Life-threatening ketoacidosis in a pregnant woman with psychotic disorder

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Abstract

Pregnancy is an insulin resistant state. Hyperglycaemia and gestational diabetes mellitus are well-recognised complications even in women without existing metabolic syndrome or obesity. Pregnant women also appear to be more vulnerable to ketoacidosis, particularly after short periods of reduced oral intake in the third trimester, and may present with very severe starvation ketoacidosis, prompting emergent delivery. We present a case of a woman with a background of depression and psychotic episodes. Olanzapine had been commenced after a psychotic episode at 20 weeks' gestation. Gestational diabetes mellitus was diagnosed at 28 weeks, and she was then admitted at 31 weeks with severe euglycaemic ketoacidosis following a short period of vomiting. She underwent caesarean section when the metabolic disturbances did not resolve with medical treatment. We believe atypical antipsychotic therapy contributed to the profound insulin resistance seen here, and that obstetricians, physicians and psychiatrists must be aware of the risks conferred by these agents in pregnancy.

Keywords

Olanzapine, starvation ketoacidosis, high anion gap metabolic acidosis, hyperglycaemia

Date received: 14 August 2015; accepted: 14 November 2015

Introduction

Obesity is an increasingly common problem in pregnancy. It poses a number of challenges for physicians caring for pregnant women. One of the biggest issues is that of increased insulin resistance. This is evidenced by the increasing prevalence of gestational diabetes mellitus (GDM) and the number of women requiring oral hypoglycaemic agents or insulin during pregnancy.

Pregnancy is also a time at which mental health may deteriorate, and psychiatric disorders are an important cause of maternal death in the UK.¹ Newer classes of antipsychotics, in particular the 'atypical' or second-generation antipsychotics, are increasingly being used. Olanzapine, a commonly used atypical antipsychotic, is known to be associated with significant metabolic disturbances in the non-pregnant population, in particular weight gain and type 2 diabetes mellitus.^{2,3} Of concern is also the reported association of olanzapine use and unheralded diabetic ketoacidosis, which has been fatal in a number of cases.⁴

Ketoacidosis is most commonly seen in pregnancy in the setting of diabetes mellitus, but a number of cases of ketoacidosis with euglycaemia have also been reported following short periods of starvation.^{5,6} Starvation ketoacidosis is associated with a more severe acidosis than is seen in non-pregnant individuals. We describe a woman who was on olanzapine from 20 weeks of gestation, and then developed ketoacidosis after a short period of reduced oral intake. However, treatment was more challenging than in other reported cases and we attribute this to very profound insulin resistance as a consequence of concurrent olanzapine use. We speculate that olanzapine in combination with the insulin resistance attributable to pregnancy contributed to the presentation in this case.

Case

A 27-year-old female in her fourth pregnancy presented at 31 weeks' gestation to the delivery suite with reduced fetal movements on a background of a week-long history of vomiting, poor oral intake and intermittent upper abdominal pain radiating to her back.

Her past medical history was notable for depression and a psychotic episode 2 years prior to this pregnancy. Her previous pregnancies were not complicated by GDM. She had stopped her antipsychotic medication prior to her booking appointment, but was admitted to

a psychiatric hospital at 20 weeks of gestation with a further episode. At that time olanzapine 20 mg daily was commenced in addition to the 40 mg fluoxetine that she had been taking regularly prior to and throughout pregnancy. At 23 and 27 weeks of gestation, glycosuria was identified on urine dipstick testing. Metformin was commenced after an abnormal oral glucose tolerance test (fasting glucose 8.1 mmol/L, 2 h glucose 12.7 mmol/L) at 28 weeks. Metformin resulted in some improvement in glycaemic control. She had taken no other medications during pregnancy and denied any substance misuse. Booking body mass index was 37 kg/m².

On examination she looked unwell. She was tachypnoeic, tachycardic and hypertensive (heart rate 130 beats per minute, blood pressure 162/103 mm Hg). On abdominal palpation there was tenderness in the epigastric region without peritonism. The gravid uterus was an appropriate size for gestational age. Cardiotocography was reassuring.

Blood tests were notable for anaemia (haemoglobin 10.4 g/dL) and neutrophilia ($20.1 \times 10^9/L$). Urinalysis was positive for protein (trace) and ketones (4+). Arterial blood gas analysis showed a profound metabolic acidosis with partial respiratory compensation (pH 7.24, PaCO₂ 1.4 kPa, PaO₂ 15.5 kPa, base excess -22 mmol/L, HCO₃ 8.8 meq/L, lactate 2.2 mmol/L, glucose 7.8 mmol/L, anion gap 20.4 mmol/L).

