# Diabetic Ketoacidosis in Pregnancy: A Case Report

**Febrian Daru Setiawan [1], Hermina Novida[2]**

*[1]Resident, Department of Internal Medicine Dr. Soetomo Hospital – Faculty of Medicine Airlangga University, Surabaya Indonesia, [2]Lecturer, Division of Endocrinology, Metabolic Diseases and Diabetes, Department of Internal Medicine, Dr. Soetomo Hospital – Faculty of Medicine Airlangga University, Surabaya Indonesia*

## Abstract

A 31-year-old pregnant woman complained of vomiting, shortness of breath, fever, general weakness, painful and frequent urination with sign of hypertension, tachycardia, Kussmaul breathing. Laboratory studies showed neutrophilia, leukocytosis, hyperglycemia, hypokalemia, ketonuria, metabolic acidosis, low C-peptide, low Thyroid Stimulating Hormone, high FT4 and Staphylococcus in blood culture was diagnosed with Diabetic Ketoacidosis, pregestational Type 1 Diabetes Mellitus, hyperemesis gravidarum, 14 weeks of pregnancy, suspect Urinary Tract Infection, hypokalemia, hypertension, and subclinical hyperthyroidism. Besides, the patient blamed the fetus on causing the disease and financial problem so that the patient also was diagnosed with episode of moderate depression. The patient received KVT1 diet therapy, fluid replacement therapy, insulin therapy, correction of hypokalemia, correction of acidosis metabolic antibiotic and anti-hypertension. The therapies aimed to prevent maternal and fetal morbidity. Supportive psychotherapy therapy, relaxation therapy, and family psychoeducation were also needed to improve patient's compliant. The patient was also suggested to consult for family planning and glucose control before conception.

***Keywords:*** *Diabetic Ketoacidosis, Pregnancy, Diabetes Mellitus, Type 1 DM*

## Introduction

Diabetic ketoacidosis in pregnancy (DKP) is a serious condition causing several challenges. Incidence of Diabetic Ketoacidosis (DKA) among pregnant patients who have pregestational type 1 DM is 1.73%. DKP is related to maternal complications, such as acute kidney failure, acute respiratory distress syndrome, cerebral edema, coma and even death.(1) In recent years, the maternal mortality rate in DKA is less than 1% with a reported fetal mortality rate of 9-36%. Perinatal morbidity such as preterm labor, hypoxia, and acidosis remains high. (2) DKP requires immediate medical attention to prevent maternal and fetal morbidity and mortality. (2) (3)

Pregnancy is associated with physiological changes leading to DKA. (4) Pregnancy causes respiratory alkalosis associated with decreased compensation in bicarbonate levels. This impairs the capability of buffering so that pregnant women tend to have DKA. Relative insulin resistance in pregnancy along with increased lipolysis and increased free fatty acids. Increase of human placental lactogen, progesterone, and cortisol impair maternal insulin sensitivity. (5)

**Corresponding author:**
**Hermina Novida,**
Departement of Internal Medicine, Faculty of Medicine, Airlangga University, Jl.Mayjen Prof. Dr.Moestopo 47, Surabaya, East Java, Indonesia.
Phone: +6231-5020251,
Email: hermina-n@fk.unair.ac.id

A case of a DKP with T1DM are reported to discuss about proper treatment to avoid severe complications.

## Case Report

### History Taking

A woman, 31 years old, complained of nausea, shortness of breath, fever, painful and decrease in urination one week before admission.

Past medical history taking found DM since 19 years old. The last dose of insulin used is subcutaneous Aspart injection 34 units twice a day. During the first pregnancy in 2017, the patient also experienced the same complaint several times hospitalized and finally miscarried at 3 months of gestation. The patient had a history of hospitalization 4 times with the same complaints and treated in the intensive care unit (ICU).

At that time, the patient was on second pregnancy with a gestational age of 13-14 weeks. The insulin consumed was Aspart 6 units 3 times a day 15 minutes before eating and glargine 10 units in the morning and 18 units at night.

Frequently changed the insulin dose by herself, her compliance was not good. The patient also complained that she wanted to end her pregnancy because she thought that the fetus caused illness and economic problems.

### Physical Examination

The patient was compos mentis with general weakness. She weighed 50 kg and 160 cm in height. The body mass index was 19.53 kg/m$^2$. The vital sign examination found blood pressure (BP) of 90/60 mmHg, heart rate (HR) of 110 beats per minute with regular rhythm, Kussmaul breathing with respiratory rate (RR) of 26 times per minute, axillary temperature of 37.2$^o$C, and peripheral oxygen saturation of 99% using nasal cannula.

Physical examination showed normal head, neck, thorax, lung, heart, abdomen and extremity

Obstetrical examination found fundal height of 3 fingers above symphysis, fetal heart rate (FHR) of 148 beats per minute, no contraction. Vaginal examination showed no opening.

