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A Comprehensive Review on Management of Euglycemic Diabetic Ketoacidosis (EDKA) in Pregnancy

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ABSTRACT

Diabetic Ketoacidosis (DKA) is a life-threatening medical emergency. Euglycemic Diabetic Ketoacidosis (EDKA) is a condition that is relatively rare but if missed out can have grave consequences. The primary difference between the two conditions lies in the extent of hyperglycemia in both conditions. In EDKA, the blood glucose levels can be near normoglycemia as well. The clinical features are similar. Good glycemic control in pregnancy is an effective method of preventing complications of EDKA in pregnancy. For EDKA, the glucose levels in blood can be mildly raised; it poses a significant challenge to diagnose EDKA. Therefore, a high index of suspicion is the cornerstone of management of EDKA in pregnancy. The key diagnostic tests are serum electrolytes, arterial blood gas analysis, and ketone level measurements. The treatment includes fluid resuscitation, insulin therapy, acidosis correction, electrolyte monitoring and treating the underlying root cause. Continuous monitoring of both maternal and fetal well-being is crucial throughout treatment. A multidisciplinary and systematic approach to diagnosis and treatment is essential for an optimized outcome.

Keyword: Euglycemic DKA, hyperglycemia, diabetic, pregnancy, ketogenesis, acidosis

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INTRODUCTION

Diabetic Ketoacidosis (DKA) is a well-known life-threatening complication of diabetes mellitus. It can occur in both Type 1 and 2 diabetes mellitus. DKA consists of the triad of hyperglycemia, ketonemia and high anion gap metabolic acidosis. In the case of euglycemic diabetic ketoacidosis (EDKA), it is characterized by ketonemia and metabolic acidosis that occur at milder hyperglycemic conditions <200 mg/dl (<11.0mmol/L). [1] This often leads to delayed diagnosis and therefore bringing about various multiorgan and metabolic consequences. The various risk factors of developing EDKA include pregnancy, the use of Sodium Glucose Transporter 2 inhibitors (SGLT2i), insulin therapy, heavy alcohol drinking, recreational drug abuse, decreased calorie intake, chronic liver disease and liver cirrhosis. [1]

DKA in pregnancy constitutes a medical emergency. The clinical features of DKA & EDKA may have similar characteristics.[2] The incidence of DKA in pregnancy has been reported as 3% while EDKA occurs between 0.8% to 1.1% of all the cases of DKA in pregnancy. [3] [4] Euglycemia presents a diagnostic challenge as ketoacidosis can be less severe. This makes EDKA go unrecognized consequently. Thus, the possibility of DKA and EDKA in pregnant women especially with gestational diabetes mellitus or overt diabetes mellitus should always be kept in mind.

As EDKA is not a commonly occurring condition in pregnancy, the management protocols and planning may suffer indecision or missed diagnosis leading to further morbidity and mortality. In this review, the emphasis has been made on this condition, so that the management of EDKA in pregnancy is kept in mind while treating patients showing manifestations of DKA.

Pathophysiology

One of the main contributing factors to DKA in pregnancy is the rise of various counter regulatory pregnancy hormones in the body such as estrogen, progesterone, human placental lactogen (HPL), cortisol and tumor necrosis factor-alpha (TNF-a).[4] [5] The normal response to the secretion of these hormones is the increased utilization of glucose by the body by activating insulin. During pregnancy, the body's natural physiology is altered whereby there is decreased sensitivity to insulin to provide more glucose to the growing fetus and placenta. [5] This subsequently leads to a decrease in mother's circulating glucose levels, especially maternal fasting glucose. This in turn leads to lipolysis and releases free fatty acids which are then oxidized and converted to ketone bodies in the liver. [6] [7] The high progesterone levels during pregnancy can lead to nausea and vomiting subsequently leading to dehydration and starvation ketoacidosis. Progesterone can also increase glomerular filtration rate leading to glycosuria. These conditions cause ketoacidosis in states of normal or

low glucose levels i.e. EDKA. [6] On the contrary to EDKA but in the context of DKA, progesterone also has antagonistic properties to insulin and causes decrease gastric motility rendering more carbohydrate absorption leading to hyperglycemia. [7] [8]

In pregnancy, there is increased alveolar ventilation leading to a state of respiratory alkalosis. The natural compensation is the increased renal secretion of bicarbonates. This lowers the body's buffering capacity contributing to the state of metabolic acidosis seen in DKA especially at lower glycemic levels. [8]

