Received: 17 July 2021 | Revised: 12 March 2022 | Accepted: 15 March 2022

DOI: 10.1002/ccr3.5680

CASE REPORT

Clinical Case Reports Open Access WILEY

Euglycemic diabetic ketoacidosis in pregnancy with COVID-19: A case report and literature review

Sameena Wazir[1] | **Saheed Shittu**[1] | **Khaled Dukhan**[2] | **Maram Sharief**[2] | **Stephen Beer**[2] | **Waseem Malik**[3] | **Lolwa Alansari**[1]

[1]Department of Obstetrics and Gynecology, Hamad Medical Corporation (HMC), Al Wakra Hospital (AWH), Doha, Qatar

[2]Department of Medicine, HMC, AWH, Doha, Qatar

[3]Department of Emergency Medicine, HMC, Hamad General Hospital (HGH), Doha, Qatar

Correspondence
Sameena Wazir, Department of Obstetrics and Gynecology, AWH, HMC, Doha, Qatar.
Email: swazir@hamad.qa

Funding information
Open access funding of this publication is provided by Qatar National Library

Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes and is considered a medical emergency. Euglycemic DKA (EKDA) is a variant of DKA with a normal or minimally elevated glucose level <200 mg/dl. The condition can be difficult to diagnose due to the relatively normal glucose levels. Pregnancy, infection, and a low-calorie intake are some of the contributing common etiologies of EDKA. Despite a rapid increase in scientific publications on COVID-19, there are still knowledge gaps regarding the course of COVID-19 in some patient subset. This is especially the case for pregnant women. In this case report, we discuss the course of COVID-19 infection in a pregnant woman with gestational diabetes who developed severe euglycemic diabetic ketoacidosis triggered by various precipitating factors, including starvation, caused by COVID-19 infection and its gastrointestinal effects.

KEYWORDS

COVID-19 infection, euglycemic diabetic ketoacidosis, pregnancy

1 | INTRODUCTION

The coronavirus (SARS-CoV-2) pandemic and the associated illness coronavirus disease 2019 (COVID-19) with a diversity of clinical manifestations is currently the most challenging situation physicians are facing. Pregnant women are a potentially highly vulnerable population during the pandemic due to pregnancy related anatomical, physiological, and immunological changes.[1] Papers are being published and research is ongoing to gain more information on clinical characteristics and outcomes of pregnant women infected with COVID-19, in order to improve its management in pregnant patients.[2]

Pregnancies complicated by diabetic ketoacidosis, which is a life-threatening emergency, are associated with increased rates of perinatal morbidity and mortality.[1–4] A high index of suspicion is required because diabetic ketoacidosis in pregnancy can be difficult to diagnose as it can occur at lower glucose levels and can progress more rapidly than in the non-pregnant state. Euglycemic DKA (EDKA) is defined as a variant of DKA with increased anion gap metabolic acidosis and ketosis, but with glucose levels less than 200 mg/dl or within normal range.[3,4] It is much less common than hyperglycemic DKA and is relatively harder to diagnose due to the potentially misleading normal or only slightly elevated blood glucose levels. Morbidity and mortality can be reduced with early

detection of the precipitating factors, prompt hospitalization, and targeted therapy with intensive monitoring provided by a multidisciplinary team including obstetrician, endocrinologist, and intensivist.[3,4]

Pregnant women are more likely to develop DKA compared with non-pregnant women with diabetes (8.9% vs 3.1%, respectively).[5] Pregnant women with pre-existing or gestational diabetes are also at high risk of severe COVID-19 infection which can precipitate complications of diabetes including DKA and hyperosmolar hyperglycemic state (HHS) although to date, only a few cases of EDKA in pregnancies with COVID-19 have been reported.[2] We describe a case of a pregnant woman who developed EDKA in the third trimester while being treated for severe pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[6]

2 | CASE PRESENTATION

A 35-year-old Qatari woman (Gravida 3, Para 2) known to have gestational diabetes managed by lifestyle modification alone and hypothyroidism treated with 50 mcg of levothyroxine presented to our Emergency Room at 29 weeks' gestation complaining of fever, cough, and shortness of breath of 2 days' duration. Subsequently, she was diagnosed with COVID-19 infection with a positive reverse transcriptase polymerase chain reaction test (RT PCR). On initial assessment, she had normal vital signs and was maintaining oxygen saturation on room air. Based on clinical symptoms, basic laboratory investigations (Table 1) and chest X-ray were requested. Her chest X-ray (Figure 1) revealed increased broncho-vascular markings and infiltrates in both lung fields with no obvious consolidation or cavitation seen. Patient was managed as mild pneumonia and was started on hydroxychloroquine, antiviral (Kaletra), antibiotics, and thromboprophylaxis as per hospital protocol.

