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Review article

DIABETIC KETOACIDOSIS IN PREGNANCY

Novaković Ivana,[1, 2] Todorović Jovana,[3] Dugalić Stefan,[1, 2] Macura Maja,[1, 2] Milinčić Miloš,[1, 2] Gojnić Miroslava[1, 2]

[1] University Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia
[2] University of Belgrade, Faculty of Medicine, Belgrade, Serbia
[3] University of Belgrade, Faculty of Medicine, Institute for Social Medicine, Belgrade, Serbia

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Abstract: Diabetic ketoacidosis (DKA) is one of the most serious and life-threatening complications of diabetes mellitus (DM), especially when it occurs during pregnancy, with a prevalence ranging from 0.5% to 3%. Pregnancy is considered a susceptible environment for the development of this type of metabolic imbalance due to its inherent physiological changes. Unspecific symptoms (vomiting, diarrhea, abdominal pain, etc.), especially in pregnant women, and the fact that ketoacidosis can develop even with normal glucose values (defined as euglycemic ketoacidosis), often lead to a delayed diagnosis. Evidence suggests that timely diagnosis and appropriate management of ketoacidosis are crucial in preventing adverse outcomes for both the mother and the fetus. Fetal outcomes are often dichotomous, resulting in either fetal demise (miscarriage/stillbirth) with a prevalence of 10% to 35%, or the birth of a healthy baby, with possible complications primarily related to diabetes mellitus itself. Additionally, case reports of ketoacidosis developing even in non-diabetic women due to other diseases (such as acute pancreatitis, appendicitis), as well as in those with gestational diabetes mellitus (GDM), further emphasize the importance of considering this condition in everyday clinical practice. The aim of this paper is to further elucidate the causes and course of this complication, as well as the outcomes for both mother and fetus, to contribute to a better overall understanding.

Keywords*:* diabetes mellitus, diabetic ketoacidosis, pregnancy.

INTRODUCTION

Diabetic ketoacidosis (DKA) represents one of the most severe complications of diabetic pregnancies, posing a life-threatening risk for both mother and fetus. Initially mostly associated with type 1 diabetes mellitus (DM), it can also develop in type 2 DM and gestational diabetes mellitus (GDM). Its significance lies not only in the metabolic imbalance it causes but also in the potentially fatal consequences for both mother and fetus, necessitating immediate and proper management (1)**.** The prevalence of DKA in pregnancies complicated by either pregestational or gestational DM is estimated to be around 0.5-3% (2).

Physiological aspects of pregnancy make it a state susceptible to ketoacidosis. Pregnancy is recognized as a state of accelerated starvation, associated with an increase in insulin counter-regulatory hormones (human placental lactogen, progesterone, prolactin, tumor necrosis factor α), as well as impaired buffering capacity due to respiratory alkalosis (with compensatory renal loss of bicarbonates), and a notable rise in insulin demands, especially in the second trimester (2). Additionally, there is an increase in gluconeogenesis and glycogenolysis, a decrease in peripheral glucose uptake, followed by lipolysis and enhanced ketone production in the liver. All these factors, along with increased fetoplacental glucose demands, in the context of relative or absolute insulin deficiency, contribute to the development of DKA (3, 4, 5).

DKA can be provoked by vomiting, starvation, non-compliance with insulin therapy, poor glycemic control, infection, glucocorticoid therapy, β-mimetic therapy, stress, labor, etc. (2). The classic triad of hyperglycemia, ketonemia (beta-hydroxybutyrate, acetoacetate, and acetone), and a high anion gap clearly suggests the presence of DKA (1). Diagnostic criteria for DKA, proposed by The Joint British Diabetes Societies Inpatient Care Group, include: ketonemia > 3 mmol/L or ketonuria (> 2+ on urine strips), blood glucose > 11.0 mmol/L or known diabetes, bicarbonates < 15 mmol/L, and/or venous pH < 7.3 (3). DKA can

be further classified based on pH values as mild (7.25-7.30), moderate (7.0-7.24), or severe (< 7.0) (1).

