

Impact of Diabetic Ketoacidosis in Pregnancy

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ABSTRACT

Background: Pregnant women with type 2 diabetes mellitus (T2DM) pose an important public health problem, because diabetes not only affects the maternal and the fetal outcome but the women suffering with DM, their fetuses are also at an increased risk of developing diabetes and related complications later in their life.

Case description: A 28-year-old woman with the diagnosis of G3P1L1A1 with 32 weeks' gestational age with previous vaginal delivery and known case of chronic T2DM and hypothyroidism since 4–5 years. On admission, she was having altered sensorium, breathlessness, and palpitations. She was in latent phase of labor. Fetal heart sound was not heard on Doppler. Ultrasonography (USG) revealed intrauterine death of fetus. Her investigation reports suggested severe diabetic ketoacidosis (DKA). She was managed in medicine intensive care unit (ICU) where her labor progressed spontaneously and delivered a male dead baby, weighing 1500 g. It was sent for autopsy. Patient had postpartum hemorrhage and managed medically. But medical management did not suffice for her and so decision of laparotomy was taken with the plan of obstetric hysterectomy.

Objectives: We examined the precipitating factors, laboratory abnormalities, treatment strategies, and clinical recovery in pregnancies complicated by DKA.

Conclusion: Diabetes during pregnancy is associated with higher maternal and fetal morbidity. Early screening, detection of complications, close monitoring, and intervention are essential to reduce maternal and fetal short- and long-term adverse effects, especially in high-risk pregnancies. Pregnancy provides an opportunity to clinician to control the disease process and inculcate healthy lifestyle practices in these patients.

Keywords: Diabetes mellitus, Diabetic ketoacidosis, Intrauterine death, Obstetric hysterectomy, Postpartum hemorrhage.

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INTRODUCTION

The occurrence of diabetic ketoacidosis (DKA) in pregnancy compromises both, the fetus and the mother. It usually occurs in the later stages of pregnancy and is also seen in newly presenting patients with type 1 diabetes mellitus (T1DM). Despite improvement in its incidence rates and outcomes over the years, it still remains a major clinical problem since it tends to occur at lower blood glucose levels and more rapidly than in non-pregnant patients often causing delay in the diagnosis. This study illustrates a typical case of DKA in pregnancy and reviews the literature to provide an insight into its pathophysiology and management.

Diabetic ketoacidosis is a serious metabolic complication with high mortality, if undetected. Its occurrence in pregnancy compromises both the fetus and the mother profoundly. Although predictably more common in patients with T1DM, it has been recognized in type 2 diabetes mellitus (T2DM) as well as gestational diabetes, especially with the use of corticosteroids for fetal lung maturity and β_2 -agonists for tocolysis.^{1–3} Diabetic ketoacidosis usually occurs in the second and third trimesters because of increased insulin resistance, and is also seen in newly presenting patients with T1DM.

CASE DESCRIPTION

A 28-year-old woman with T1DM of 5 years' duration, and with no evidence of diabetic microvascular or macrovascular complications, presented at 31.6 weeks of gestation in her second pregnancy. She presented with breathlessness and pain in abdomen since 12 hours with palpitations since 5–6 hours. She is known case of T2DM since 4–5 years and was on injection insulin mixtard since 5 months.

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She had previous admissions for diabetes 3–4 years ago and had, in general, been an infrequent attendee at the diabetes clinic and took poor care of her diabetes. She was advised admission multiple times during antenatal care (ANC) period but patient was not willing and did not get admitted.

She was also diagnosed as hypothyroidism since 5 years and on tablet thyroxine 100 μ g once daily. Patient's previous delivery was uneventful.

During this unplanned pregnancy, she had defaulted on majority of her diabetes specialist clinic appointments and her glycaemic control as measured by glycosylated hemoglobin (HbA1c) had been poor throughout with the readings of 11.5, 6.4, and 7.5% in the first, second, and third trimesters, respectively.

On general examination, she was obese, average height, and disoriented. On systemic examination, she was tachypneic,

hyperventilating, tachycardia, and dehydrated. There were no foci of infection. Fetal heart sounds were not located by Doppler ultrasound.

