pain or jaundice. She was not on any medications or had recently traveled. Her vomiting responded promptly to antiemetics. Her previous pregnancy was complicated by early obstetric cholestasis at 20 weeks . Gastroenterology team were involved for further investigations. She had full liver screen including tests for hepatitis A, B and C, autoimmune liver screen, iron study and ceruloplasmin level-which were all normal. Abdominal ultrasound showed multiple stones in the gall bladder with normal Common Bile Duct (CBD) calibre, which she was known to have from previous liver scan done in her first pregnancy at 21 years old. Diagnosis of early onset ICP was made. She received Ursodeoxycholic acid 300 mg TDS. Repeat ALT and bile acid showed gradual improvement, yet their level remained high throughout pregnancy till delivery. At 24 weeks, she developed Gestational Diabetes (GDM). She was induced at 37 weeks pregnancy with good outcome. She is awaiting postnatal liver function tests which will be followed up by the hepatology team.



Multiple gallstones within thin walled gallbladder



## Discussion

We initially thought that the deranged LFT is due to vomiting as mild elevated liver enzyme is expected in 50% of cases of hyperemesis gravidarum and as a general rule correlate with the severity of hyperemesis.

What makes ICP likely to be the cause of deranged LFT in this case rather than hyperemesis is the fact that our case presented with mild vomiting with inappropriately high ALT 1461 Int Unit/L and responded promptly to antiemetics. Furthermore, The ALT remained persistently elevated throughout pregnancy; this together with a history of previous early ICP and significantly raised bile salts points more to the diagnosis of ICP and made hyperemesis as a cause of deranged LFT unlikely.

ICP is a liver disorder which mostly occurs at the end of the second trimester or in the third trimester of pregnancy. This case is unique for the following reasons: ICP presented early in pregnancy at 8 weeks with severe deranged liver function tests; there were elevated GGT; and a history of gall bladder stones at a very young age. All these, together with negative liver screen, raise the possibility of biliary transporter gene mutation particularly ABCB4.

The *ABCB4* gene encodes a protein known as multidrug resistance protein 3 (MDR3). Mutations in the *ABCB4* gene result in the absence or low levels of functional MDR3 enzyme. This leads to decreased level of phospholipids in Individuals with no residual enzyme activity resulting in severe forms of MDR3 deficiency. Individuals with mild forms of the MDR3 deficiency have varying degrees of enzyme activity and of subsequent phospholipid concentrations in bile. In all untreated patients with MDR3 deficiency, serum GGT activity is elevated.

Molecular genetic testing for mutations in the *ABCB4* gene used to diagnose MDR3 deficiency. Also, if bile can be collected during ERCP or surgery, a biliary lipid analysis could be performed. The decrease in biliary phospholipid supports the diagnosis.

Genetic testing should be offered for our case if the repeat LFT following delivery is still deranged. Unfortunately LFT wasn't followed up following her first pregnancy and still pending.

Ursodeoxycholic acid (UDCA) therapy is effective in some patients (especially those with milder disease) and should be part of the initial treatment options for affected individuals. UDCA helps the excretion of phospholipid in the bile, restores the balance in the biliary composition and thus facilitates the solubilization of cholesterol. This is evident in our case where ALT, GGT and bile acid levels improved following the use of UDCA.

## Conclusion

Although the etiology of ICP is unclear in many cases, certain features of the clinical presentation should alert the practitioner to the possibility of an underlying genetic mutation. Genetic testing should be considered in those women with severe or early onset of ICP associated with elevated GGT, strong family history of cholestasis or a history of gall stones at young age. As those women will benefit from early treatment with UDCA and long-term follow up to detect the development of liver disease.

## References

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