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Review

Management of diabetic ketoacidosis in pregnancy

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Key content
- Diabetic ketoacidosis in pregnancy (DKP) is a serious complication that poses several challenges with respect to diagnosis, management and prevention.
- This article covers the precipitating factors for DKP in pregnancy as well as diagnosis, management and prevention of the complication.

Learning objectives
- To manage the acute crisis of DKP.
- To increase awareness of DKP.
- To reduce the perinatal morbidity and mortality associated with DKP.

Ethical issues
- Despite adequate knowledge and care of patients with diabetes, is DKA a major cause for concern?
- To increase awareness, and reduce the perinatal morbidity and mortality associated with DKP.

Keywords: diabetes / diagnosis / management / pregnancy / prevention

Linked resource: Single best answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

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Introduction

Diabetic ketoacidosis in pregnancy (DKP) is a serious complication that poses several challenges with respect to diagnosis, management and prevention. It develops because of relative or absolute insulin deficiency and the simultaneous increase in counter-regulatory hormones (cortisol, catecholamines, glucagon and growth hormone). This causes significant changes in metabolism,[1] such as lipolysis and proteolysis, which increase gluconeogenesis, and together with glycogenolysis, contribute to the development of hyperglycaemia. This is accompanied by a decrease in glucose uptake by peripheral tissues. Lipolysis provides excess free fatty acids to the liver, enhancing the process of ketogenesis, with subsequent ketoacidosis.[1]

At present, most obstetric centres offer specialised care for diabetes in pregnancy, which reduces the chance of DKP occurring. 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 obesity. Pregnancy is also associated with physiological changes that can predispose a pregnant woman with diabetes to diabetic ketoacidosis.

Some specific physiological reasons for DKP are as follows:[2,3]
- Pregnancy is a state of respiratory alkalosis associated with a compensatory drop in bicarbonate levels; this impairs the buffering capacity and renders the pregnant woman more prone to develop diabetic ketoacidosis.
- Relative insulin resistance in pregnancy along with enhanced lipolysis and elevated free fatty acids form the base for DKP.
- Hormonal changes including increased levels of human placental lactogen, progesterone, and cortisol impair maternal insulin sensitivity.

DKP is more commonly observed along with type I diabetes, but can also be observed with type II diabetes and gestational diabetes. It is likely to be precipitated by specific factors such as protracted vomiting, hyperemesis gravidarum, starvation, infections, insulin non-compliance, medications precipitating DKP (e.g. beta sympathomimetic agents),

steroid prophylaxis/steroid treatment, insulin pump failure (as pumps deliver rapid-acting insulin, interruption for a few hours completely deprives the patient of insulin) and conditions such as diabetic gastroparesis (Box 1).[2]

Diagnosis of diabetic ketoacidosis in pregnancy (DKP)

In pregnant women with any combination of the signs and symptoms specified in Box 2, DKP should be excluded; occasionally, DKP may be the first presentation of diabetes in pregnancy.[2,3]

When DKP is suspected, laboratory investigation is required to confirm the diagnosis, and to assess the severity of DKP and its possible cause (Box 3). The Joint British Diabetes Societies Inpatient Care Group guidelines[4] state the following diagnostic criteria for DKP:

- Blood ketone level more than or equal 3.0 mmol/l (or) urine ketone level more than 2+
- Blood glucose level more than 11.0 mmol/l or known diabetes mellitus
- Bicarbonate level less than 15.0 mmol/l and/or venous pH less than 7.3

Box 1. Precipitating factors for diabetic ketoacidosis in pregnancy

Protracted vomiting
Hyperemesis gravidarum
Infections
Insulin non-compliance
Medications precipitating diabetic ketoacidosis in pregnancy
Insulin pump failure
Conditions such as gastroparesis

Box 2. Signs and symptoms

Nausea or vomiting
Abdominal pain
Polyuria or polydipsia
Blurred vision
Muscle weakness
Drowsiness
Lethargy
Change in mental status
Hyperventilation (Kussmaul breathing)/pear drop odour
Tachypnoea
Hypotension
Tachycardia
Coma
Shock
Abnormal fetal heart tracing

Box 3. Investigation for diabetic ketoacidosis in pregnancy (DKP)