During any acute illness like urinary tract infections and more, glucose utilization is increased, therefore fasting or short starvation can trigger ketogenesis in pregnancy. Lastly, any unexplained acidosis with a history of gastrointestinal loss or decreased oral intake should raise a suspicion of euglycemic DKA. [8] [9]

Clinical Features

The signs and symptoms of DKA and euglycemic DKA are similar. Patients can complain of abdominal pain, nausea, vomiting, lethargy, loss of appetite, shortness of breath and dehydration in the presence or absence of fever. [2]

On examination, patients may present with rapid and deep breathing called Kussmaul respiration, which represents respiratory compensation for severe metabolic acidosis. Due to loss of acetone, they can have a fruity odor to their breaths. Altered mental status, tachycardia, hypotension, increased skin turgor, delayed capillary refill seen in these patients all indicate total body fluid loss. [2] [10]

Diagnosis

The primary difference between DKA and EDKA is the glucose levels on presentation. DKA consists of the triad of high anion gap metabolic acidosis, hyperglycemia and ketonemia. EDKA can present as ketoacidosis in otherwise normoglycemic or milder hyperglycemia states. The diagnostic criteria of blood glucose levels for DKA proposed by the American Diabetes Association (ADA) and the Joint British Diabetes Societies is over 250mg/dl(13.9mmol/L) and over 200mg/dl(11mmol/L) respectively. In EDKA blood glucose levels are often <200mg/dl (11mmo/L) which can contribute to a delay in its diagnosis and prompt treatment. Pregnancy is a known risk factor for developing EDKA, but its occurrence is exceedingly rare. Therefore, clinicians must always have a high index of suspicion of its probabilities especially in pregnancy. [2] [11] [12]

Complications

Prevention of EDKA is the best way to avert complications. [13] If EDKA is not diagnosed early and the treatment gets delayed, it can lead to grave complications to both mother and fetus. Severe dehydration and metabolic derangement can cause maternal cardiac

arrhythmias, hypovolemic shock, respiratory failure requiring artificial ventilation, cerebral edema, seizures, thrombosis and myocardial infarction. These can further progress into cardiorespiratory failure, coma and ultimately death. Data available on fetal outcome following EDKA is limited. The complications reported are extremely severe namely fetal lactic acidemia and hypoxia that occurs resulting from the passing of the lactate and hydroxybutyrate ketone bodies from mother to fetus via the placenta leading to fetal cardiac arrhythmias, neurological insults such as basal ganglia infarction and encephalomalacia. Maternal EDKA increases both the fetal mortality (up to 9%) and maternal mortality rate. [4] [14] [15]

Management

The key to successful management of EDKA in pregnancy is first and foremost, its early detection. A multidisciplinary approach is of utmost importance. If EDKA is suspected in a primary setting or a secondary hospital, immediate consultations and referral to the nearest tertiary center is recommended with appropriate medical escorts. The principles of EDKA management include aggressive volume replacement, initiation of intravenous insulin therapy, correction of acidosis, correction of electrolyte imbalance and management of precipitating factors while closely monitoring maternal-fetal vitals and treatment response throughout. [13]

Management of EDKA in pregnancy follows the same principle as that of DKA. Fluid replacement with isotonic saline at 10-15mls/kg/hr is recommended for the first hour. Then after, the fluid replacement should be adjusted according to the hemodynamic status of the patient including blood pressure and urine output. The goals are to maintain systolic BP more or equal to 90mmHg and a urine output of 0.5cc/kg/hr. An indwelling urinary bladder catheter insertion is crucial. Strict input and output of fluids should be properly monitored. [13] [14]

Insulin initiation at a fixed dose of 0.1 U/kg/hr (to a maximum of 15U/hr) is recommended. A priming bolus dose is not required. Capillary blood glucose levels should be monitored hourly. If the metabolic target is not achieved, the insulin infusion can be increased by 1U/hr while carefully monitoring the capillary glucose levels until the serum ketones reach the desired levels. [6] [12][13]

The target is to decrease ketone rate by at least 0.5mmol/L every hour thus it should be checked every hour for the first 6 hours. Other biochemical markers, such as pH and bicarbonate can be monitored every two hours. The goal for bicarbonate levels is an increase of 3 mEq/L every hour. [6] [12] [13]