The patient was transferred immediately to the intensive care unit. Metformin was discontinued. Capillary ketone concentration was 5.2 mmol/L. An infusion of 10% dextrose was initiated at 70 mL/hr, with a variable rate insulin infusion running concurrently. A sodium bicarbonate infusion was then added (1.26% at 175 mL/hr, increased after an hour to 200 mL/hr). Over the next 36 hr it was possible to normalise her pH and bring about a gradual fall in ketone concentration with increasing rates of insulin infusion (Table 1). This resulted in a need to switch from 10 to 50% dextrose to minimise the risk of

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Table 1. Serial arterial blood gas results with concurrent capillary ketone measurements.

Day	0	1	2
Time	1900	1100	2000
pH	7.24	7.26	7.39
Bicarbonate (mmol/L)	8.8	10.3	15
Potassium (mmol/L)	4.2	3.6	3.3
Base excess (mmol/L)	-22	-19.7	-12.8
Insulin (units/hr)		16	20
Dextrose (g/hr)		30	25
Glucose (mmol/L)	7.8	14.3	13.3
Lactate (mmol/L)	2.2	2.1	2.4
Ketones (mmol/L)	5.2	4.3	4.3

volume overload. Two doses of 12 mg betamethasone were given intramuscularly at this stage, to aid fetal lung maturation should early delivery be warranted.

Though the ketosis was slowly improving with aggressive insulin therapy, and the pH remained normal, failure to achieve complete resolution of ketosis coupled with a relatively brisk rise in serum lactate led to a decision to perform a caesarean section under spinal anaesthesia. The procedure was uncomplicated and there was no intra-abdominal pathology. A live male infant weighing 2200 g was delivered and taken to the special care baby unit in view of gestational age and concern about the maternal metabolic disturbance. The maternal ketoacidosis resolved within 12 hr of delivery. However, the patient remained hyperglycaemic, requiring continued metformin.

Discussion

Ketoacidosis and pregnancy

Ketoacidosis in pregnancy is most commonly seen in women with type 1 diabetes mellitus. The risk factors for developing diabetic ketoacidosis are the same as in the non-pregnant population, but the condition may also be precipitated by the use of β -agonists as tocolytics, such as ritodrine.^{7,8} Starvation ketoacidosis has been described more frequently in pregnant women compared with the non-pregnant population, and can cause a more severe acidosis in this setting (in a recent review of all published cases, the mean bicarbonate concentration was 8.8 mmol/L).⁶ Fetal death has been reported in severe cases of diabetic ketoacidosis and in one case of non-diabetic ketoacidosis.^{5,9}

Antipsychotics and insulin resistance

Pregnancy is an insulin resistant state, as a result of the placental production of placental growth hormone, human placental lactogen and insulin-like growth factor 1.¹⁰ It is known that many factors contribute to the development of GDM, a state of impaired glucose handling and relative insulin insufficiency, including multiple pregnancy, increasing maternal age, obesity and a family history of diabetes mellitus.¹¹

Antipsychotics are associated with hyperglycaemia and a higher rate of type 2 diabetes mellitus in non-pregnant patients with schizophrenia.¹² Olanzapine can cause weight gain, which is thought to be the main cause of the metabolic changes that occur.¹³ Olanzapine contributes directly to insulin resistance in an animal model,¹⁴ but there have been conflicting results in human subjects. In one study of insulin resistance in people on antipsychotics, only clozapine was shown to affect insulin resistance.¹⁵ However, in another study of healthy men given olanzapine, the resultant insulin resistance was independent of any change in adiposity.¹⁶ Recent studies indicate that an obesity-independent effect of olanzapine on glucose homeostasis may be

mediated by an action on the cholinergic muscarinic M3 receptor, which is present on pancreatic β -cells, as well as within the hypothalamus and brain stem. The M3 receptor is important for the regulation of insulin secretion, amongst other functions.¹⁷

Taking all these observations together, it is reasonable to postulate that olanzapine use in pregnancy would be associated with an increased risk of GDM. One case of olanzapine as a potential contributory factor to the development of GDM has been described.¹⁸ Interestingly, in this case there was a clear temporal relationship between an increase in olanzapine dose and worsening hyperglycaemia. There are no large studies examining antipsychotic use as an independent risk factor for GDM, but recently published guidelines on antenatal and post-natal mental health recommend routine monitoring for GDM in pregnant women receiving antipsychotic agents.¹⁹

Antipsychotics and ketoacidosis

Atypical antipsychotics have been associated with the development of diabetic ketoacidosis in non-pregnant individuals not previously diagnosed with diabetes mellitus. One autopsy series included 17 deaths to diabetic ketoacidosis precipitated by the use of antipsychotics, mainly quetiapine and olanzapine.⁴ Several studies have demonstrated that the risk of developing diabetes mellitus and diabetic ketoacidosis is significantly higher when clozapine and olanzapine are prescribed rather than other atypical antipsychotics.^{2,3}