On second day of admission, she started complaining of nausea, vomiting, loss of appetite, and diarrhea. She was hemodynamically stable, afebrile, and maintaining her oxygen saturation above 96% on room air. In her subsequent stay in hospital, she continued to have loss of appetite. Repeat laboratory tests revealed persistent ketonuria, low potassium levels and hypomagnesaemia with worsening of symptoms of COVID-19 infection. Her oxygen saturation started to drop, and her tests results showed elevated C-reactive protein, ferritin, and interleukin-6 suggesting a picture of cytokine storm.

Repeat chest X-ray (Figure 2) revealed increase in bilateral infiltrates with patchy opacities. She was started on intravenous remdesivir, ertapenem, and methylprednisolone as per hospital protocol. Blood results revealed a severe metabolic acidosis with bicarbonate level in

TABLE 1 Patient's biochemical parameters on admission to MICU and afterwards

Investigations	Result before MICU admission	Result after MICU discharge	Normal laboratory range
Blood glucose (mmol/L)	4.7	4.3	3.3–5.5
HBA1c (%)	4.6%	–	4.8–6.0
Hemoglobin (g/dl)	9.9	10.3	12–15
Arterial pH	7.26	7.34	7.35–7.45
PaO2 (mmHg)	51	57	83–108
PaCO2 (mmHg)	22	35	35–45
Base Excess (mmol/L)	−11.8	−0.9	−2 to +2
Bicarbonates (mmol/L)	9.6	23	22–29
Lactate (mmol/L)	0.5	1.0	0.5–2.2
Urinary Ketones (+)	4+	Negative	Negative
Serum hydroxybutyrate (mmol/L)	4.6	0.90	0.0–0.6
Alanine transaminase (μ/L)	8	6	0–55
Aspartate transaminase (μ/L)	19	21	5–34
Interleukin-6 (pg/ml)	19	15	<7
Ferritin (mcg/L)	449.2	256	11–304
C-RP (mg/L)	22	136	0–5

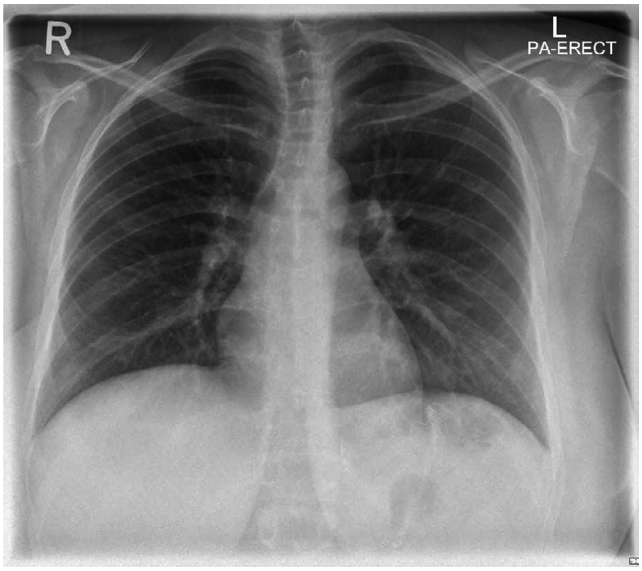

FIGURE 1 Chest X-ray on admission to the ward

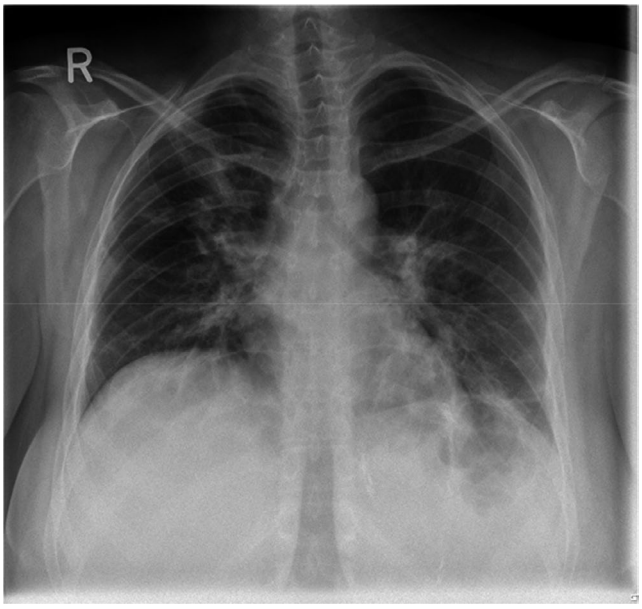

FIGURE 2 Chest X-ray of the patient while in MICU

critical range (refer to the table) and high anion gap of 14. Urinalysis ruled out urinary tract infection. Her blood sugars were within normal range (4.0 mmol/L). A diagnosis of EDKA was made. She was moved to Medical Intensive Care Unit (MICU) where she stayed for 2 days receiving vigorous intravenous hydration, electrolyte replacement, and insulin and dextrose infusions.

