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Liver enzyme elevation induced by hyperemesis gravidarum: aetiology, diagnosis and treatment

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ABSTRACT

Three primigravidae were admitted during the first trimester of pregnancy with nausea, vomiting, ketonuria and liver enzyme elevation of varying severity. A 29-year-old woman had elevated aminotransferase values, at levels described in the literature (ASAT 112 U/l, ALAT 214 U/l). The second patient, a woman aged 26 years, had undergone *in vitro* fertilisation and showed higher liver enzyme elevation, including the total bilirubin level (ASAT 250 U/l, ALAT 474 U/l, total bilirubin 59.8 µmol/l). A 30-year-old woman had extremely high aminotransferase values (ASAT 705 U/l, ALAT 1674 U/l) and she is the first reported patient with ALAT values exceeding 1000 U/l in connection with hyperemesis gravidarum. Gallstone disease, viral and drug-induced hepatitis were excluded in all of these patients. Treatment was symptomatic and the abnormal liver tests returned to normal promptly when the vomiting resolved, independent of the severity of liver enzyme elevation. The pregnancies proceeded normally and all three patients delivered healthy babies.

INTRODUCTION

Nausea and vomiting are very common in early pregnancy, occurring in 50% of pregnant women until 16 weeks of gestation.[1] Hyperemesis gravidarum is characterised by intractable nausea and vomiting during the first trimester of pregnancy, which in severe cases may lead to dehydration and require hospitalisation. There is no definite delimitation between 'morning sickness' and hyperemesis gravidarum: the latter is considered as the severe end of a gradation of symptoms. The incidence of hyperemesis gravidarum varies from 0.3 to 1% of pregnancies.[2-4]

Liver enzyme elevation occurs in 50% of patients who are hospitalised with hyperemesis. An increase in serum aminotransferases is the most common abnormality and alanine aminotransferase (ALAT) is usually higher than aspartate aminotransferase (ASAT).[5-6] This elevation is usually two to three times the upper limit of normal; it may be in the low hundreds and rarely as high as 1000 U/l.[7-9]

In this article we describe three patients with hyperemesis gravidarum and liver enzyme elevation of varying severity. We also discuss the aetiology, differential diagnosis and recommended diagnostic approach and therapy.

CASE A

A 29-year-old primigravida was admitted for the fourth time because of nausea and vomiting at 13 weeks of gestation. Her medical history revealed appendectomy, cholecystectomy and nephrolithiasis. She occasionally took ipratropium for asthmatic bronchitis. There were no signs of dehydration on physical examination. A transvaginal ultrasonography showed a normal foetus conform the gestational age. Laboratory findings on admission included increased ketones in the urine as well as increased levels of aminotransferases: ASAT 112 U/l, ALAT 214 U/l (*table 1*). Total bilirubin, alkaline phosphatase (ALP), γ-glutamyltransferase (γGT) and serology for hepatitis B were normal. Treatment consisted of intravenous fluids, meclozine/pyridoxine suppositories and occasional omeprazole for heartburn. During admission an abdominal ultrasono-

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graphic examination showed no abnormalities of the liver, bile ducts and spleen. After a few days the patient recovered well and she was discharged after reintroducing a normal diet. Blood controls showed improvement of aminotransferase levels: ASAT 50 U/l and ALAT 145 U/l.
At 17 weeks of gestation, she visited the outpatient clinic for nausea, vomiting and abdominal pain. Hospitalisation followed again because of insufficient intake and high ketonuria. Routine liver tests revealed values similar to those at discharge: ASAT 53 U/l, ALAT 96 U/l. An abdominal ultrasonography and a gastroscopy showed no abnormalities. She was treated in the same way as before and discharged after nine days. Control of serum aminotransferases showed an improvement again: ASAT 31 U/l and ALAT 55 U/l (*table 1*).
The pregnancy then progressed uneventfully and she delivered a healthy daughter of 3690 g at 40 weeks gestation.

