

A woman pregnant with twins and with polyuria and polydipsia

A woman pregnant with twins was monitored because of the increasing weight deviation of the one twin. The patient gradually developed polyuria and polydipsia. Blood tests on hospitalisation pointed to serious disease and an acute caesarean was performed.

A woman in her late twenties, gravida II, came for routine screening in week 19 of pregnancy. She was healthy and prior to pregnancy had a BMI of 18.5. The twins were found to be monochorionic/diamniotic (single placenta, individual amniotic sacs) and twin 2 was measured as being somewhat smaller than twin 1. The patient was known to have uterus didelphys (double set of uterus/portio/vagina) and she was now pregnant in the left uterus. In her first pregnancy, in the right uterus, her waters broke prematurely in week 35 and the birth was uncomplicated.

Uterus didelphys is due to a congenital defect in the development of the Müllerian ducts, causing increased risk of primary infertility, ectopic pregnancy, repeated abortions and premature birth. In one study, only one of five pregnancies went to term (1).

The patient was monitored by means of regular ultrasound scans in accordance with the guidelines for gravida with monochorionic twins (2). In gestation week 26, 16 % growth restriction was found in twin 2, while twin 1 was of average size. She felt life from both daily, but less from twin 2. She related that she was thirstier than prior to the pregnancy, but she had also been thirstier during her first pregnancy, and perceived this as normal.

Ultrasound in week 28 revealed increasing growth restriction, of 25 % in twin 2 and 5 % in twin 1. In light of normal findings from blood flow measurement using Doppler imaging of umbilical arteries, and amniotic fluid quantity within the reference range, twin-twin transfusion syndrome was excluded (3). A transvaginal ultrasound revealed a long and closed cervix. She still felt less life from twin 2. She felt tired during the day, and had high fluid intake of more than 2 l daily. Her blood pressure was 125/75 mm Hg and urine dipstick test was negative. HbA_{1c} of 4.7 % (4–6) and normal blood glucose excluded the possibility of gestational diabetes.

At this stage the patient was hospitalised for the first time during the pregnancy. The risk of a premature birth was considered in

view of her medical history, anatomical features and the twins' increasing weight deviation. She was given a lung-maturing injection and discharged after two days.

The woman was hospitalised again in week 32 of her pregnancy. The weight deviation was now –35 % in twin 2 and –12 % in twin 1. Doppler findings were still satisfactory for both twins. She was now complaining of cold symptoms such as a blocked nose, dyspnoea on exertion and headache. She had little appetite, but was still drinking large quantities of fluid and passing water frequently. This had developed gradually over a period of months, with a noticeable exacerbation during the last month.

Frequent passing of water attributable to physiological changes in the urinary tract during pregnancy is common. Polyuria, defined as a passing > 3 l of water over 24 hours is not common, and calls for further tests (4).

She was also sleeping poorly at night and was increasingly tired during the day. She was afebrile, did not have dysuria or oedema and was normotensive. Initial blood tests showed alanine amino transferase (ALT) of 415 U/l (10–45). A review of her drinking and diuresis chart showed that she had drunk 3 l and had diuresis of 4 l in the last 24 hours. Blood tests taken early in her pregnancy showed a previous hepatitis B infection. Medical monitoring and further blood tests were requested.

Normal pregnancy causes little change in liver function readings. Amino transferases, total bilirubin and serum bile should be within the normal range. Alkaline phosphatase (ALP) is moderately elevated in the third trimester, while albumin is lower than in non-pregnant women. The cholesterol level is higher (5). The differential diagnoses for elevated liver enzymes in pregnancy include hyperemesis gravidarum, intrahepatic cholestasis in pregnancy, preeclampsia/HELLP syndrome and acute fatty liver of pregnancy (AFLP). Hepatitis, cholelithiasis and malignancy must also be excluded (6).

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BOX 1

Criteria for the diagnosis acute fatty liver of pregnancy [the Swansea criteria] (7).