Treatment focuses on excessive fluid resuscitation, continuous insulin therapy, potential need for electrolyte (potassium) or bicarbonate replacement, treatment of contributing factors (such as infection), and close monitoring of maternal and fetal responses. Maternal monitoring involves hourly measurements of blood glucose and ketones, with other parameters (blood urea nitrogen, creatinine, electrolytes, venous pH) measured every 2 hours, along with monitoring blood pressure and urine output (6). A potential improvement in maternal monitoring in diabetic pregnancies could be the implementation of continuous glucose monitoring devices, which, due to their precision and non-invasiveness, might lead to prompt detection of glycemic excess (7).

Fetal monitoring in diabetic pregnancies is crucial due to the risk of congenital malformations, macrosomia, polyhydramnios, etc. In the case of ketoacidosis, fetal monitoring involves confirming viability (with further ultrasound assessments as needed), cardiotocography (if suitable), and delivery if indicated. Recovery is defined by pH > 7.3, ketonemia < 0.6 mmol/L, anion gap < 12 mEq/L, and bicarbonates > 15 mmol/L (6, 8). Suggested glucose values post-DKA are 5.6-8.3 mmol/L (9).

CLINICAL POINT OF VIEW

Being extremely endangering but not very frequent, previous experiences in clinical practice are reflected through retrospective studies and case reports. This complication has been observed mostly in women with type 1 diabetes mellitus (DM) and in the third trimester of pregnancy, most frequently precipitated by infections, vomiting, steroid therapy, and medical malpractice. The main associated risk factors include lower socioeconomic status and at least one microvascular complication of DM before pregnancy (9).

A retrospective study conducted at Mayo Clinic showed that most women with DKA events had poor preconceptual glycemic control with high HbA1c values (9%), which improved during pregnancy but still remained high (7.5% and 7.6%). Cases of fetal loss (17%) mostly occurred either at the time of admission or within 1 week after discharge from the hospital after DKA treatment (miscarriage or stillbirth). More than half of the neonates required admission to the neonatal intensive care unit (NICU), 2/3 experienced neonatal hypoglycemia, 1/3 were large for gestational age (LGA), and every 10th had a congenital anomaly. Additionally, it was observed that administering antenatal corticosteroids might precipitate this condition, therefore, the need for an adjustment of insulin doses when administering these drugs was pointed out (4).

Another retrospective study conducted in South Africa showed similarly that DKA occurs predominantly in women with type 1 DM, in the early third trimester, in poorly controlled DM cases (with an average HbA1c of 9.2% at the time of diagnosis). The most often observed conjoined factors were infections (especially of the urinary tract) and discontinuation of insulin therapy. Overall, a higher rate of fetal losses occurred (28%), with a significant association between low potassium levels and fetal demise (1). No maternal deaths were noted in any of the previously mentioned studies (1, 4, 10).

Considering these facts, the developing fear of fetal loss seems justified. However, an approach which attempts to reverse maternal metabolic acidosis rather than undergoing immediate delivery seems to be preferable. Submitting a mother with unregulated ketoacidosis to an emergency cesarean section might lead to the worsening of her condition with not much benefit to the fetus itself. One of the many studies that supported this approach is a case report of a woman at 29 weeks gestation, with poorly regulated type 1 DM and diagnosed DKA. Despite reduced variability of the fetal heart rate pattern, and repeated unprovoked decelerations presented at admission, a decision was made to mainly handle maternal metabolic imbalance. After successful and prompt treatment, the patient was discharged and later regularly controlled by obstetricians and endocrinologists. She delivered vaginally at 34 weeks due to premature spontaneous rupture of the membranes, to a healthy baby (11). Although uncommon, this condition was also observed in gestational DM at 30 weeks gestation, unfortunately, with intrauterine fetal demise at the time of DKA presentation (12).

FETAL OUTCOMES

In addition to the well-known consequences DKA might have on maternal health (acute renal failure, respiratory distress syndrome, cerebral edema, and even death) with reported maternal mortality rates ranging from 5 to 15%, short- and long-term outcomes for children have also been of interest (6, 9).