### Workup

Laboratory study found leucocytosis (18,330/ µL), neutrophilia (81.9%). Blood gas analysis (BGA) showed metabolic acidosis (pH 7.28; pCO2 21; pO2 205; BE -16,8; HCO3 9.9). Urinalysis found ketonuria (+3), proteinuria (+1), Leukosituria (10/ hpf) and Nitrituria (+), C-peptide of <0.01 ng/ml on the second day, and Procalcitonin 0,42 ng/ml, TSH 0.017mU/l, FT4 1.66ng/dL on the seventh day. Blood culture found bacteria *Staphylococcus haemolyticus* and urine culture did not found any germs.

Electrocardiogram (ECG) found sinus tachycardia rhythm (112x/min) with normal axis. Chest X ray was within normal limit.

### Diagnosi

According to the results of history taking, physical examination and workup examination, the patient was diagnosed with DKA, Pregestational T1DM, Hyperemesis gravidarum, G2P0010 13-14 weeks, suspect Urinary Tract Infection (UTI), hypokalemia, hypertension, Episode of moderate depression, and subclinical hyperthyroidism.

### Treatment

The patient was given central venous access to facilitate fluid administration. Diet planned was 2100 kcal of KVT1 diet. The fluid therapy given was 2 liters of NaCl 0.9% within 2 hours intravenously, followed by 80 dpm per 4 hours, 30 dpm per 18 hours. The insulin given to the patient was short-acting pump 1.5 IU per hour intravenously continued by 1 IU per hour on the second day and basal bolus regimen on the seventh day with adjusted dose according to the

BSL. Other treatment given were ceftriaxon 1 gram twice per day intravenously, 10 mg metoclopramide 3 times per day intravenously, vitamin B6 1 tablet once per day, 400 mcg folic acid twice per day, Calcium 500 mg twice per day. Premixed KCl 25meq and sustained-release potassium 3x600 mg orally were given on the second day due to hypokalemia. Sodium bicarbonate 250 mEq was given on the fourth day due to metabolic acidosis. Paracetamol 3x500 mg orally was given due to fever on the fourth day. Methyldopa 2x250mg orally was given due to hypertension. Phosphomycin injection 1x3000 mg was given intravenously on the seventh day based on the blood culture results. Spironolacton 1x50 mg orally was administered on the thirteenth day.

The patient was consulted to the Department of Psychiatry and diagnosed as episodes of moderate depression with somatic symptoms and was given supportive psychotherapy therapy, relaxation therapy, and family psychoeducation. Psychopharcologic treatment was postponed.

The patient was self-discharged against medical advice and suggested to visit endocrine outpatient unit. Patient was given subcutaneous detemir injection 18 units in the morning, subcutaneous aspart injection 10 units 3 times a day 15 minutes before meals, sustained release potassium 3x600 mg orally, Calcium tablet 1x500 mg orally, sodium bicarbonate 3x1 tablet orally, methyldopa 3x250 mg orally, folic acid tablet 3x1 orally.

One day after discharge, the patient's condition worsened and eventually miscarried and curetted. Eventually, the patient's condition improved and she was discharged.

## Discussion

ADA defines DKA as a triad of ketonemia or ketonuria, hyperglycemia and acidosis. [6] [7] The criteria for diagnosis of DKA are polyuria, polydipsy, nausea, vomiting, Kussmaul breathing, weakness, dehydration, hypotension to shock, awareness disturbed to coma accompanied by hyperglycemia (more than 300 mg/dL), hyponatremia (125-135 mEq/L), normal or hyperkalemia, normal magnesium, normal chlorine, hypophosphatemia, slightly increased creatinine, hyperosmolarity (300-320 mOsm/ml), Ketonemia (more than 3 mmol/L), low serum bicarbonate (less than 20 mEq/L), metabolic acidosis (pH less than 7.35; PCO2 20-30 mmHg), anion gap more than 10 mEq/L, glucosuria and ketonuria (more than 2+). [8] [9]

DKA can be triggered by specific factors such as prolonged vomiting, hyperemesis gravidarum, hunger, infections, non-compliance with the insulin use, beta sympathomimetic agents, steroid use, insulin pump failure and conditions such as diabetic gastroparesis. [5]

The patient in this case complained of nausea, vomiting, shortness of breath, fever, general weakness weaker, loss of appetite, painful and decreased urination. The patient had hyperemesis gravidarum, starvation, possible infection and inadequate use of insulin, which might trigger DKA. Physical examination obtained hypotension, tachycardia and Kussmaul breathing. Laboratory test found, hyperglicemia, metabolic acidosis, anion gap, ketonuria and hyperosmolality. Therefore, the patient was diagnosed with DKA.

