Available online at www.sciencerepository.org

Science Repository

Case Report

Acute Starvation as a Trigger for Non-Diabetic Ketoacidosis in a Third-Trimester Pregnant Woman Undergoing Severe SARS-CoV-2 Pneumonia

L. R. Villalobos-Lopez, O. R. Jimenez-Flores, L. Del Carpio-Orantes*, M. Martinez-Rojas and A. A. Basulto-Herrera

Intensive Care Unit, General Hospital No. 71 Instituto Mexicano del Seguro Social, Veracruz, Mexico

ARTICLE INFO

Article history:
Received: 27 January, 2022
Accepted: 22 February, 2022
Published: 3 March, 2022

Keywords:
Non-diabetic ketoacidosis
pregnancy
starvation
COVID-19 severe pneumonia
SARS-CoV-2

ABSTRACT

Acute starvation was found as the single probable triggering cause for this condition, since most-common causes of high-anion gap metabolic acidosis were dismissed. We report the case of a 34-year-old woman undergoing a 25-weeks pregnancy and suffering COVID-19 severe pneumonia who developed severe and persistent metabolic acidemia caused by non-diabetic ketoacidosis in whom we found a background of 48-hours starvation prior to ICU admission. The patient underwent 13-days mechanical ventilation and comprehensive care as well as an addressed treatment for this complication. Further the metabolic acidosis got solved and lately we were able to discharge her from the ICU and, ultimately, from hospital to home with the only need of supplementary oxygen. Ketosis is common in prolonged fasting, but it rarely impacts pH in an acute patient. In conditions of increased metabolic demand, such as pregnancy and pneumonia, starving could increase metabolic stress and finally alter the acid-base status affecting the clinical situation for the patient.

Introduction

Starvation ketoacidosis rarely occurs in non-diabetic patients as there are glucose-production pathways compensating for the lack of carbohydrates intake. So far, 12 cases have been reported sharing similar traits but, to this moment, no case has been reported related with the SARS-CoV-2 pandemics [1]. Those alterations entailed by an acid-base disorder have a significant impact on the clinical condition of the mother and the fetus. The importance of an early approach to metabolic acidosis in critically-ill patients have a significant impact on its management and prognosis [2]. During the third trimester of pregnancy, placenta plays an essential role, increasing the production of glucagon, cortisol and lactogen, causing an increase in peripheral insulin resistance and consequently a greater production of ketone bodies as a biochemical source of energy [3].

Case Report

A 34-year-old woman, undergoing a second pregnancy without obstetric complications until the beginning of COVID-19 symptoms. She has a history of an abortion. Last menstrual period date was January 20, 2021. Had no history for any chronic disease. She started with symptoms on July 21, 2021. Presenting with a clinical condition characterized by temperature elevation of up to 38.5 ºC associated to myalgias and arthralgias as well as the presence of rhinorrhea and productive cough. In the following 4 days the patient developed a worsening of symptoms and dyspnea on exertion together with fatigue are added to the persisting fever. For this reason, she looks for medical assistance in her family medicine unit. As to evaluation, SARS-CoV-2 antigen test was performed obtaining a positive result. The obstetrics approach reported fundal height at the level of the umbilicus, pregnant uterus holding a single alive product, no uterine activity neither vaginal loss. As to respiratory evaluation, the patient was dependent on supplemental oxygen support at 4 liter/minute with a low-flow nasal cannula, had a respiratory rate of 26 bpm and a Pa/Fi ratio of 461. At initial ABG we found a pH 7.41, pCO2 27 mmHg, pO2 172 mmHg, HCO3 17.1 mol/L, base deficit -6.4 mmol/L. Lactate 1.6 mmol/L. It was to be noted a high anion gap metabolic acidosis (20 mmol/L) with a central glucose of 126 mmol/L, urea and BUN were reported in normal ranges: creatinine 0.61 mg/dL, BUN 7.8 mg/dL, urea 16.7 mg/dL, urine ketones 50 mg/dL. In CBC we found no anemia, normal platelets, leukocytes 5.6 $\times 10^9$/L, lymphocytes 1020/mm^3. Initial CT scan dating July 15 provided a report diagnosing a CORADS V pneumonia.

Correspondence to: L. Del Carpio-Orantes, Intensive Care Unit, General Hospital No. 71 Instituto Mexicano del Seguro Social, Veracruz, Mexico; E-mail: neurona23@hotmail.com

http://dx.doi.org/10.31487/j.JCMCR.2022.01.01

She was admitted to the COVID-19-E.R. area, where she remained 72 hours until being admitted to our ICU. She received support treatment according to international guidelines. During her ICU standing, the patient showed a deterioration of respiratory function initially treated with high-flow oxygen therapy with a 2-hours iROX of 2.8, so in need for intubation and mechanical ventilation being performed on July 30, 2021, under a lung-protective ventilation strategy plus neuromuscular blockade and left lateral decubitus position. The obstetric evaluation reported a 26 cm fundal height, a fetal heart rate of 155 bpm, no uterine activity, gestational age by US 26.6 WOG. Estimated fetal weight of 665 g, a fundal placenta with maturation grade I. Fetal movements were present. On August 1st with 27 WOG the patient suffered a hypertensive emergency and deterioration of pulmonary function and pre-eclampsia-addressed treatment was started with hydralazine and alpha-methyl-dopa. On August 3rd, lung maturation treatment was completed. Report of glycated haemoglobin 6%, A1c fraction 0.464 mmol/L. On August 4 required an increase in antihypertensive management. Report of cultures demonstrated no growth. At 28 WOG, growth restriction was reported and blood pressure stats kept rising. With this, the patient begins a high-severity data to which moderate anemia is added.