Fetal outcomes can be severe, and fetal mortality rates vary from 10 to 35%, with developed countries such as the United Kingdom and the United States reporting rates around 16% (4, 10). To provide an updated assessment of fetal outcomes in DKA-complicated pregnancies, a retrospective cohort study covering a 20-year period in Boston was conducted. The authors reported that the most frequent outcomes were NICU admissions (59%), preterm birth (46.3%), and fetal de-

mise (15.6%), all of which were significantly higher than in the general population of women with diabetes mellitus. Contributing factors to fetal demise were mainly associated with the severity of DKA event (the need for maternal intensive care unit admission and higher serum osmolarity), while factors associated with preterm birth and NICU admissions were more related to maternal health (smoking, preeclampsia, higher HbA1c, etc.) (13).

The true pathophysiological mechanisms that lead to fetal complications are still to be fully understood, but several are presumed: maternal dehydration due to osmotic diuresis leading to fetal distress in the light of decreased uteroplacental perfusion; fetal acidosis induced by maternal acidosis; maternal hypophosphatemia leading to fetal hypoxia; fetal hyperinsulinemia followed by hypokalemia causing fetal arrhythmias, etc. (11, 14). Overall, complications such as miscarriage and stillbirth have mainly been related to the metabolic imbalance of DKA itself. Other outcomes, such as large for gestational age (LGA), NICU admissions, neonatal hypoglycemia, shoulder dystocia, etc., are more related to diabetes mellitus itself (3). Higher rates of fetal demise are more frequently seen in newly discovered type 1 diabetes mellitus, and better outcomes seem to be associated with lower glycemia values, lower insulin requirements, gestational age at DKA presentation, as well as a shorter duration of metabolic imbalance (14).

Concerns regarding long-term outcomes for children are predominantly based on the exposure of the fetal brain to increased maternal ketone and lactate concentrations, which are presumed to be associated with fetal brain injury (6). Contributing to these findings, an inverse connection between maternal ketonemia and mental development was found in 2-year-old children, suggesting impaired brain development in these children might be present (15). Furthermore, subsequent neurological and intellectual problems, including autism and seizures, have also been noted (16).

EUGLYCEMIC DIABETIC KETOACIDOSIS IN PREGNANCY

Euglycemic ketoacidosis also represents an acute, life-threatening condition, with the diagnosis being often unintentionally delayed due to unspecific symptoms and the absence of hyperglycemia, and the prevalence of up to 30% of all DKA cases in pregnancy (2).

It is defined as ketoacidosis with normal or marginally elevated levels of serum glucose, but is still presumed as a diagnosis of exclusion because other causes of high anion gap must first be excluded (alcohol intoxication, drug overdose, sepsis, renal failure, etc.) (2, 17).

Treatment resembles the one used for diabetic ketoacidosis, but it is to be noted that fluid replacement requires an additional 5% dextrose along with saline, to avoid hypoglycemia caused by insulin infusion (which remains necessary to prevent further ketone production) (6). Although some evidence-based clinical approaches had suggested that lowering insulin dose in half might be equally effective, Algaly et al. had a different experience. Their case included a 28-year-old woman with DM type 1 presenting with normal glucose levels and anion gap, low pH, and bicarbonate levels. Initial therapy, besides intensive rehydration with crystalloids and potassium supplementation, included insulin at a dose of 0.05 units/kg/h and resulted in further slow progression of metabolic acidosis. Only when the insulin dose was increased to the usual 0.1 units/kg/h, her condition began to improve. The authors concluded that starting insulin rate at a lower dose might not be as effective, and suggesteded that the insulin treatment should resemble the one given for non-euglycemic DKA (16). The significant role of placental counterregulatory hormones in the development of this complication was pointed out in a case report of a woman at 33 weeks gestation with DM type 1 and diagnosed with euglycemic DKA. Despite close monitoring and adequate therapy, her condition had not improved (and unfortunately resulted in fetal demise 8 hours after admission), until the delivery of the fetus and more importantly, the placenta. Soon after delivery, her insulin sensitivity and acidosis rapidly improved, pH continued to rise and the anion gap eventually closed. She was soon discharged without any further events (15). Nevertheless, two cases of euglycemic DKA in the same DM type 1 patient, with contrary outcomes (first pregnancy resulting in fetal demise and the second one with the late preterm birth of a healthy baby), demonstrated the impact of immediate and proper management of this condition, as well as the necessity for further education of pregnant women, obstetricians and diabetologists regarding this entity (2). Frise et al. pointed out the importance of having this condition in mind even in non-diabetic pregnant women because in the 3 case reports, acute pancreatitis was the cause of ketoacidosis (without detected hyperglycemia or previously diagnosed DM) (18). Also, Dikowita et al. reported a case of ketoacidosis in a non-diabetic woman due to fasting and vomiting because of appendicitis, therefore, the need to avoid and prevent long periods of starvation in pregnant women was emphasized (19).