According to the American Diabetes Association (ADA), DM is diagnosed based on several criteria, including HbA1C $\geq$ 6.5% standardized by the Diabetes Control and Complications Trial (DCCT) and is certified by the National Glycohemoglobin Standardization Program (NGSP) or fasting BSL $\geq$ 126 mg/dL or BSL 2 hours after an oral glucose tolerance test $\geq$ 200mg/dL or classic symptoms of hyperglycemia or hyperglycemia crisis with random BSL $\geq$ 200 mg/dL. [6]

Family history taking, measurement of autoantibodies to Langerhans islets, and measurement of plasma or urine C-peptide concentrations help to distinguish T1DM and T2DM.

C-peptide measurements represent a better alternative index of insulin secretion and residual ß-cell function. (10)

In this case, the patient was a woman, 31 years old, with classic clinical symptoms of hyperglycemia, history of DM since 12 years ago and consumption of insulin injection. BSL was 380 mg/dl, HbA1C was 7.4% and C-Peptide was 0.01 ng/ml. Therefore, the patient was diagnosed with T1DM.

One of the life-threatening complications of DM is DKA. The incidence of DKA has increased by 30% in the last few decades. DKA can occur in 15-20% of adult patients with type 2 DM. The mortality rate due to DKA reaches 5%, especially in patients with concomitant diseases.

Pregnant women have more risk of developing DKA than non-pregnant women. Pregnancy creates condition of respiratory alkalosis associated with decreased compensation in bicarbonate levels. This impairs capacity buffering so that pregnant women tend to have DKA. Relative insulin resistance in pregnancy along with increased lipolysis and increased free fatty acids. Increase of human placental lactogen, progesterone, and cortisol impair maternal insulin sensitivity. (5) Vomiting and use of betamimetic drugs also lead to DKA. Pregnant women with DM on chronic corticosteroid therapy have high risk of developing DKA due to increased serum glucose and risk of infection. (2)

Severe maternal dehydration and acidosis in DKA reduces uteroplacental perfusion. Severe maternal electrolyte disturbances result in maternal and fetal cardiac arrhythmias. Changes in fetal heart rate is a sign of acidosis due to maternal metabolic acidosis. (11)

DKA in pregnancy is considered as an emergency so that it has to be managed in high care unit (HCU) or ICU. The care provider team usually consists of obstetricians, endocrinologists, obstetric anesthesiologists, and trained nurses/midwives. There are 6 main management aspects that must be done simultaneously, including intravenous fluid therapy, intravenous insulin therapy, electrolyte correction, evaluation of the need for bicarbonate administration, identification and treatment of all trigger factors and monitoring. (3)

The goals of DKA management therapy include replacement of body fluids and salts, suppression of lipolysis and gluconeogenesis using insulin, overcoming triggering factors and restoring the normal physiological state. DKA therapy consists of 2 phases: phase I (emergency phase) and phase II (rehabilitation phase). The border between those phase is blood glucose of 250 mg/dL. (12)

Phase I DKA consists of fluid replacement, insulin rapid acting, potassium correction, acid-base correction, and antibiotics. Rehydration using isotonic fluid (ringer lactate or NaCl 0.9%) 2 liters in 2 hours, then 8 followed by 80 drops/minute in 4 hours, then continued with 30 drops/minute in 18 hours, and then with 20 drops/minute for 24 hours. This hydration formula is called "2-4-18-24" formula. Insulin is given using the formula "minus 1" for intravenous bolus or "times 12" for continuous infusion. However, insulin administration is delayed in hypokalemia. If the BGA showed pH $\leq$ 7.2 or HCO-3 <12 mEq/L, bicarbonate is given 50-100 mEq/500 ml in 24 hours intravenously. If pH $\leq$ 7.0, bicarbonate is given 50 mEq IV in 10 minutes, then 50 mEq is given in 2 hours.

Phase II consists of fluid maintenance, electrolyte maintenance, insulin and nutrition. If the patient is able to eat and ketosis is resolved, insulin is given with the formula of "times 2" subcutaneously. (13)

The targets of BSL in DM with pregnancy are fasting BSL of 80-110mg/dl, 1-hour post-prandial BSL of 100-155mg/dl, HbA1c of <7% without the risk of frequent hypoglycemia. (14) Upon admission, DKA patients require insulin infusion and close monitoring of electrolyte and BSL with subsequent transitioning to subcutaneous insulin and oral nutrition.

No recommendations exist regarding the appropriate timing for initiation of oral nutrition. Early reinstitution of oral nutrition did not result in worsening of DKA complications and was associated with improvement in ketoacidosis, hypokalemia and hypophosphatemia. Finally, on-demand oral nutrition reinitiated within the first 24 h of admission has the potential to shorten ICU and overall hospital lengths of stay. (15) However, the patient may meet difficulties in oral nutrition in the first 24 hours, including difficulty in BSL monitoring and insulin dosing, altered mental status predisposing to aspiration, and worsening of nausea, vomiting, and abdominal pain.