She improved clinically, and her laboratory tests improved with resolution of DKA. She was transferred back to the antenatal ward where her vomiting and diarrhea improved and was subsequently discharged home. Her fetal movement perception, cardiotocography (CTG), and fetal ultrasound all remained normal while she was in the hospital. A week after discharge she remained well when reviewed in clinic and continued to have normal pregnancy follow-up. She had normal vaginal delivery at 40 weeks with normal neonatal and maternal outcome and was discharged home on regular medications after 24 h. She was planned for glucose tolerance test after 6 weeks.

3 | DISCUSSION

Euglycemic diabetic ketoacidosis (EDKA) is a type of diabetic ketoacidosis where glucose is either in the normal range or only minimally elevated and can be difficult to diagnose. Our patient presented with mild respiratory symptoms and was diagnosed as COVID-19 positive by real-time reverse transcription polymerase chain reaction (RT PCR). Initially symptoms were attributed to COVID-19 infection. However, the presence of ketonuria, metabolic acidosis, and high anion gap in a pregnant woman with gestational diabetes led to the suspicion of EDKA. 6.4% of patients with COVID-19 infection that require hospitalization, have ketosis or ketoacidosis, and 35% of them are affected by diabetes; hence, COVID-19 infection in itself is an independent risk factor for ketoacidosis even in normoglycemic individuals.[7] EDKA can be provoked by *acute starvation because of gastrointestinal symptoms* due to severe COVID-19 infection as it was the case for our patient.[7] A number of other factors may also be responsible for development of diabetic ketoacidosis according to the literature.

Endocrine changes in pregnancy are associated with decreased release of insulin and increased insulin resistance because of placental hormones (including human placental lactogen, catecholamines, glucagon, growth hormone, and cortisol) that are antagonistic to insulin.[3] *Stress* associated with COVID-19 infection also increases these hormones which promote lipolysis and increased free fatty acid and ketone body production.[7] Pregnancy tends to lead to production of more ketones two to four times higher than in non-pregnant females and it tends to increase risk of metabolic acidosis as it is a hypermetabolic state.[3]

Direct toxic effect of the virus on islet cells which show increased expression of angiotensin converting enzyme 2 (ACE2) receptors may lead to higher rate of cell death among insulin producing islet cells leading to increased ketoacidosis and insulinopenia.[8] Furthermore, *increased pro-inflammatory cytokine release (Cytokine Storm)* characterized by high ferritin and interlukin-6 level as seen in our patient also plays some role in the development of ketoacidosis in patient with COVID-19 by increasing lipolysis and ketogenesis.[9,10]

Abdulrahman et al. demonstrated that *use of Hydroxychloroquine* in COVID-19 patients is associated with increased risk of hypoglycemia and diarrhoea[11] and it could have played a role in the glucose level being in normal range while our patient was in diabetic ketoacidosis. Likewise, *use of steroids* in the treatment of severe COVID-19 infection can precipitate ketoacidosis, but usually with hyperglycemia in pregnant patients with pre-existing or gestational diabetes. The magnitude and duration of such effect depends on the dose and type of steroid used.[12]

All the above factors could have contributed to the development of ketoacidosis in our patient who was pregnant, had gestational diabetes and severe COVID-19 infection which needed steroid treatment. However, given her normal blood sugars, we postulate that acute starvation, being pregnant and the tendency of COVID-19 infection to cause ketosis (and ketoacidosis in some cases) were the main driving factors to develop EDKA in her case. A pregnant diabetic Muslim developing ketoacidosis at the time of Ramadan, readily brings to mind the effect of fasting on such patients.[13] Though our patient was not fasting, there is need to counsel such patients regarding proper dietary intake, hydration and good glycemic control.[13]

Maternal ketoacidosis can lead to fetal acidosis and hypoxia which can manifest as abnormal antenatal CTG.[14,15] The CTG should normalize with correction of maternal acidosis and supportive treatment. Immediate delivery is not always automatically indicated unless there is no improvement in CTG despite the correction and there are red flags suggesting emergency Cesarean delivery is necessary.[14] The CTG probably remained normal in our patient because of the prompt detection and correction of maternal ketoacidosis and she later had a normal vaginal delivery.