Management of ketoacidosis

Cessation of contributory medication

If a medication is potentially contributing to significant metabolic derangement, then it is appropriate to review the choice of agent and consider an alternative with a lower incidence of that particular side effect. This is a judgement about balancing risk of abrupt cessation of an antipsychotic with risk from the ongoing metabolic disturbance. The clearance of a medication is also a consideration. Diabetic ketoacidosis has been reported more than a month following an increase in olanzapine dose. Olanzapine was stopped at the time of the acute presentation in that case, and insulin was required at a gradually decreasing dose for a month.²⁰ There may therefore be little or no benefit of stopping the contributory medication in an acute presentation such as that described here.

A decision about the administration of high-dose parenteral steroids for fetal lung maturation is also challenging, given this will tend to worsen maternal insulin resistance. The risks of preterm delivery to the fetus have therefore to be balanced against the risks of worsening maternal biochemical disturbance for both mother and fetus.

Suppression of ketosis

There has been an important shift in the management of diabetic ketoacidosis in recent years. Historically, normalisation of blood glucose was the focus of therapy, and resolution of accompanying ketosis almost incidental. Now, however, the focus has shifted primarily to suppression of ketone production with high-dose intravenous insulin infusions. In concert with this, infusion of crystalloid and dextrose with appropriate intravenous potassium supplementation is provided continuously.²¹

In the reported cases of starvation ketoacidosis in non-diabetic pregnant women, the blood glucose is often at the lower end of the normal range and glucose administration is frequently sufficient in its own right to suppress ketosis by stimulating endogenous insulin secretion. The case described here differs because the combination of pregnancy and olanzapine generated an exaggerated insulin resistant state. This is illustrated by the failure of high insulin infusion rates to suppress ketosis adequately. However, though failure of ketosis

completely to resolve contributed to the decision to proceed to caesarean section in this case, it is important to highlight that the ketosis was slowly improving. Were it not for other considerations in this case, particularly the rising lactate, even higher rates of insulin infusion may have been sufficient to bring about complete resolution of ketosis. Very high insulin infusion rates are employed, for example in a hyperinsulinaemic euglycaemic clamp, which may be used in the treatment of beta-blocker and calcium-channel-blocker overdose. With this technique, significant episodes of hypoglycaemia are rare despite infusion rates of insulin 5- to 10-fold higher than those given in many guidelines for the management of diabetic ketoacidosis.²² Clinicians should therefore not be unduly fearful of a trial of high rates of insulin infusion, particularly since these women will invariably be cared for in a critical care setting with continuous physiological monitoring and very frequent measurement of blood glucose and electrolytes. An alternative in this case would also have been to reduce the dextrose infusion rate even further in view of the hyperglycaemia that developed, as this may have contributed to the hyperlactataemia.

Bicarbonate is not generally recommended in the management of diabetic ketoacidosis as it is argued that it may contribute to intracellular acidosis, peripheral hypoxaemia and hypokalaemia.²¹ It may be appropriate as a temporising measure in very severe cases, where the pH is less than 6.9. Its use may also therefore be reasonable in non-diabetic ketoacidosis if the acidosis is profound and other therapies are proving ineffective.

Delivery

When diabetic ketoacidosis occurs in the absence of fetal compromise, medical treatment alone is usually sufficient to bring about resolution of the metabolic abnormalities. In contrast, in the reported cases of starvation ketoacidosis, emergency delivery appears to be frequent, and usually follows the failure of metabolic derangement to improve with administration of non-glucose-containing fluids. The removal of the feto-placental unit at delivery will invariably improve problems related to insulin resistance, but can result in additional neonatal morbidity, particularly if performed pre-term. Clearly emergency delivery is advisable if there is evidence of fetal compromise, or, as in this case, a failure of medical treatment to lead to resolution. However, it does appear to be the case that these women are often subjected to emergency delivery when medical therapies have not been given for a sufficient duration and intensity to have provided a meaningful benefit.

Conclusion

All clinicians caring for pregnant women should be aware that the inherently insulin resistant state of pregnancy predisposes to both diabetic and non-diabetic ketoacidosis, particularly in the third trimester. Additionally, as highlighted by this case, it should be appreciated that atypical antipsychotics such as olanzapine may make endocrine emergencies of this sort more common. An evidence base for management will not come from randomised-controlled studies; at the present time we would encourage those caring for these women to consider early aggressive medical therapy in the hope that fetal distress and emergency delivery, with all their attendant sequelae, may be avoided.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Written consent was obtained from patient for publication.

Guarantor

LM

Contributorship

Case summary by BA, article conceived and written by CJF. Final draft approved by all authors.

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