Even though in view of normoglycemia, initiation of insulin should not be delayed except for hypokalemia. Therefore, the use of Dextrose 5% intravenous drips is necessary from the beginning of treatment to prevent hypoglycemia caused by the insulin infusion. If the serum glucose drops drastically and the metabolic and ketone level target has not been achieved, it is recommended to adjust the percentage of dextrose in the intravenous fluids while maintaining the appropriate fixed insulin infusion rate according to body weight. [6] [12] [13]

In the context of hypokalemia, if serum potassium is less than 3.3 mEq/L, potassium supplements should be started prior to initiating insulin and should be continued throughout the duration of intravenous insulin treatment. Frequent serum potassium checks are recommended to ensure maintenance between 4 to 5 mEq/L. Administration of oral or intravenous sodium bicarbonate is not routinely practiced. [12]

The use of glucocorticoids for fetal lung maturation can often lead to poor glycemic control especially in patients with gestational diabetes or overt diabetes. Glucocorticoids are commonly given when the patient is at risk of preterm labor triggered by stressful conditions such as urinary tract infections or chorioamnionitis. The combined release of endogenous stress hormones and exogenous glucocorticoids can eventually cascade into DKA or EDKA. Use of glucocorticoids are risky but pivotal for the fetal outcome. A study by Mathiesen et al, showed that increasing insulin dose up to 40% in diabetic patients can reduce the metabolic impact of the conditions combined preventing EDKA. [16] If the patient is already experiencing EDKA, thus the same regime continues as described with careful monitoring while administering the glucocorticoids.

The occurrence of euglycemic DKA during pregnancy poses a diagnostic and management challenge due to the atypical presentation and potential rapid deterioration if not promptly addressed. [2] [3] [17] The hormonal shifts increased metabolic demands, and reduced glucose utilization in pregnant women to provide glucose to the fetus can obscure the usual hyperglycemic presentation of DKA, making it difficult to detect early. [7] [8] [17] [18] Common precipitating factors include infections, gastrointestinal losses causing dehydration, and increased insulin insensitivity. [6] A systematic approach to both DKA and EDKA is pertinent in effective management [19] Key diagnostic tests include serum electrolytes, arterial blood gas analysis, and ketone measurements.[18] [20] The insulin infusion rate should be adjusted based on continuous monitoring of blood glucose and ketone levels. [12] [13] [14] [21]

Prevention

The prevention strategy of EDKA is to create awareness of the state targeting both the medical fraternity and pregnant women. All doctors, be it in primary or tertiary setting, should be well informed on EDKA and its detection to ensure prompt treatment to avoid progression into further complications. Pregnant mothers should be educated about the risks of DKA, precipitating factors and the importance of reporting signs and symptoms accordingly. [13]

CONCLUSION

Diagnosis of EDKA requires a high degree of clinical suspicion. The key diagnostic criteria include elevated serum ketones, a high anion gap metabolic acidosis with a normal or near-normal blood glucose level. Routine glucose monitoring may not reveal the condition, thus comprehensive metabolic evaluations are essential. Key diagnostic tests include serum electrolytes, arterial blood gas analysis, and ketone measurements. Additionally, a thorough assessment to rule out other causes of metabolic acidosis is critical such as investigating septic parameters and more. The mainstay of management of EDKA are fluid resuscitation, insulin therapy, acidosis correction, electrolyte monitoring and treating the underlying root cause. Administration of isotonic fluids, such as normal saline, helps to correct dehydration, restore circulating volume, and improve perfusion as well. Intravenous insulin infusion should be initiated to suppress ketogenesis and manage blood glucose levels. Close monitoring of electrolytes, particularly potassium, is crucial. Insulin therapy can lead to shifts of potassium into cells, risking hypokalemia. Potassium levels should be corrected accordingly. Appropriate antibiotics should be administered following culture and sensitivity testing, while addressing other stressors is also important. Continuous monitoring of both maternal and fetal well-being is imperative. Regular assessments are made in monitoring of maternal blood glucose, ketone levels, arterial blood gases, and fetal heart rate. Post-recovery, it is vital to ensure rigorous control of diabetes to prevent recurrence and mitigate risks to both the mother and fetus. Effective management of euglycemic DKA during pregnancy requires a multidisciplinary approach involving obstetricians, endocrinologists, and intensivists. High index of suspicious along with early recognition, timely intervention, and comprehensive monitoring are key to optimizing outcomes. Owing to the complexity of this condition and its potential for rapid deterioration, a proactive and systematic approach to diagnosis and treatment is essential.

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