Positive serum/urine ketones
Lab glucose hyperglycaemia (≥ 11.0 mmol), but DKP can occur at lower glucose levels
Low serum bicarbonate (<15 mEq/l)
Arterial pH ≤7.30
Anion gap >12
Elevated base deficit ≥4 mEq/l
Potassium level may be falsely normal/elevated

Management of diabetic ketoacidosis in pregnancy (DKP) (Figure 1)

DKP is considered as an emergency that needs to be managed in at least Level 2 critical care units,[5] such as a high-dependency unit (HDU) or intensive care unit (ICU), by a team of professionals experienced in dealing with similar cases. This team usually consists of an obstetrician, a diabetologist/endocrinologist, an obstetric anaesthesiologist, and well-trained nursing staff/midwives.[2] It is important to stabilise a patient with DKP and insert large intravenous accesses or central venous line and continuous maternal monitoring with a cardiac monitor and pulse oximetry.[6] The management incorporates six main aspects (Box 4), which should be carried out simultaneously. The six aspects are described below.

Intravenous fluid therapy

Fluid replacement should be commenced by infusing isotonic saline (0.9%), as most patients have a negative fluid balance of about 100 ml/kg of body weight.[4] This represents a total fluid deficit of approximately 6–10 l. The intravenous (IV) infusion should be started at 10–15 ml/kg/h in the first hour,[1] after which the rate should be adjusted according to the haemodynamic status of the patient, guided by monitoring of blood pressure, urine output, and central venous pressure in selected cases.[4] For example, in a healthy adult weighing 70 kg, IV fluid therapy should be performed as follows:

If her systolic blood pressure (SBP) is less than 90 mmHg, she should be resuscitated with 500 ml of normal saline infusion over 10 to 15 minutes and if the SBP does not improve this can be repeated. Senior medical staff evaluation should be undertaken to diagnose other causes of hemodynamic instability such as sepsis.[4] After stabilisation of the SBP above 90 mmHg the patient can be maintained with normal saline infusion of 1 l over 1 hour, then 500 ml/hr for 4 hours, followed by 250 ml/h for 8 hours, after which the infusion rate can be reduced to 150 ml/h.[4] This fluid

Box 4. Management of diabetic ketoacidosis in pregnancy (DKP)

Multidisciplinary approach

1. Intravenous fluid therapy
2. Intravenous insulin therapy
3. Electrolyte correction
4. Evaluation of the need for bicarbonate administration
5. Identification and treatment of any precipitating factors
6. Monitoring of maternal and fetal responses