The patient was given 2100 kcal of KVT1 Diet. Fluid therapy given was 2 liters of NaCl 0.9% within first 2 hours, continued by 80 dpm in 4 hours, and 30 dpm in 18 hours. Other therapies given were short-acting insulin pump 1.5 IU/hour, continued by 1 IU/hour, and basal bolus regimen. Other therapies given are ceftriaxon 2x1gr intravenously, metoclopramide 3x10mg intravenously, sodium bicarbonate 250 Meq, NaCl 0.9% 500ml/24 hours, vitamin B6 1x1 tablet orally, folic acid 2x400 mcg orally, calcium 2x500 mg orally.

Sodium bicarbonate has been assigned to pregnancy category C by the FDA. Some authors recommend bicarbonate administration during severe acidemia (pH less than 7) or in patients complicated by cardiac dysfunction, sepsis, or shock. Administration of bicarbonate may be associated with profound alkalosis or worsening acidemia secondary to increased partial pressure of carbon dioxide, leading in turn to impaired fetal oxygen transfer. However, further research is required to assess the potential risks and benefits of such therapy. (5) (16)

Metabolic acidosis and insulin deficiency cause extracellular potassium movements, causing total body potassium levels decrease in spite of normal or increasing serum potassium level. The total potassium deficit is around 3-5 mEq/kg. Insulin therapy lowers causes potassium to return to the intracellular compartment. Thus, potassium replacement must begin when the serum concentration is less than 5.2 mEq/L to maintain levels of 4-5 mEq/L. Giving 20 to 30 mEq of potassium per liter of fluid is sufficient for most patients, but lower doses are needed for patients with acute or chronic kidney failure. In patients with serum potassium levels less than 3.3 mEq/L, insulin can cause severe symptomatic hypokalemia leading to impaired insulin secretion, muscle weakness and cardiac arrhythmias. Potassium replacement must begin 10 to 20 mEq/h and insulin therapy must be postponed. (7) Serum potassium monitoring is done every 2-6 hours according to the clinical and patient response. Indications of potassium replacement are serum potassium <3.3 mEq/L, or serum potassium <4 - 5 mEq / L accompanied by urine output > 50 mL/hr with the addition of 20 - 40 mEq potassium every 1 liter of infusion fluid. (4) (17)

Potassium sustained release has been assigned to pregnancy category C by the FDA. There are no human data related to use of potassium sustained release during pregnancy, and animal reproduction studies have not been conducted. Potassium supplementation that does not lead to hyperkalemia is not expected to cause fetal harm. (18)

The decision to terminate is individualized which must be based on evaluating the clinical status of the mother to ensure safe delivery, gestational age of the fetus, and fetal heart rate. The most DKP aims to maintain the fetus and mother in stable state to continue the pregnancy with complete DKA resolution. (3)

The patient had TSH of 0.017 mU/L and FT4 of 1.6ng/dL, showing subclinical hyperthyroidism. In pregnancy, high human chorionic gonadotropin (hCG) levels supresses TSH. The syndrome of gestational hyperthyroidism is defined as transient hyperthyroidism, limited to the first half of pregnancy, characterized by normal or borderline elevated FT4 or adjusted TT4 and suppressed or undetectable serum TSH. This causes thyrotoxicosis in pregnancy. It is diagnosed in about 1–3% of pregnancies, caused by a

TSH-like effect of the hCG and self-limiting disorder, resolving spontaneously. [19]

Many people with T2DM fail to achieve glycaemic control promptly after diagnosis due to clinical inertia related to the physician (50% relative contribution), the patient (30%) and the healthcare delivery system (20%). Potential solutions require a multiple approaches involving fundamental changes in medical care due to multiple factors leading to clinical inertia. [20]

In this case, patient compliance is low and strict examinations are rather difficult. Likewise, correction of hypokalemia should be more aggressive, especially patients already with central venous access. But electrolyte testing every 6 hours is also rather difficult.

Girls with T1DM should consult about metabolic control and family planning prior to conception in order to prevent DKP. [10]

## Conclusion

DKP may lead patient to maternal and fetal morbidity and mortality. Pregnancy also lead the patient to insulin resistance and decrease ability to physiologically buffer metabolic acidosis, which worsen patient with DM. Prompt treatments, including fluid replacement, insulin therapy, potassium correction, acidosis correction, and management of triggering factors are needed to prevent morbidity and mortality. Besides, family planning and metabolism control before conception are required to prevent women with DM from falling into DKA.

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