

REVIEW

Diabetic ketoacidosis in pregnancy

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Postgrad Med J 2003;**79**:454–457

The occurrence of diabetic ketoacidosis 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 type 1 diabetes patients. 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 article illustrates a typical case of diabetic ketoacidosis in pregnancy and reviews the literature to provide an insight into its pathophysiology and management.

Diabetic ketoacidosis is a serious metabolic complication of diabetes with high mortality if undetected. Its occurrence in pregnancy compromises both the fetus and the mother profoundly. Although predictably more common in patients with type 1 diabetes, it has been recognised in those with type 2 diabetes 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 type 1 diabetes patients.

With increasing practice of antepartum diabetes screening and the availability of early and frequent prenatal care/surveillance, the incidence and outcomes of diabetic ketoacidosis 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 the diagnosis. The purpose of this article is to illustrate a typical patient who may present with diabetic ketoacidosis in pregnancy and review the literature on this relatively uncommon condition and provide an insight into the pathophysiology and management.

MAGNITUDE OF THE PROBLEM

In non-pregnant patients with type 1 diabetes, the incidence of diabetic ketoacidosis is about 1–5 episodes per 100 per year with mortality averaging 5%–10%.⁴ The incidence rates of diabetic ketoacidosis in pregnancy and the corresponding fetal mortality rates from different retrospective studies^{5–8} are summarised in the table 1. As is evident from the table, 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 a fetal loss rate of 30% with maternal acidosis and a rate of 64% if complicated by coma.⁹ With improvement in overall diabetes and pregnancy

Box 1: Case report

A 28 year old woman with type 1 diabetes of five years' duration, and with no evidence of diabetic microvascular or macrovascular complications, presented at 36 weeks' gestation in her fifth pregnancy with a two day history of persistent vomiting and decreased fetal movements. On direct questioning she admitted to have skipped her last two doses of insulin because of persistent vomiting. She had previous admissions for diabetes and had, in general, been an infrequent attendee at the diabetes clinic and took poor care of her diabetes. During this unplanned pregnancy, she had defaulted on the majority of her diabetes specialist nurse clinic appointments and her glycaemic control as measured by glycated haemoglobin (HbA1c) had been poor throughout with readings of 11.5%, 6.4%, and 7.5% (upper reference range 5.5%) in the first, second, and third trimesters respectively. On examination she was tachypnoeic, hyperventilating, tachycardic, and dehydrated. Systemic examination was normal and there were no foci of infection. Fetal heart sounds were absent.

Investigations

Biochemistry: venous plasma glucose 13 mmol/l, sodium 142 mmol/l, potassium 3.3 mmol/l, bicarbonate 10 mmol/l, chloride 100 mmol/l, urea 8 mmol/l, and creatinine 136 μ mol/l. Arterial blood gas: pH 7.10, oxygen tension 13 kPa, carbon dioxide tension 2.3 kPa. Urine dipstick showed 4+ ketones, 4+glucose. The chest radiograph was normal; urine and blood cultures were negative.

Management

She was admitted to the high dependency unit and resuscitated with supplemental oxygen, intravenous fluids, and insulin infusion as per the protocol for diabetic ketoacidosis. She was placed in left lateral position to decrease aortocaval compression. Ultrasound and cardiotocogram confirmed intrauterine death of the fetus. After maternal stabilisation and reversal of acidosis, delivery was induced. Postmortem examination of the fetus confirmed stillbirth with no congenital anomalies.

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Submitted
22 February 2002
Accepted
11 December 2002

Table 1 Incidence and fetal mortality rates in diabetic pregnancies complicated by diabetic ketoacidosis

Reference	Period	Incidence	Fetal mortality
Lufkin <i>et al</i> ⁶	1950–79	18/277 (7.9%)	5/18 (27.7%)
Kilvert <i>et al</i> ⁶	1971–90	11/635 (1.73%)	22%
Chauhan <i>et al</i> ⁷	1976–81	51/227 (22%)	35%
	1986–91	9/301 (3%)	10%
Cullen <i>et al</i> ⁸	1985–95	11/520 (2%)	1/11 (9%)

Box 2: Factors precipitating ketoacidosis in diabetic pregnancies

- Emesis.
- Infection.
- Non-compliance.
- Insulin pump failure.
- β -Sympathomimetic drugs.
- Corticosteroids.
- Poor management.

care these figures have dropped significantly and according to recent reports the incidence of diabetic ketoacidosis in pregnancy is 1%–3%¹⁰ with fetal loss rate of 9%.¹¹ The majority (78%–90%) of presentations occur in the second and third trimesters of pregnancy.^{6–8} The exact rate of maternal mortality due to this condition is unknown but previous reports suggest it to be around 4%–15%.^{12–13} Confidential inquiries into maternal deaths in the UK for the period between 1979 and 1990 revealed 10 diabetes related deaths, of which three were due to diabetic ketoacidosis.¹⁴

FACTORS CONTRIBUTING TO INCREASED RISK OF DIABETIC KETOACIDOSIS IN PREGNANCY

The metabolic changes that accompany pregnancy predispose to ketosis. The factors that contribute to the increased risk of diabetic ketoacidosis and their differential impact at various trimesters of pregnancy¹⁵ are discussed below.