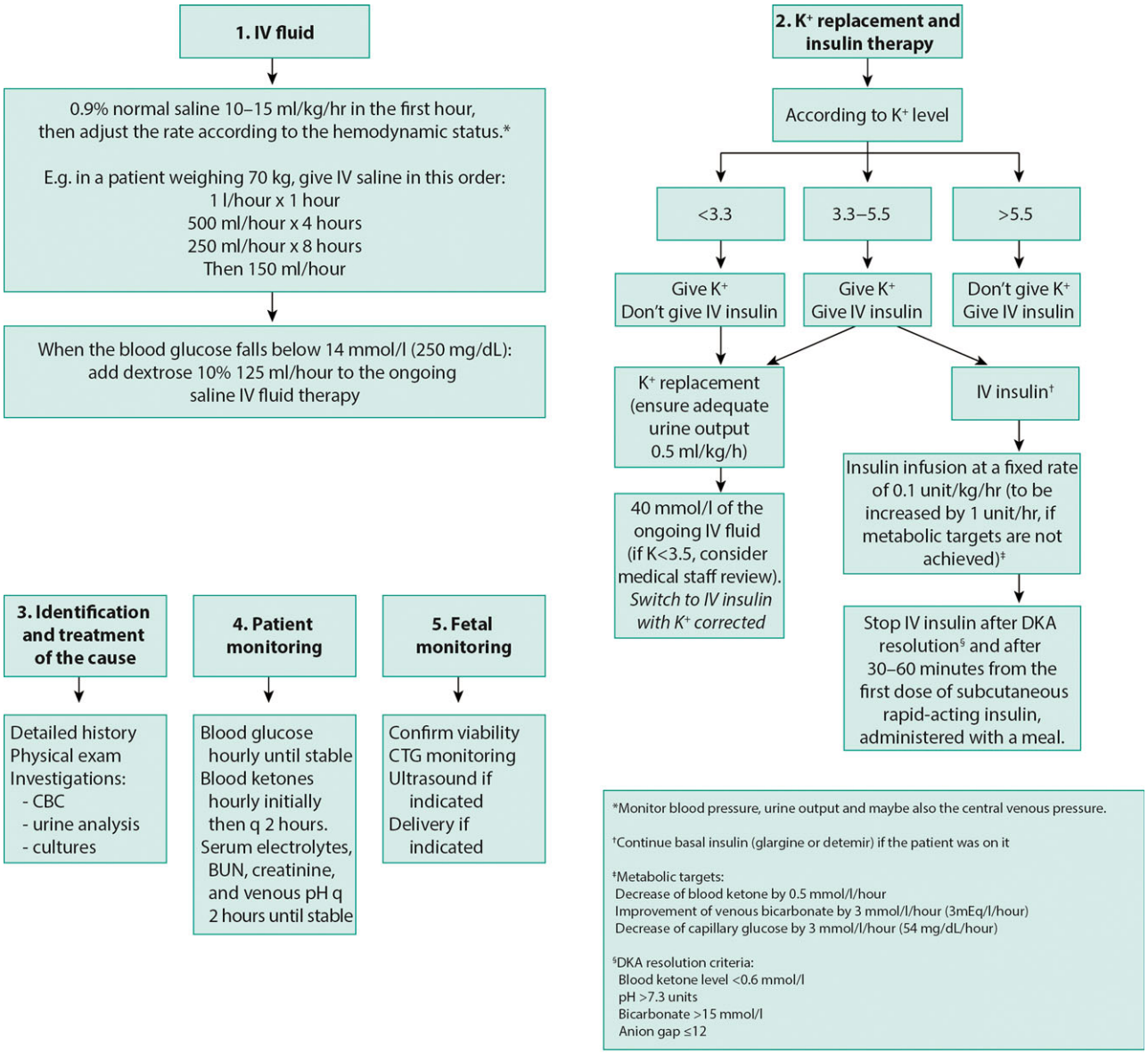

Figure 1. Algorithm. BUN = blood urea nitrogen; CBC = complete blood count; DKA = diabetic ketoacidosis; IV = intravenous; K = potassium; q = every (Latin quaque)

maintenance regimen will be adequate for a patient who presents with an SBP more than or equal to 90 mmHg. The patient should be closely monitored by adjusting the IV fluid therapy according to her response.

IV fluid therapy improves tissue perfusion, decreases stress hormone levels, and causes haemodilution; this, in turn, lowers the hyperglycaemia and increases the response to insulin therapy.[2] Adequate perfusion should be ensured, taking into account fluid losses, through close monitoring of urine output. Urine output should be monitored using an indwelling catheter, and it should be more than or equal to 0.5 ml/kg/h to ensure that the patient is well hydrated.[4]

If the blood glucose level falls below 14 mmol/l (250 mg/dl), 10% dextrose should be added to the ongoing normal saline IV fluid therapy at a rate of 125 ml/h.[4] Careful fluid management is imperative in patients with impaired heart or kidney function.[7]

Insulin therapy

The development of DKP could be attributed to absolute or relative insulin deficiency. Therefore, IV insulin therapy not only corrects the hyperglycaemia but also inhibits the ongoing synthesis of keto acids. IV therapy with regular insulin should be commenced promptly in patients with serum potassium

level more than or equal to 3.3 mmol/l.[1] However, insulin administration should be postponed if serum potassium is low, until it is corrected to more than or equal to 3.3 mmol/l, because the insulin pushes the potassium into the intracellular space, which aggravates the existing hypokalaemia and may precipitate fatal cardiac arrhythmias.[1] Regular insulin infusion should be commenced at a fixed rate of 0.1 unit/kg/h, and it is recommended not to initially exceed 15 units/h.[4] Priming with an IV insulin bolus (0.1 unit/kg) is not required unless there is a delay in the preparation of the fixed rate IV insulin infusion.[4] If the metabolic targets (Box 5), primarily blood ketone levels, cannot be achieved by the current infusion rate, the insulin infusion rate should be increased by 1 unit/h until ketones reach the desired level.[4]

IV regular insulin has been compared with the new IV rapid-acting insulin analogues (in men and non-pregnant women), and both preparations have demonstrated the same efficacy, without any difference in treatment duration or the total number of insulin units administered.[8] Therefore, regular insulin is adopted as it is more cost effective. If the patient is already maintained on basal insulin e.g. detemir or glargine, then this should be prescribed and administered concomitantly with the IV insulin infusion.[4] This ensures the presence of insulin in case of interruption in the insulin infusion and allows a smooth transition to the usual subcutaneous insulin regimen of the patient when he or she is able to sufficiently eat and drink, and the period of ketoacidosis has resolved.