CASE B

A 26-year-old primigravida visited the outpatient clinic for nausea, vomiting and itching. Her medical history revealed primary subfertility, and she was at six weeks of gestation after undergoing *in vitro* fertilisation.
Blood tests showed elevated liver tests: ASAT 107 U/l, ALAT 330 U/l, total bilirubin 27.3 µmol/l, ALP 456 U/l. Serology to hepatitis A, B, C and cytomegalovirus was negative and there was no evidence for autoimmune hepatitis, haemochromatosis or hyperthyroidism. The β-hCG level was 87,000 U/l, which is very high at week 6 of gestation. Ultrasound examination showed, besides ovarian follicular cysts, no abnormalities and there was no evidence of ovarian hyperstimulation syndrome. Hyperemesis gravidarum was diagnosed and she was treated with metoclopramide and meclozine/pyridoxine.
One week later she was admitted for persistent vomiting, itching and a loss of 3 kg in weight. Liver tests revealed higher levels than before: ASAT 250 U/l, ALAT 474 U/l, total bilirubin 59.8 µmol/l, conjugated bilirubin 47.8 µmol/l (*table 1*). Urine test showed ketosis (2+). Treatment consisted of intravenous fluids and chlorpromazine. She left the hospital without symptoms and medication after two weeks. At week 12 she was readmitted because of vomiting, a weight loss of 2 kg, jaundice and ketosis. Serum aminotransferase levels were no higher than previously, but there was a persistent hyperbilirubinaemia of 47.8 µmol/l. The abdominal ultrasound revealed normal liver and bile ducts. She followed the same treatment as before for two weeks. Symptoms resolved at 14 weeks of gestation and she recovered the lost weight.
The pregnancy proceeded normally until week 31, when she was admitted because of premature contractions. Delivery was postponed using ritodrine and she delivered two healthy neonates of 900 g at 35 weeks gestation.

CASE C

A 30-year-old primigravida was hospitalised three times for intractable nausea, vomiting and liver enzyme elevation, between weeks 13 and 17 of pregnancy. Medical history only revealed hiatal hernia with mild reflux oesophagitis. She had no history of alcohol use or hepatitis. Before the last admission she had been vomiting for four days and initial treatment with meclozine/pyridoxine had had no effect at home.
On admission she had slight signs of dehydration but no signs of jaundice or hepatomegaly. Routine blood samples showed elevated liver tests: total bilirubin 44.9 µmol/l, ASAT 614 U/l, ALAT 1065 U/l and γGT 87 U/l (*table 1*). There were no signs of hyperthyroidism or haemochromatosis. Serology to hepatitis A, B, C and to cytomegalovirus were negative, as were antinuclear and antimitochondrial antibodies. Urine samples showed increased ketones. An abdominal ultrasonography showed no abnormalities of the liver, gallbladder, bile ducts and spleen.
Following admission she was treated with metoclopramide and oral fluids. Within a few days the symptoms had

Table 1
Serum aminotransferase levels of the three cases

	TEST*	ADMISSION	HIGHEST VALUE	AT DISCHARGE	AFTER DISCHARGE
Case A	ASAT	112	112	50	31
	ALAT	214	214	145	55
Case B	ASAT	250	250	49	37
	ALAT	474	474	110	87
Case C	ASAT	614	705	78	19
	ALAT	1065	1674	641	33

* *Normal values: ASAT 5-35 U/l, ALAT 5-35 U/l.*

resolved and the liver tests stabilised (*table 1*). The patient was discharged at day 8, and one week later all the liver tests except the ALAT (141 U/l) had normalised. Three weeks later, she remained symptom-free and all liver tests were normal. The pregnancy proceeded normally and she delivered a healthy child of 3700 g at 39 weeks gestation.

DISCUSSION

There are several classic features of hyperemesis gravidarum. It presents early in the first trimester of pregnancy, usually in the fourth to tenth week of gestation, with intractable vomiting and associated pytialism (excessive salivation). Abdominal pain is infrequent. Patients may present with dehydration, liver test abnormalities, ketosis, electrolyte disturbances and weight loss.
The syndrome is associated with nulliparous women, obesity and multiple gestations. Advanced maternal age (>35 years) and cigarette smoking seem to be protective factors.[1,10,11] Case A showed typical features of this syndrome regarding presentation – nulliparity, classic symptoms and ketosis – liver test abnormalities and spontaneous recovery after admission.

Several causal factors for hyperemesis gravidarum have been described, but the aetiology remains uncertain. Some proposed theories in the pathogenesis of hyperemesis gravidarum include psychological factors (emotional instability, conversion),[12,13] hyperthyroidism,[14] liver abnormalities and changes in gestational hormone levels (especially hCG peak during the first trimester).[15,16] In case B, β-hCG levels were very high for the gestational age, possibly related to the twin pregnancy. On the other hand, Goodwin *et al.* described a significant difference in total hCG and β-hCG between women with hyperemesis and healthy pregnant women.[16]
Other theories to explain hyperemesis include abnormal gastric motility,[17] autonomic nervous system dysfunction,[8] alterations in lipid levels[18] and nutritional deficiencies. On examination, no single theory seems to provide an adequate explanation for hyperemesis gravidarum.[5]
In most cases, nausea and vomiting resolve by 20 weeks of gestation. Only seldom do these symptoms persist into the second half of the pregnancy. A recurrence of hyperemesis with subsequent pregnancies is uncommon.[19]