On August 7, the obstetrics evaluations showed a product in pelvic presentation with a fetal HR 153 bpm, grade II fundal placenta, estimated fetal weight by US of 870 grams, and US-estimated gestational age of 27.1 WOG. On august 8, in the US was found oligohydramnios data and negative crystallography. On August 9, she was diagnosed with severe preeclampsia at 28 WOG by LMP and 27 WOG by US to which it was added delayed fetal growth and anhydramnios as well as fetal tachycardia of 176 bpm. Because of all this, interruption of pregnancy was decided, and she underwent an emergency C-section. A Kerr-type C-section was performed. On surgery, a male product of 890 grams Apgar 0/0 was obtained. As for the patient, in the immediate postoperative period, ventilatory progression and antihypertensive adjustment were performed. On August 10, 2021, the patient emerged from sedation, and we were able to progress the mechanical ventilation up to spontaneous mode. On August 11, the patient was successfully withdrawn from mechanical ventilation. In the immediate puerperium, we found a clinical for depression, her caloric intake decreased, and high anion gap metabolic acidosis arose once again. A urine test strip showed ketones about 15 mg/dL. Tricyclic antidepressant and restart of caloric intake treatments were started with further recovery for the acid-base status. Finally, she was discharged from our ICU and three days later she was discharged from hospital without complications.

Discussion

Among the various manifestations of the disease having loss of homeostasis in critically-ill patients within or outside the intensive care unit are acid-base imbalances (ABI), the clinical scenario in which the concentration of hydrogen ions increases is called acidosis, and the status where its concentration lowers is called alkalosis, out of this two entities, metabolic acidosis is one of the most commonly diagnosed disorders, therefore the third step after identifying the primary and/or secondary disorder will always be to determinate an anion gap status (AG) for analysis and diagnosis [4, 5].

Anion-gap formula:
$AG = Na^{+}-(Cl^{-}+HCO3^{-})$

For the approach of metabolic acidosis, an AG calculation and evaluation has been proposed as an important resource, considered as a mandatory step for this approach. This tool provides us with a bifurcation to move into the diagnosis of the etiologic pathology underlying the acid-base disorder, emerging from it, numerous pathologies have been classified as etiologies for metabolic acidemia in the two branches of either high AG or normal AG, within the first mentioned, the most common are: diabetic ketoacidosis, uremia due to CKD or ARD, lactic acidemia and poisonings by ASA, ethylene glycol, methanol, isoniazid, iron, paraldehyde, and recently added to the list include congenital heart disease, carbon monoxide poisoning, cyanide poisoning, as well as acetaminophen and toluene poisoning [5, 6]. In the second classification, acidemias preserving a normal AG are predominantly GI losses of $HCO3^{-}$ (fistulas), type I and II renal tubular acidosis and use of acetazolamide [7].

The origin of the status of ketoacidosis that is triggered by glycemic lack of control in DM1 or DM2 is widely described, in this, insulin resistance stands out with an absolute or relative insulin deficiency and, in turn, lack of capacity for production of energy through glycolysis, increasing the release of counter-regulatory hormones (mainly glucagon), which generates an increase in beta-oxidation within the liver with the subsequent creation of the 3 ketone bodies derived from the use of free fatty acids as the main source for obtaining energy, which then produces a decrease in $HCO3^{-}$ in the serum anions segment with a resulting increase in AG, manifesting this way acidemia, a process that can arise in a similar way in intermittent or prolonged fasting due to a decrease in serum glucose together with the consumption of hepatic glycogen, which is usually 80 to 100 grams, being equivalent to a pool able to provide carbohydrates for approximately 12 to 24 hours when in fasting without physical activity, and having a calculated top of 14 days fasting for the expression of ketoacidosis on healthy patients [8, 9].

The increased risk for ketosis in pregnancy was described back in 1970 by Feling and Lynch who demonstrated an overproduction of ketone bodies when fasting in pregnant women vs non-pregnant women [10]. This was supported by Metzger when measuring glucose concentrations, alanine, B-hydroxybutyrate and concentrations of free fatty acids in pregnant women in third trimester vs non-pregnant women. After 12 hours an increase in serum levels of free fatty acids and B-hydroxybutyrate was demonstrated [11].