Six or more of the following signs must be present and other explanation for the symptoms must be absent

- Vomiting
- Abdominal pain
- Polyuria/polydipsia
- Encephalopathy
- Elevated bilirubin
- Hypoglycaemia
- Elevated urea
- Leukocytosis
- Ascites or «bright liver» on ultrasound scan
- Elevated ALT/AST
- Elevated ammonia
- Renal impairment
- Coagulopathy (PTT > 14 sec, APTT > 34 sec)
- Microvesicular steatosis on liver biopsy

Ultrasound abdomen showed no steatosis, bile duct dilation or other signs of liver disease. The blood tests showed liver affection with AST 214 U/l (15–35), ammonia 60 µmol/l (10–50), bilirubin 45 µmol/l (5–25), albumin 20 g/l (36–48), INR 1.3 (≤ 1.1) and activated partial thromboplastin time (APTT) 52 sec (30–40). C-reactive protein (CRP) was 12 mg/l (0–5), leukocytes 12.9 g/l (3.5–10), glucose 4.6 mmol/l (4.0–6.3) and haptoglobin 0.28 (0.30–2.0). Fibrinogen and thrombocytes were normal. Creatinine was 88 µmol/l (45–90) and glomerular filtration rate (GFR) > 60. Hormone tests were normal. Biochemical and clinical findings pointed to the diagnosis acute fatty liver of pregnancy.

The clinical picture of acute fatty liver of pregnancy is broad and varies from asymptomatic rise in the aminotransferases to fulminant hepatic failure with jaundice, pronounced coagulopathy, liver encephalopathy and hypoglycaemia. Common symptoms are anorexia, vomiting, abdominal pain and polydipsia/polyuria. Laboratory tests often show elevated transaminases, ammonia, bilirubin and uric acid. Most patients have leukocytosis. More than half have hypoglycaemia and abnormal thrombocyte and creatinine values. Coagulatory disorders with prolonged APTT or partial thromboplastin time (PTT) are common (Box 1) (7). Abdominal ultrasound has low sensitivity and specificity and is most useful retrospectively. CT is only recommended if the diagnosis is not clear. Liver biopsy will reveal microvascular steatosis, but is not recommended as a matter of routine because of the high per-

tage of patients with coagulopathy and at risk of haemorrhaging (8).

In light of the large volume of water passed by the patient, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and diabetes insipidus were postulated as the cause of polyuria. Given U-osmolality of 88 mosmol/kg (300–900) and S-electrolytes and osmolality in the normal range, SIADH was an improbable diagnosis (9).

Intense thirst and polyuria in third trimester gravida should trigger suspicion of diabetes insipidus. S-osmolality, sodium and U-osmolality should be checked. In a normal pregnancy, S-osmolality will be less than 280 mosmol/kg and S-sodium will be less than 140 mmol/l. When U-osmolality is lower than S-osmolality, diabetes insipidus is probable (10).

The following morning, the patient's waters broke spontaneously. The fluid was discoloured. A gynaecologist at the University Hospital was consulted and it was agreed that acute fatty liver of pregnancy was a probable diagnosis. Immediately delivery by acute caesarean section was decided upon. Two boys were delivered with birth weights of 1 245 g and 1 610 g respectively, both with Apgar scores of 9, 9, 9. Bleeding was estimated to be 500 ml, and haemorrhage prophylaxis was not considered necessary.

When fatty liver of pregnancy is suspected, rapid delivery should be considered irrespective of whether the condition is regarded as mild or serious or whether it is early or late in the pregnancy. The recommended delivery method is a section, unless vaginal birth is going to take place immediately (8).

During the first twenty four hours after the operation the patient was clinically stable, with satisfactory diuresis and a fall in liver function readings. On the second post-operative day the patient seemed to be increasingly somnolent. She smelt of ammonia, and felt dizzy and very thirsty. She was polyuritic, with diuresis of 4 000 ml over the past twenty four hours. At the same time her blood tests showed a fall in ALP, ALT/AST, CK and bilirubin. APTT was still prolonged. Albumin and ammonia were barely rising. An improvement was seen in urine concentration ability, with U-osmolality rising to 226 mosmol/kg. S-Na was not tested. There was also a tendency to hypoglycaemia with S-glucose 3.0 mmol/l, but her blood sugar normalised the following day. Owing to stable clinical findings and limited capacity in the Intensive Care Department, the patient was moved back to the Neonatal Department.

Over half of patients with acute fatty liver of pregnancy are kept under observation in the Intensive Care Department after delivery. The median period spent there is three days (7), and most of them stabilise after delivery (6). Supportive therapy until the liver function is normal is very important in the postpartum period. Complications occur, the most common being severe liver and kidney failure, liver encephalopathy and disseminated intravascular coagulation (/DIC). Other complications include postpartum bleeding, sepsis, cerebrovascular events and seizures. Deaths are rare, but do occur. Multiple organ failure is the most common cause of death (8).