Hyperemesis gravidarum and liver enzyme abnormalities

There are very few reports about abnormal liver tests in patients with hyperemesis gravidarum.[7,8,18-21] In a prospective study, liver tests were more frequently abnormal in 12 patients with hyperemesis than in healthy controls. Elevations in either ASAT or ALAT occurred in 50% of patients with hyperemesis.[8]
Aminotransferase values can rise to 200 U/l (six times the upper limit of normal)[7] and exceptionally as high as 1000 U/l.[8] Case C developed extremely high serum aminotransferase values: as far as we know, this is the first reported patient with ALAT values higher than 1000 U/l induced by hyperemesis gravidarum.
Mild hyperbilirubinaemia (less than 68 μmol/l) with elevation of both direct and indirect fractions has been found in half the women hospitalised for this condition.[7,19] ALP may be elevated to twice the normal value, but this could also be a physiological increase of placental origin. However, it is known that ALP levels increase gradually during the first seven months of pregnancy and then rise rapidly to peak at term.[9] Abnormal liver tests in connection with hyperemesis gravidarum return to normal promptly when the vomiting resolves.
Although the pathogenesis of the liver injury is unknown, the combined effects of hypovolaemia, malnutrition and lactic acidosis are believed to play a role.[9] Hyperbilirubinaemia is probably related to malnutrition and impaired secretion of bilirubin.[7]

Diagnosis

The differential diagnosis of liver enzyme elevation presenting in the first trimester of pregnancy includes hyperemesis gravidarum – as the only pregnancy-related syndrome – gallstone disease, viral and drug-induced hepatitis (*table 2*). The diagnosis of hyperemesis gravidarum is a clinical one that rests on the exclusion of other causes

Table 2
Differential diagnosis of common causes of elevated serum aminotransferase levels and/or jaundice in pregnancy[9]

TRIMESTER	DIFFERENTIAL DIAGNOSIS*
First	*Hyperemesis gravidarum*
	Gallstones
	Viral hepatitis
	Drug-induced hepatitis
Second	*Intrahepatic cholestasis of pregnancy*
	Gallstones
	Viral hepatitis
	Drug-induced hepatitis
	Pre-eclampsia/eclampsia†
	HELLP syndrome†
Third	*Intrahepatic cholestasis of pregnancy*
	Pre-eclampsia/eclampsia
	HELLP syndrome
	Acute fatty liver of pregnancy
	Hepatic rupture
	Gallstones
	Viral hepatitis
	Drug-induced hepatitis

* *Diseases unique to pregnancy in cursive,* † *uncommon in this trimester.*

in combination with spontaneous recovery of liver test abnormalities when the symptoms resolve.[5]
Regarding other disorders unique to pregnancy, *intrahepatic cholestasis of pregnancy* usually begins in the second trimester and very rarely in the first trimester. The disorders associated with *(pre-)eclampsia* and *HELLP syndrome* (haemolytic anaemia, elevated liver tests and low platelets) occur in the second half of pregnancy, usually in the third trimester toward term. *Acute fatty liver of pregnancy* and *hepatic rupture* generally occur in the third trimester as well as in the immediate postpartum period.[9]

There are certain things to bear in mind when a patient complains of nausea and vomiting in combination with liver test abnormalities. Arguments for hyperemesis gravidarum are: first pregnancy, young age, overweight, non-smoker and onset of vomiting before 15 weeks.
In patients with hyperemesis gravidarum, hospitalisation is prompted by dehydration and ketosis; physical examination only reveals excessive salivation. Laboratory test findings can be normal but often ketonuria is found. In case of liver test abnormalities, viral and drug-induced hepatitis as well as gallstones should be excluded. For this purpose, viral serologies and abdominal ultrasonography should be performed.[5] A liver biopsy is rarely needed to exclude other causes for the laboratory findings. In those cases where a liver biopsy was performed, it was either normal or showed non-specific findings such as steatosis.[6]
On the other hand, further investigation is required in patients with severe serum aminotransferase elevation (ASAT/ALAT >500 U/l), as well as in those patients with persistent liver enzyme abnormalities after the symptoms resolve.

Treatment
The treatment of hyperemesis gravidarum is symptomatic; hospitalisation for intractable vomiting, dehydration or malnutrition may be necessary.[9] Rehydration with intravenous fluids and treatment with antiemetics are often required. No comparative trials exist, but antiemetics such as promethazine, odansetron or droperidol have been reported to be useful.[22]
Further therapy in selected patients may include enteral and parenteral nutrition.[5] Corticosteroids have been reported to be effective, although the mechanism of action is not well understood.[23-25]

CONCLUSION

Hyperemesis gravidarum is a poorly understood disorder in the first trimester of pregnancy. Increased levels of aminotransferases, especially ALAT, are found in 50% of patients who are hospitalised with hyperemesis. Although the pathogenesis of liver abnormalities is unknown, the combined effects of hypovolaemia and malnutrition are believed to play a role.
Gallstone disease, viral and drug-induced hepatitis should be considered in the differential diagnosis of patients with elevated liver tests and hyperemesis. Management is symptomatic and abnormal liver tests return to normal promptly when symptoms resolve.