Her investigations revealed random blood sugar level 625 mg/dL, HbA1c 8.8, serum sodium 130 mmol/L, serum potassium 7.6 mmol/L, serum bicarbonate 12.4 mmol/L, serum chloride 101 mmol/L, serum urea 42 mmol/L, serum creatinine 1.4 μ mol/L, and serum TSH levels were 20.2 mIU/L. Her arterial blood gas analysis reports were pH 7.4, PO₂-224, carbon dioxide tension 29.4 kPa, urine dipstick showed 4+ ketones, 4+ glucose. Chest radiograph was normal; urine and blood cultures were negative. Bedside ultrasonography (USG) revealed intrauterine fetal death without signs of placental separation.

MANAGEMENT

She was admitted to the high-dependency unit (HDU). Blood sugar monitoring was performed and revealed high blood sugar >500 mg/dL and urine ketones +3. She was resuscitated with oxygen, intravenous fluids, and insulin infusion as per protocol for DKA.

She was placed in left lateral position to decrease aortocaval compression. She went into spontaneous labor. She delivered an intrauterine dead (IUD) baby. Later, she went into postpartum hemorrhage and underwent obstetric hysterectomy. She received 2 units of whole blood, 4 units of fresh frozen plasma, and 2 units of platelets intraoperatively. Patient was into severe acidosis since the day of admission and intraoperatively and postoperatively and was managed appropriately for it. Postmortem examination of the fetus confirmed stillbirth with no congenital anomalies. After a due course of stay in intensive care unit (ICU), patient recovered well and was discharged from the hospital.

DISCUSSION

In non-pregnant patients with T1DM, incidence of DKA is an about 1–5 episode per 100 per year with mortality averaging 5–10%.⁴ Both the incidence and rates of fetal loss in pregnancies have fallen in recent times compared with those before. In 1963, Kyle published an extensive review and reported fetal loss rate of 30% with maternal acidosis and a rate of 64% if complicated by coma.⁴

At present, most obstetric centers offer specialized care for diabetes in pregnancy, which reduce the chance of diketopiperazine derivative (DKP). However, DKP does occur and can result in significant morbidity and mortality for both the mother and the fetus. The rate of pregnancy associated with diabetes is rising, especially with the rise in global pandemic of obesity. Pregnancy is also associated with physiological changes that can predispose pregnant woman with diabetes to DKA. Being a state of respiratory alkalosis, pregnancy is associated with compensatory drop in bicarbonate levels; this impairs buffering capacity and renders pregnant woman more prone to develop DKA.

Relative insulin resistance in pregnancy along with enhanced lipolysis and elevated free fatty acids form base for DKP. Increased levels of human placental lactogen, progesterone, and cortisol impair maternal insulin sensitivity. DKP is more commonly observed along with T1DM, but can also be observed with T2DM and gestational diabetes. It is likely to be precipitated by specific factors, such as protracted vomiting, hyperemesis gravidarum, starvation, infections, insulin non-compliance, and medications precipitating DKP (e.g., beta-sympathomimetic agents).

Factors Contributing to Increased Risk of Diabetic Ketoacidosis in Pregnancy

The metabolic changes that accompany pregnancy predispose to ketosis. Pregnancy is a state of insulin resistance. Insulin sensitivity has been demonstrated to fall by as much as 56% through 36 weeks of gestation.⁵ The production of insulin antagonistic hormones, such as human placental lactogen, prolactin, and cortisol, all contribute to this. The insulin requirement, for this reason, progressively rises during pregnancy explaining the higher incidence of DKA in the second and third trimesters. In addition, physiological rise in progesterone with pregnancy decreases gastrointestinal motility that contributes to an increase in the absorption of carbohydrates, thereby promoting hyperglycemia.

A relative state of accelerated starvation, especially in the second and third trimesters makes the fetus and the placenta to use large amounts of maternal glucose as a major source of energy and this leads to decreased maternal fasting glucose. This associated with relative insulin deficiency leads to an increase in free fatty acids, which are then converted to ketones in the liver.

Nausea and vomiting are common due to increased human chorionic gonadotropin in early pregnancy and increased esophageal reflux in the later stages. The resulting stress and fasting state in turn increases insulin antagonistic hormones. This, along with the dehydration that ensues contributes to the development of ketoacidosis.

