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Case Report

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Euglycaemic ketoacidosis during pregnancy: More common than you think

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Abstract

Background: Euglycaemic ketoacidosis is a rare type of metabolic acidosis, with increased production of ketonic bodies and normal serum glucose. When it occurs during pregnancy, it might lead to adverse maternal and fetal outcomes. Pregnancy itself is a diabetogenic state that might predispose the patient to develop ketoacidosis following even relatively short periods of starvation and as such, a high index of suspicion is required for the diagnosis to be made and for the management plan to be established.

Case presentation: We present a case of euglycaemic ketoacidosis in a twin pregnancy, which occurred in the second trimester, necessitating prompt and aggressive management, that eventually required early delivery due to the development of preeclampsia.

Discussion/Conclusion: The physiology and pathology of euglycaemic ketoacidosis during pregnancy and the management required to avoid the potential maternal and fetal risks that such a condition might be complicated with.

Key words: Euglycaemic, ketoacidosis, pregnancy

Introduction

Pregnancy is associated with increased insulin resistance and , enhanced lipolysis ,while free fatty acid concentrations rise and ketogenesis is promoted due to the presence of placentally produced hormones such as glucagon, cortisol and human placental lactogen.[1] Even brief periods of superimposed stress, fasting or starvation might exacerbate the above mentioned ketogenesis which may present as severe anion gap metabolic acidosis.[2] Interestingly, the clinical diagnosis may often be delayed as patients appear deceptively better than the unaffected the severe underlying acidosis would suggest. Such a delay in the initiation of treatment may lead to profound acidosis and its sequalae.

In terms of complications, a number of studies have demonstrated that acidosis may cause poor fetal outcomes including fetal loss or severe neurological impairment.[3]

We present a rare case of a Dichorionic Diamniotic twin pregnancy which presented with severe ketoacidosis caused by persistent vomiting and prolonged starvation. The euglycemic acidosis was promptly detected and managed resulting in good maternal and fetal outcome.emphasising the need for early diagnosis and etiologic treatment.

Case presentation

A 41-year-old ,obese, Caucasian pregnant woman at 23+0 weeks of gestation, gravida II, para 0, carrying dichorionic diamniotic (DCDA) twins, conceived via in vitro fertilization, conceived via in vitro fertilisation (IVF), presented to the emergency department of our institution due to fatigue, shortness of breath, tachypnoea and hypertension. The woman's past medical history was uneventful.

The patient mentioned multiple episodes of vomiting since the 3rd week of her pregnancy, while the last week she noted an increase of these episodes to 20 per day. The patient underlined her inability to tolerate any food consumption the previous 3 days.

On her admission, the blood pressure was 190/110mmHg, her heart rate was 80bpm, oxygen saturation was 97% and her body temperature was 36.7°C. On clinical examination she was tachypnoeic (the respiratory rate was 30 breaths per minute) and had peripheral vasoconstriction as suggested by cold limbs, with no other notable findings. Initial laboratory findings revealed 16,900 white blood cells / μL (92.5% neutrophils), CRP 1.28 mg/L, PLT 508,000/μL, Glu 108mg/dL, uric acid 8 mg/dL, while the urinalysis was negative for proteins and glucose but positive for ketones (2+). Arterial blood gases (pH 7.2, pO_2 109, pCO_2 9.2, HCO_3^- 4.4) revealed severe anion gap metabolic acidosis with respiratory compensation.

She was initially treated with intravenous fluids (10% glucose at 125 ml/h in conjunction with insulin at a rate of 7 ml/h), diuretics, amlodipine and labetalol, supplemental oxygen, histamine-H2 antagonists, magnesium sulphate IV, bicarbonate and ceftriaxone 2gr (due to the increased white blood cell count, CRP and tachypnoea) and was then admitted to the high dependency unit (HDU). Due to the suboptimal response to oral antihypertensives, IV infusion of labetalol was initiated. The cardiological assessment along with a transthoracic echocardiogram revealed no abnormalities. An ultrasound of the abdomen showed gall bladder sludge and mild dilatation of the intrahepatic bile ducts.

The obstetrical sonographic examination revealed a dichorionic diamniotic twin pregnancy with positive cardiac functions, the growth of both fetuses being appropriate for the gestational age and the amniotic fluid of both sacs being within the normal range.

Based on the symptoms, the differential diagnosis included: diabetic ketoacidosis (DKA), sepsis, acute fatty liver of pregnancy, euglyceamicketoacidosis, hyperemesis gravidarum, alcohol consumption, substance abuse and recent COVID infection.

The patient had no previous history of diabetes mellitus and the glucose levels were within normal limits (Glucose:108mg/dl and HBA1C 4.8%). In addition, the patient had no fever, procalcitonin and CRP levels were normal and COVID molecular test was negative. Furthermore, amylase levels were normal, the hepatic biochemistry was within normal range and the abdominal ultrasound revealed no obvious abnormalities.

As such, based on the symptoms and all the diagnostic tests in whole, a working diagnosis of euglycemic ketoacidosis due to hyperemesis and prolonged starvation was established.