REFERENCES

1. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol 1985;66:612-6.
2. Kallen B. Hyperemesis during pregnancy and delivery outcome: a registry study. Eur J Obstet Gynecol Reprod Biol 1987;26:291-302.
3. Hallak M, Tsalamandris K, Dombrowski MP, Isada NB, Pryde PG, Evans MI. Hyperemesis gravidarum. Effects on foetal outcome. J Reprod Med 1996;41:871-4.
4. Tsang IS, Katz VL, Wells SD. Maternal and foetal outcomes in hyperemesis gravidarum. Int J Gynecol Obstet 1996;55:231-5.
5. Abell TL, Riely CA. Hyperemesis gravidarum. Gastroenterol Clin North Am 1992;21:835-49.
6. Knox TA, Olans LB. Liver disease in pregnancy. N Engl J Med 1996;335:569-76.
7. Adams RH, Gordon J, Combes B. Hyperemesis gravidarum. I. Evidence of hepatic dysfunction. Obstet Gynecol 1968;31:659-64.
8. Wallstedt A, Riely CA, Shaver D, et al. Prevalence and characteristics of liver dysfunction in hyperemesis gravidarum [abstract]. Clin Res 1990;38:970A.
9. Wolf JL. Liver disease in pregnancy. Med Clin North Am 1996;80:1167-87.
10. Depue RH, Bernstein L, Ross RK, Judd HL, Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. Am J Obstet Gynecol 1987;156:1137-41.
11. Burroughs AK. Liver disease and pregnancy. In: Bircher J, Benhamou JP, McIntyre N, Rizzetto M, Rodes J, editors. Oxford Textbook of Clinical Hepatology, 2nd ed. Oxford: Oxford University Press, 1999:1901-13.
12. LaFerla JJ. Psychological and behavioural factors in hyperemesis gravidarum [letter]. Am J Obstet Gynecol 1988;159:532-3.
13. El-Mallakh RS, Liebowitz NR, Hale MS. Hyperemesis gravidarum as conversion disorder. J Nerv Ment Dis 1990;178:655-9.
14. Colin JF, Mathurin P, Durand F, et al. Hyperthyroidism: a possible factor of cholestasis associated with hyperemesis gravidarum of prolonged evolution. Gastroenterol Clin Biol 1994;18:378-80.
15. Kimura M, Mino N, Tamaki H, et al. Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. Clin Endocrinol 1993;38:345-50.
16. Goodwin TM, Hershman JM, Cole L. Increased concentration of free β-subunit of human chorionic gonadotropin in hyperemesis gravidarum. Acta Obstet Gynecol Scand 1994;73:770-2.
17. Riezzo G, Pezzolla F, Darconza G, Giorgio I. Gastric myoelectrical activity in the first trimester of pregnancy: a cutaneous electrogastrographic study. Am J Gastroenterol 1992;87:702-7.

18. Järnfelt-Samsioe A, Eriksson B, Waldenstrom J, Samsioe G. Serum bile acids, gamma-glutamyltransferase and routine liver function tests in emetic and nonemetic pregnancies. Gynecol Obstet Invest 1986;21:169-76.
19. Larrey D, Rueff B, Feldmann G, Degott C, Danan G, Benhamou JP. Recurrent jaundice caused by recurrent hyperemesis gravidarum. Gut 1984;25:1414-5.
20. Morali GA, Braverman DZ. Abnormal liver enzymes and ketonuria in hyperemesis gravidarum. A retrospective review of 80 patients. J Clin Gastroenterol 1990;12:303-5.
21. Orazi G, Dufour PH, Puech F. Jaundice induced by hyperemesis gravidarum. Int J Gynaecol Obstet 1998;61:181-3.
22. Riely CA. Liver disease in the pregnant patient. Am J Gastroenterol 1999;94:1728-32.
23. Nelson-Piercy C, DeSwiet M. Corticosteroids for the treatment of hyperemesis gravidarum. Br J Obstet Gynaecol 1994;101:1013-5.
24. Taylor R. Successful management of hyperemesis gravidarum using steroid therapy. QJM 1996:89:103-7.
25. Safari HR, Alsulyman OM, Gherman RB, Goodwin TM. Experience with oral methylprednisolone in the treatment of refractory hyperemesis gravidarum. Am J Obstet Gynecol 1998:178:1054-8.

Rectification

In the review 'Autoimmunity in Addison's disease' by P. Martín Martorell, B.O. Roep and J.W.A. Smit, published in The Netherlands Journal of Medicine 2002;60(7):269-5, an error was made in the first author's name. It should be P. Martín Martorell instead of P.M. Martorell. Our apologies for any inconvenience caused.