Insulin antagonistic state

Pregnancy is a state of insulin resistance. Insulin sensitivity has been demonstrated to fall by as much as 56% through 36 weeks of gestation.¹⁶ The production of insulin antagonistic hormones like 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 diabetic ketoacidosis in the second and third trimesters. In addition the physiological rise in progesterone with pregnancy decreases gastrointestinal motility that contributes to an increase in the absorption of carbohydrates thereby promoting hyperglycaemia.

Accelerated starvation

In pregnancy, there is a relative state of accelerated starvation, especially in the second and third trimesters. The fetus and the placenta 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.

Effect of emesis

Nausea and vomiting are common due to increased human chorionic gonadotrophin in early pregnancy and increased oesophageal reflux in 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.

Lowered buffering capacity

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.

The clinical implication of these metabolic changes is not only that pregnant diabetics are at risk of developing ketoacidosis, but this can occur rapidly and at a much lower glucose level compared to non-pregnant diabetics as seen in our illustrated case above.

PRECIPITATING FACTORS (SEE BOX 2)

The usual precipitating factors include intercurrent illness, infections especially of the urinary tract, emesis and dehydration, non-compliance, insulin pump failure, and undiagnosed pregnancy. Unrecognised new onset diabetes accounted for 30% of the cases of diabetic ketoacidosis.¹⁷ A retrospective survey conducted by Rodgers and Rodgers to identify the precipitant of diabetic ketoacidosis in pregnant women, revealed non-compliance to be the cause in 17% and a contributory factor in a further 25%.¹⁸ This certainly was a major factor in our illustrated case.

Premature onset of labour in pregnancies complicated by diabetes pose a risk for diabetic ketoacidosis because of the need for tocolysis and systemic steroids for fetal lung maturation.^{1–3} 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 hyperglycaemia and ketosis. Similarly, the use of corticosteroids in diabetic pregnancy for fetal lung maturation may worsen hyperglycaemia and insulin resistance leading to ketosis.

FACTORS CONTRIBUTING TO INCREASED FETAL LOSS

The exact mechanism by which maternal diabetic ketoacidosis affects the fetus is unknown. Ketoacids as well as glucose readily cross the placenta. Whether it is the maternal acidosis, hyperglycaemia, severe volume depletion, or electrolyte imbalance that has the most detrimental effect on the fetus is unclear.¹⁵ Cardiotocography done during diabetic ketoacidosis in pregnancy has shown absence of baseline heart rate variability, persistent late deceleration, and non-reassuring biophysical profile all suggesting fetal distress.¹⁹ The high mortality rate associated with diabetic ketoacidosis certainly suggests a hostile intrauterine environment.

Possible mechanisms include:

- Decrease in uteroplacental blood flow due to: (a) osmotic diuresis leading to volume depletion and (b) maternal acidosis²⁰ that can cause fetal hypoxic insult.
- Maternal acidosis could lead to fetal acidosis and electrolyte imbalance.
- Maternal hypokalaemia and fetal hyperinsulinaemia if severe could cause fetal hypokalaemia leading to fetal myocardial suppression and fatal arrhythmia.²¹
- Maternal hypophosphataemia associated with diabetic ketoacidosis can cause decrease in 2,3-diphosphoglycerate leading to impaired delivery of oxygen to the fetus.²²
- Fetal hyperinsulinaemia resulting from maternal hyperglycaemia increases fetal oxygen requirement by stimulating oxidative metabolic pathway.²³

The long term effect of diabetic ketoacidosis episodes during pregnancy on surviving fetus is lacking. Some studies

Box 3: Common symptoms and signs of diabetic ketoacidosis in pregnancy

Symptoms

- Polyuria.
- Polydipsia.
- Nausea.
- Vomiting.
- Abdominal pain.
- Weakness.
- Weight loss.