The patient remained in the HDU for 4 days and was then transferred to the high-risk pregnancy unit. She remained stable without any episodes of vomiting under antacid and anti-sickness per os regimen and her vital signs and air blood gases were normalized.

She was discharged 7 days later.

The patient returned to the hospital on the 28th week of pregnancy with similar symptoms and increased blood pressure. She was initially treated with the same combination of IV fluids, antacids, anti-sickness and antihypertensive medications. During her hospitalization, the control of blood pressure became challenging with no response to increasing doses of antihypertensive medications and at 31+1 weeks of gestational age she developed peripheral oedema and proteinuria (580mg of protein in a 24 hour urine sample collection). She received a course of corticosteroids and she delivered at 31+3 weeks of gestation with caesarean section two live, female newborns weighing 1475gr and 1442gr with the same APGAR scores of 7 and 8 at 1 and 5 minutes, respectively.

Discussion

It is well established that, under the normal circumstances of sufficient glucose availability and insulin production, glucolysis will lead to the generation of pyruvate which, through the citric acid cycle, will result in the production of ATP as the available energy source. In cases of glucose or insulin deficiency, free fatty acids are oxidized ,generating acetyl coenzyme A, which will produce the necessary ATP, forming as such an alternative source of energy.

Pregnancy is a state of relative insulin resistance, enhanced lipolysis and elevated levels of free fatty acids and studies have demonstrated that even short periods of starvation may be complicated with starvation ketoacidosis. Euglycaemic ketoacidosis or refers to metabolic acidosis caused by prolonged starvation.[4] In non pregnant individuals, maximal ketone production can be established after three days of starvation and fully developed ketoacidosis can be met after fasting of 2-3 weeks or even longer.[5] In pregnancy, however, a condition of ''accelerated starvation'' might be developed in an effort for adequate amounts of glucose and amino acids to be provided to the fetus for its growth and development with an exaggeration of such a process taking place especially in the third trimester.[6] This process was underlined by Metzger et al[2] by revealing increased levels of free fatty acids and ketone bodies after fasting for 12 hours in pregnant women compared to control non pregnant women with the already discussed hormone alterations of pregnancy further intensified during periods of stress such as vomiting. Such cases of starvation ketoacidosis are rarely reported and are mostly sequelae of diabetes mellitus.[7]

A state of metabolic acidosis during gestation - of any cause – is alarming as it has been associated with varying degrees of neural impaired development or even fetal loss[8,9] and its finding needs to initiate an investigation of the underlying cause. Anion Gap (AG) is useful in guiding the investigation as a normal AG metabolic acidosis is seen in patients with increased bicarbonate loss either from the gastrointestinal tract due to diarrhoea, pancreatic fistulas and ureteroenterostomies or through renal losses as seen in chronic renal failure. On the contrary, an elevated AG acidosis may be attributed to increased levels of lactic acid (e.g. sepsis), excessive ketone production (diabetes mellitus, starvation, pregnancy, alcohol intake or certain inborn errors of metabolism, or with genetic predisposition), uraemia, acute fatty liver of pregnancy, excessive alcohol consumption, or ingestion of exogenous acids such as in poisoning with methanol, salicylates or ethylene glycol.

In our case, the combination of high anion gap metabolic acidosis (pH 7.2, pO_2 109, pCO_2 9.2, HCO_3^- 4.4) in combination with normal glucose,HbA1c and lactic acid levels ,as well as, the history of hyperemesis and starvation during pregnancy led us to the establishment of the diagnosis of euglycaemic metabolic acidosis.

The accurate and prompt diagnosis will eventually lead to the rapid management of the condition minimizing the adverse maternal and fetal complications. Treatment should be focused on intravenous fluid

replacement ,which constitutes of a combination of 5% or 10% dextrose solution as well as 0.9% normal saline, along with antihistamines or phenothiazines (as first line antiemetics) or metoclopramide, ondasetron and prednisolone (as second line antiemetics) and close monitoring of the vital signs, ABSs and electrolytes to identify and manage possible derangements.[10] Attention should be paid in the administration of intravenous glucose containing solutions in patients with severe starvation as it may be complicated with Wernicke's encephalopathy and eventually, Korsakoff's psychosis.

Finally, delivery should not be guided by the mental status of the patient as its seems that an emergency caesarean section in an unstable, acidotic patient may lead to complications such as further metabolic derangements and excessive bleeding, bearing in mind that the appropriate management might lead to the rapid improvement of the patient.[11]

The above presented case shows a unique interest given the severity of ketoacidosis due to the preceded hyperemesis and starvation in an otherwise healthy pregnant individual with the outcome, though, being favourable after the rapid investigation and treatment.

Conclusion

Eyglycaemic ketoacidosis during pregnancy is a cause of severe metabolic acidosis even after periods of brief starvation and hyperemesis due to the underlying predisposition of pregnancy to ketosis.. Knowledge of the condition, its precipitating factors and its diagnostic approach will achieve the timely recognition and management of the entity minimizing the maternal and fetal complications it is associated with.

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