The increased minute alveolar ventilation in pregnancy leads to respiratory alkalosis and this is compensated by increased renal excretion of bicarbonate. The net result is a lowered buffering capacity when exposed to an acid load like ketones.

Precipitating Factors

The usual precipitating factors include intercurrent illness, infections especially of the urinary tract, emesis and dehydration, non-compliance, insulin pump failure, and undiagnosed pregnancy. Unrecognized new onset diabetes accounted for 30% of the cases of DKA.⁶ A retrospective survey conducted by Rodgers and Rodgers to identify precipitant of DKA in pregnant women, revealed non-compliance to be the cause in 17% and a contributory factor in a further 25%. This certainly was a major factor in our illustrated case.⁷

Premature onset of labor in pregnancies complicated by diabetes pose a risk for DKA because of the need for tocolysis and systemic steroids for fetal lung maturation. β 2-agonists, used to suppress premature uterine contractions, cause an increase in blood glucose, free fatty acids, and ketones through stimulation of gluconeogenesis, glycogenolysis, and activation of lipolysis leading to hyperglycemia and ketosis. Similarly, use of corticosteroids in diabetic pregnancy for fetal lung maturation may worsen hyperglycemia and insulin resistance leading to ketosis.

Factors Contributing to Increased Fetal Loss

Ketoacids as well as glucose readily cross the placenta. Whether it is the maternal acidosis, hyperglycemia, severe volume depletion, or electrolyte imbalance that has the most detrimental effect on the fetus is unclear.⁸ Cardiotocography performed during DKA in pregnancy has shown absence of baseline heart rate variability, persistent late deceleration, and non-reassuring biophysical profile all suggesting fetal distress.⁹ The high mortality rate associated with DKA certainly suggests a hostile intrauterine environment.

The possible mechanisms include decrease in uteroplacental blood flow due to osmotic diuresis leading to volume depletion maternal acidosis that can cause fetal hypoxic insult. Maternal acidosis could lead to fetal acidosis and electrolyte imbalance. Maternal hypokalemia and fetal hyperinsulinemia if severe could cause fetal hypokalemia leading to fetal myocardial suppression and fatal arrhythmia.⁴ Maternal hypophosphatemia associated with DKA can cause decrease in 2,3-diphosphoglycerate leading to impaired delivery of oxygen to the fetus.¹⁰ Fetal hyperinsulinemia resulting from maternal hyperglycemia increases fetal oxygen requirement by stimulating oxidative metabolic pathway.¹¹ The long-term effect of DKA episodes during pregnancy on surviving fetus is lacking.

The incidence of DKA has dropped significantly and according to recent reports incidence of DKA in pregnancy is 1–3% with fetal loss rate of 9%.¹² Seventy-eight to ninety percent of presentations occur in the second and third trimesters of pregnancy.^{13,14} The exact rate of maternal mortality due to this condition is unknown but previous reports suggest it to be around 4–15%.¹⁵ Confidential inquiries into maternal deaths in UK between 1979 and 1990 revealed 10 diabetes-related deaths, of which 3 were due to DKA.¹⁶

Diketopiperazine derivative is considered as an emergency that needs to be managed in at least level 2 critical care units, such as HDU or ICU, by a team of experienced professionals. This team consists of an obstetrician, a diabetologist/endocrinologist, an obstetric anesthesiologist, and well-trained nursing staff/midwives. Initially, it is important to stabilize a patient with DKP and insert large intravenous accesses and continuous maternal monitoring with a cardiac monitor and pulse oximetry. The management incorporates six main aspects, which should be carried out simultaneously and they are intravenous fluid therapy, intravenous insulin therapy, electrolyte correction, evaluation for need of bicarbonate administration, identification and treatment of any precipitating factors, and monitoring of maternal and fetal responses.¹⁷

With increasing practice of antepartum diabetes screening and availability of early and frequent prenatal care, incidence and outcomes of DKA in pregnancy have vastly improved. However, it still remains a major clinical problem in pregnancy since it tends to occur at lower blood glucose levels and more rapidly than in non-pregnant patients often causing delay in diagnosis. With adequate surveillance and timely management, the maternal and the fetal outcome can be improved.

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