The clinical case here depicted demonstrates the relevance of fasting ketoacidemia in a pregnant woman undergoing second to third trimester, without a history of diabetes mellitus, which was ruled out by a normal HbA1c value, intoxications were ruled out along with hyperlactatemia as etiologic causes. The patient underwent COVID-19 with lung-protecting mechanical ventilation and close-to-prone sessions. The pathophysiological causes explaining the development of non-diabetic ketoacidosis genesis with ketone bodies are given by the following causes:

i. The increased risk of ketosis in pregnancy occurs due to being in a hypermetabolic status, with an incidence of relative starvation following intense vomiting that is mostly marked in the second half of pregnancy when the woman has a shortened period prior the initiation of use of fatty acids as the main source of energy following short periods of fasting, thus, even is more frequently developed in labour [10].

ii. During pregnancy, there is a relative insulin deficit, which is promoted by the serum presence of hormones from the placenta such as glucagon, cortisol and human placental lactogen. These hormones are also increased during periods of stress, inflammation or even vomiting [10].

iii. Likewise, the respiratory minute volume in the pregnant woman is increased by an increase in the respiratory rate with development of respiratory alkalemia and a decrease in plasma CO2, a situation compensated by an increase in excretion of $HCO3^-$ at proximal renal tubule with a subsequent serum decrease [12].

iv. There are several drugs known to increase the risk for ketoacidosis in any context, of which B-agonists that are used as tocolytics stand out, producing an increased lipolysis, gluconeogenesis and glycogenolysis with an increase in serum free fatty acids and ketonemia. Steroids are also widely known to promote an increased insulin resistance situation present in this patient by the administration of dexamethasone 6 mg daily for 10 days because of severe COVID-19 [2].

In this particular case, the patient started with general symptoms such as headache, myalgia, arthralgia, persistent fever, moderate dehydration produced by fasting, with an HR of 165 bpm and a BP of 86/56 mmHg upon arrival at the respiratory emergency department. Prolonged fasting with exclusive liquids intake began 4 days prior to her admission due to the onset of dyspnea that same day, followed by a RR of up to 52 bpm prior to placement of invasive mechanical ventilation as well as the use of steroid as addressed treatment. As starting the feeding through a nasogastric tube, ketolysis gradually appeared with a corresponding gradual increase in serum $HCO3^-$ and shortening of the base deficit (BE), until it found its equilibrium.

Consent

The patient and the relatives signed an informed consent for the purposes of publication of this text as a case report.

Ethical Approval

Ethical approval was not considered, since this report is retrospective and observational without any intervention.

Study Location

This case was held at the General Hospital No. 71, a hospital of Instituto Mexicano del Seguro Social.

Conflicts of Interest

None.

REFERENCES

1. Skalley G, Rodríguez-Villar S (2018) Nondiabetic ketoacidosis in a pregnant woman due to acute starvation with concomitant influenza A (H1N1) and respiratory failure. *Rev Esp Anestesiol Reanim (Engl Ed)* 65: 407-412. [Crossref]
2. Land JM, A'Court CH, Gillmer MD, Ledingham JG (1992) Severe non-diabetic keto-acidosis causing intrauterine death. *Br J Obstet Gynaecol* 99: 77-79. [Crossref]
3. Patel A, Felstead D, Doraiswami M, Stocks GM, Waheed U (2011) Acute starvation in pregnancy: a cause of severe metabolic acidosis. *Int J Obstet Anesth* 20: 253-256. [Crossref]
4. Rennke HG, Denker BM (2010) Renal pathophysiology, the essentials. 3rd ed. Philadelphia: Lippincott Williams & Wilkins.
5. Kraut JA, Madias NE (2007) Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol* 2: 162-174. [Crossref]
6. Mehta AN, Emmett JB, Emmett M (2008) GOLD MARK: an anion gap mnemonic for the 21st century. *Lancet* 372: 892. [Crossref]
7. Corey HE, Vallo A, Rodríguez-Soriano J (2006) An analysis of renal tubular acidosis by the Stewart method. *Pediatr Nephrol* 21: 206-211. [Crossref]
8. Frise CJ, Mackillop L, Joash K, Williamson C (2013) Starvation ketoacidosis in pregnancy. *Eur J Obst Gynecol Reprod Biol* 167: 1-7. [Crossref]
9. Owen OE, Caprio S, Reichard Jr GA, Mozzoli MA, Boden G et al. (1983) Ketosis of starvation: a revisit and new perspectives. *Clin Endocrinol Metab* 12: 359-379. [Crossref]
10. Feling P, Lynch V (1970) Starvation in human pregnancy: hypoglycemia, hypoinsulinemia, and hyperketonemia. *Science* 170: 990-992. [Crossref]
11. Metzger BE, Ravnikar V, Vileisis RA, Freinkel N (1982) "Accelerated starvation" and the skipped breakfast in late normal pregnancy. *Lancet* 1: 588-592. [Crossref]
12. Cugell DW, Frank NR, Gaensler EA, Badger TL (1953) Pulmonary function in pregnancy. I. Serial observations in normal women. *Am Rev Tuberc* 67: 568-597. [Crossref]