Signs

- Hyperventilation.
- Ketotic breath.
- Tachycardia.
- Hypotension.
- Dry mucous membranes.
- Disorientation.
- Coma.

have shown a direct relationship between plasma ketone levels in pregnant diabetic women and a lower IQ in the child.²⁴

PRESENTATION

The clinical presentation of diabetic ketoacidosis in pregnancy is similar to that of non-pregnant diabetics and is summarised in box 3. Infection may or may not be apparent. Laboratory findings include acidaemia, hyperglycaemia, a raised anion gap, ketonaemia, ketonuria, and renal dysfunction. However, a substantial minority may have glucose level less than 12 mmol/l for reasons mentioned before.^{21 25}

MANAGEMENT

Diabetic ketoacidosis in pregnancy is an emergency that demands prompt and vigorous treatment in a high dependency unit under combined medical and obstetric care to reduce the maternal and fetal mortality.

Treatment includes aggressive volume replacement, insulin infusion, careful attention to electrolytes, and a search for and correction of precipitating factors. The initial fluid deficit is higher than that of non-pregnant diabetic ketoacidosis. The presence of acidosis at lower initial glucose levels than in non-pregnant patients may necessitate simultaneous dextrose infusion to enable insulin treatment. While cerebral oedema is a theoretical risk of diabetic ketoacidosis, especially in children, its association with aggressive fluid replacement has not been consistently proven.²⁶

Continuous fetal monitoring is mandatory to assess fetal wellbeing. A non-reactive fetal heart tracing, repetitive late decelerations, or a non-reassuring biophysical profile may be present indicating some degree of fetal compromise in the ketoacidotic patient but they are not necessarily indications for immediate delivery. Subjecting a patient in diabetic ketoacidosis to emergency caesarean section could cause further maternal deterioration while offering minimal, if any, benefit to the fetus. Interestingly, once hyperglycaemia and acidosis is reversed and maternal stabilisation achieved, fetal compromise may no longer be evident.^{27 28} If preterm labour occurs, magnesium sulphate is the tocolytic of choice and β_2 -agonists are relatively contraindicated.

In essence, an approach that incorporates in utero resuscitation with maternal stabilisation, hydration, and reversal of hyperglycaemia and metabolic acidosis under combined medical and obstetric supervision is the cornerstone of management of this condition. The salient features of treatment are summarised in box 4.¹⁵

PREVENTION

Preconception counselling, intensive metabolic control, prenatal care in a combined obstetric and diabetic clinic, and educa-

Box 4: Salient features in the management of diabetic ketoacidosis in pregnancy¹⁵

(1) Fluid replacement

- 1–2 litres of isotonic saline in the first hour.
- 300–500 ml/hour of 0.9% or 0.45% saline thereafter.
- Add 5% dextrose when serum glucose approaches 12 mmol/l.

(2) Insulin therapy

- Loading dose 0.4 U/kg regular insulin.
- Continuous infusion at 6–10 U/hour
- Double infusion rate if no response in 1 hour.
- Decrease infusion to 1–2 U/hour as serum glucose drops to 12 mmol/l.
- Continue infusion 12–24 hours after resolution of ketosis.

(3) Electrolyte replacement

- Potassium replacement.
- Check phosphorus, magnesium.

(4) Search and treat precipitating factor like infection

(5) Others

- Admit to high dependency unit.
- Supplemental oxygen.
- Place in left lateral position to avoid aortocaval compression.
- Monitor fetal heart rate.
- Monitor urine output.

tion are important in preventing this catastrophic complication in diabetic pregnancies. Education of patients specifically aimed at improving their understanding of the risks of pregnancy and the requirements for successful outcome must be emphasised during each visit. Similarly, obstetric and midwifery staff require a high index of suspicion to identify patients early in the course of their illness since the development of diabetic ketoacidosis in pregnancy can be rapid and can also occur at lower blood glucose levels compared to non-pregnant women. The use of reagent strips to detect ketones in urine (Ketostix) when blood glucose levels are high, or if symptoms of intercurrent illness appear, may be one way of early identification of this complication. However, the presence of minor ketonuria in normal pregnancy, especially in the presence of significant emesis, should be borne in mind during evaluation of such patients. The use of reagent strips to detect ketones in blood may help in the differentiation of these two conditions, although this needs validation for its use in routine clinical practice. Certainly, if there are any signs of decompensation, early hospitalisation is mandatory.

CONCLUSION

While the outcomes of diabetic ketoacidosis in pregnancy have improved over the years, significant maternal and fetal mortality still remains. Prevention, early recognition and hospitalisation, and aggressive management remain the cornerstones to minimise the outcomes of this dreaded complication.

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