CONCLUSION

Diabetic ketoacidosis in pregnancy represents one of the most serious and life-endangering complications

for both mother and fetus. Due to its nonspecific symptoms, potential to be the first presentation of diabetes mellitus, and the fact that it can occur even within normal glucose values, its diagnosis might not always be immediate. The evidence so far consistently emphasizes that diagnosing this complication promptly and subjecting these women to immediate adequate treatment remains crucial. Therefore, having this entity in mind and understanding its course might help prevent misdiagnosis and subsequent adverse pregnancy outcomes in everyday clinical practice.

Abbreviations

DKA - diabetic ketoacidosis
DM - diabetes mellitus
GDM - gestational diabetes mellitus
LGA - large for gestational age
NICU - neonatal intensive care unit

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Sažetak

DIJABETIČNA KETOACIDOZA U TRUDNOĆI

Novaković Ivana,[1, 2] Todorović Jovana,[3] Dugalić Stefan,[1, 2] Macura Maja,[1, 2] Milinčić Miloš,[1, 2] Gojnić Miroslava[1, 2]

[1] Univerzitetski klinički centar Srbije, Klinika za ginekologiju i akušerstvo, Beograd, Srbija
[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[3] Univerzitet u Beogradu, Medicinski fakultet, Institut za socijalnu medicine, Beograd, Srbija

Dijabetična ketoacidoza važi za jednu od najozbljnijih i životno ugrožavajućih komplikacija dijabetes melitusa, posebno kada se javi u trudnoći, sa prevalencom od 0,5 do 3%. Trudnoća se smatra stanjem koje je podložno razvoju ovog tipa metaboličkog disbalansa, zbog već prisutnih fizioloških promena. Nespecifični simptomi (povraćanje, dijareja, bol u abdomenu itd.) posebno kod trudnica, kao i činjenica da ketoacidoza može da se razvije čak i pri normalnim vrednostima glikemije (euglikemijska ketoacidoza), dovode do kasne pretpostavke o ovoj dijagnozi. Dosadašnji dokazi sugerišu da se jedino kod blagovremeno dijagnostikovane i adekvatno tretirane ketoacidoze mogu prevenirati loši ishodi za majku i fetus. Fetalni ishodi su uglavnom isključivi, ili je u pitanju fetalni gubitak (pobačaj ili intrauterina smrt ploda) sa prevalencom od 10 do 35%, ili rođenje zdravog deteta sa mogućim komplikacijama za koje se smatra da su najviše povezani sa dijabetesom kao takvim. Dalje, prikazi slučajeva ketoacidoze koja se razvija usled prisustva drugih bolesti (akutni pankreatitis, apendicitis), kod trudnih žena koje ne boluju od dijabetes melitusa, kao i kod onih sa gestacionim dijabetes melitusom, još više naglašavaju potrebu uzimanja u obzir ovog entiteta u svakodnevnoj kliničkoj praksi. Cilj ovog rada je da se rasvetle uzroci i sam tok ove komplikacije, njene posledice po majku i fetus, kao i da se doprinese njenom celokupnom boljem razumevanju.

Ključne reči: dijabetes melitus, dijabetična ketoacidoza, trudnoća.

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Correspondence to/Autor za korespondenciju
Ivana Novaković
Address: KosteTodorovica 26, Belgrade, Serbia
Phone number: 060/132-9709
E-mail: ivananovakovic223@gmail.com

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