On the third post-operative day, the patient was transferred to the Department of Internal Medicine. Daily clinical improvement was seen, and she was discharged after seven days. She was then fine. Blood tests after 14 days showed virtually normal values. Eighteen days after delivery, the patient returned with acute vaginal bleeding. Revision of the left uterus was performed and retained membranes and clots were removed. Preoperative Hb was 10.9 and thrombocytes were 298. She was discharged the following day, clinically well, with Hb 8.6.

Discussion

Acute fatty liver of pregnancy is a rare, but serious condition in pregnancy, and has been described in a previous case report in *the Journal of the Norwegian Medical Association* (11). The condition is reported in five of 100 000 pregnancies, and up to 20 % of women with this disease are pregnant with twins (7). By way of comparison, only 1.6 % of births in Norway are twins (2). The aetiology is not clear. Enzyme failure is often seen in the fatty acid oxidation of the mitochondria in the fetus. It is postulated that women with multiple pregnancies have an increased risk of the condition because of a combination of increased maternal production of fatty acids, reduced fatty acid oxidation and increased fetal production of fatty acid metabolites (12). A higher incidence of severe preeclampsia, with or without the HELLP syndrome, is also seen in mothers with children who are affected by this enzyme failure (13).

Our patient had felt less life from the one fetus and described polydipsia/polyuria that had developed gradually. The differential diagnoses for polyuria in pregnancy are many, and a precise diagnosis can be difficult. Conditions such as diabetes mellitus, chronic renal disease, hypercalcaemia and hypokalaemia can cause polyuria in pregnancy. Common complaints such as frequent passing of water and nocturia due to

physiological changes in pregnancy must be excluded (7).

Diabetes insipidus occurs rarely, and complicates one of 30 000 pregnancies (14). Thirst and circulating vasopressin (antidiuretic hormone, ADH) maintain the water balance and osmoregulation. A pronounced increase in metabolic replacement of vasopressin is seen in pregnant women. Vasopressinase is produced by the placenta and breaks down vasopressin. In a normal pregnancy, vasopressin production will increase in order to compensate for the increased breakdown. In rare cases, breakdown exceeds production and all circulating vasopressin is eliminated. The result is impaired ability to concentrate urine, resulting in polyuria, thirst and dehydration (10).

Three types of diabetes insipidus in pregnancy are described in the literature (14). They can be classified on the basis of response to vasopressin and 1-deamino-8-D-arginin-vasopressin (dDAVP), a synthetic form of vasopressin. A distinction is made between vasopressin-resistant and dDAVP-sensitive diabetes insipidus (diabetes insipidus in pregnancy), vasopressin- and dDAVP-resistant diabetes insipidus (nephrogenic) and vasopressin- and dDAVP-sensitive diabetes insipidus (central). Transient DI of pregnancy is described as a condition exclusive to pregnancy. It typically presents in the third trimester, and must be assessed as a differential diagnosis in women with pronounced polyuria and polydipsia toward the end of their pregnancy. These women have significantly elevated vasopressinase values, up to 300 times the values seen in healthy gravida. Vasopressinase production is proportional to the placental mass. Consequently women with twin pregnancies will have higher vasopressinase values, precisely because the placental mass

is larger. Another important factor that may play a part is impaired liver function, which reduces the ability to break down vasopressinase (10). One in ten patients with acute fatty liver of pregnancy reports polyuria/polydipsia as the first symptom (7). In our patient, increasing thirst and polyuria were noticed already in the second trimester, with a pronounced exacerbation from the beginning of the third trimester. Because of acute fatty liver of pregnancy and acute delivery, it was not relevant to conduct further workup on the patient to determine the subtype of diabetes insipidus. This can be done by means of a thirst test, but is not recommended during pregnancy because of the risk of dehydration (15). The patient's symptoms disappeared a few days after delivery.

Conclusion

Diabetes insipidus and acute fatty liver of pregnancy are two rare, but serious conditions. The clinical picture is consistent with our patient having had pregnancy-conditioned diabetes insipidus which was exacerbated by impaired liver function when acute fatty liver of pregnancy developed.

The patient has consented to the publication of the article.

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