The occurrence of this serious complication can be prevented by vaccination of all pregnant women as recommended by the American College of Obstetricians and Gynecologists (ACOG)[16] and education of patients and members of the health team regarding early identification of symptoms and signs euglycemic diabetic ketoacidosis and prompt treatment when pregnant women with diabetes present with features of severe COVID-19 infection.[1,2,6]

4 | CONCLUSION

Euglycemic diabetic ketoacidosis is a rare life-threatening complication that can occur in pregnant diabetic patients who develop severe COVID-19 infection and is associated with high risk of fetal loss. Clinicians should have high index of suspicion when such patients present with ketonuria and should take appropriate steps to manage them using multidisciplinary approach with intensive care input.

ACKNOWLEDGMENT

We would like to thank our other obstetric, medical, and intensive care colleagues who contributed to the care of the patient and her baby.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

SW and SS conceived the idea and contributed to manuscript drafting. WM, MS SW, SS, and KD contributed to patient management and drafting of the manuscript. SB and LA contributed to literature review and manuscript drafting. All authors read and approved the final version.

ETHICAL APPROVAL

Ethics approval was not required for this case report. Informed consent was obtained from participants.

CONSENT

Written informed consent was obtained from the patients for their anonymized information to be published in this article. Documentation of the written consent will be provided to the journal upon request.

DATA AVAILABILITY STATEMENT

All relevant data described in the manuscript will be made available from the corresponding author upon request.

REFERENCES

1. Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Araujo Júnior E. Covid-19 and pregnancy: an overview. *Rev Bras Ginecol Obstet*. 2020;42(07):420-426. doi:10.1055/s-0040-1713408
2. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. *J Clin Endocrinol Metab*. 2020;105(8):2819-2829. doi:10.1210/clinem/dgaa360
3. Rawla P, Vellipuram AR, Bandaru SS, Pradeep RJ. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. *Endocrinol Diabetes Metab Case Rep*. 2017;2017:17-0081. doi:10.1530/EDM-17-0081
4. Modi A, Agrawal A, Morgan F. Euglycemic diabetic ketoacidosis: a review. *Curr Diabetes Rev*. 2017;13(3):315-321. doi:10.2174/1573399812666160421121307
5. Jaber JF, Standley M, Reddy R. Euglycemic diabetic ketoacidosis in pregnancy: a case report and review of current literature. *Case Rep Crit Care*. 2019;2019:8769714.
6. Mohan M, Baagar KAM, Lindow S. Management of diabetic ketoacidosis in pregnancy. *Obstet Gynaecol*. 2017;19:55-62.
7. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab*. 2020;22(10):1935-1941. doi:10.1111/dom.14057
8. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. 2021;3:149-165. doi:10.1038/s42255-021-00347-1

9. Frise CJ, Mackillop L, Joash K, et al. Starvation ketoacidosis in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2013;167:1-7.
10. Vitale RJ, Valtis YK, McDonnell ME, Palermo NE, Fisher NDL. euglycemic diabetic ketoacidosis with COVID-19 infection in patients with type 2 diabetes taking SGLT2 inhibitors. *AACE Clin Case Rep*. 2021;7(1):10-13. doi:10.1016/j.aace.2020.11.019
11. Abdulrahman A, AlSayed I, AlMadhi M, et al. The efficacy and safety of hydroxychloroquine in patients with COVID-19: a multicenter national retrospective cohort. *Infect Dis Ther*. 2021;10(1):439-455. doi:10.1007/s40121-021-00397-8
12. Alessi J, de Oliveira GB, Schaan BD, et al. Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes. *Diabetol Metab Syndr*. 2020;12:80. doi:10.1186/s13098-020-00583-7
13. Prentice AM, Prentice A, Lamb WH, et al. Metabolic consequences of fasting during Ramadan in pregnant and lactating women. *Hum Nutr Clin Nutr*. 1983;37:283-294.
14. Carroll MA, Yeomans ER. Diabetic ketoacidosis in pregnancy. *Crit Care Med*. 2005;33:S34753. doi:10.1097/01.CCM.0000183164.69315
15. Hagay ZJ, Weissman A, Lurie S, Insler V. Reversal of fetal distress following intensive treatment of maternal diabetic ketoacidosis. *Am J Perinatol*. 1994;11(6):430-432. doi:10.1055/s-2007-994613
16. ACOG. COVID-19 vaccination considerations for obstetric-gynecologic care; 2021. Accessed January 21, 2022. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-consideration

How to cite this article: Wazir S, Shittu S, Dukhan K, et al. Euglycemic diabetic ketoacidosis in pregnancy with COVID-19: A case report and literature review. *Clin Case Rep*. 2022;10:e05680. doi:10.1002/ccr3.5680