The fixed-rate infusion can be discontinued after DKP resolution[4] and after 30–60 minutes from the first dose of subcutaneous rapid acting insulin, administered with a meal, as a part of the subcutaneous insulin regimen. This is to avoid rebound hyperglycemia or recurrence of DKP.

When the DKP has resolved but still the patient cannot reliably eat or drink, a transition of variable-rate (commonly referred as sliding scale) IV insulin infusion[4] with IV fluid can be used to control the blood glucose level until the patient tolerates an oral diet and subcutaneous rapid acting insulin can be given with discontinuation of the variable-rate infusion 30–60 minutes later.

Electrolyte correction: potassium replacement

Although patients have a total potassium deficit of 3–5 mmol/kg[4] the measured serum potassium is usually normal or even high and this is related to the increased osmolality and insulin deficiency, which cause trans-cellular shift of potassium outside the cells.[1]

Box 5. Metabolic targets to be achieved using initial intravenous insulin therapy

Decrease in blood ketone levels by 0.5 mmol/l/h
Increase in venous bicarbonate levels by 3 mmol/l/h
Decrease in capillary glucose levels by 3 mmol/l/h (54 mg/dl/h)

Patients with a good urine output (at least 0.5 ml/kg/h) and serum potassium level less than 5.5 mmol/l should receive potassium chloride in order to maintain their potassium level in the range of 4–5 mmol/l, as the potassium starts to return to the cells with the ongoing IV fluids and insulin therapy.[2] Failure to replace potassium may result in hypokalaemia with life-threatening cardiac arrhythmias.

If the serum potassium level at presentation[4] is more than 5.5 mmol/l potassium should not be added to the infused fluid. However, if the level is 3.5–5.5 mmol/l, 40 mmol/l of potassium chloride should be administered with IV normal saline. The National Patients Safety Agency and Irish Medication Safety Network recommend not to infuse more than 20 mmol potassium per hour.[9,10] If the serum potassium is less than 3.3 mmol/l, review by a senior medical staff is important, as the patient may require a higher-strength potassium infusion,[4] which may require central venous access.

Phosphate replacement

Although the whole body phosphate is decreased, replacement is not recommended, unless the serum level is less than 0.32 mmol/l (1 mg/dl) or the patient develops cardiac impairment or respiratory depression.[2,4]

Evaluation of the need for bicarbonate administration

The use of bicarbonate is not recommended,[4] as there is no evidence of a beneficial effect with it, and it may be harmful to the patient and the fetus. Bicarbonate inhibits the compensatory hyperventilation that washes out carbon dioxide (CO_2), leading to an increment in CO_2 partial pressure (PCO_2), which may, in turn, decrease fetal oxygen delivery.[11] In addition, the patient may develop paradoxical cerebral acidosis, because the CO_2 diffuses through the blood brain barrier faster than the infused bicarbonate.[12] Further, bicarbonate administration delays the wash out of ketones[13] and can worsen hypokalaemia.

Identification and treatment of precipitating factors

Recognition of the condition that precipitates DKP is essential for its management, as any delay in the correction of the precipitating factor can worsen the prognosis and increase the risk of recurrence.[2] A detailed history and physical examination are very important to direct the investigations for the targeted treatment of precipitating factors. Elevated total white blood cell count is commonly observed; however, it does not always mean that the patient has an infection, as it can be secondary to dehydration. Nevertheless, a thorough clinical assessment to exclude infection should be performed, and appropriate treatment should be started if infection is suspected or confirmed.[3]

Monitoring of maternal and fetal response

Maternal response

Capillary glucose should be monitored hourly during insulin infusion. Blood ketones[4] should also be monitored hourly for the first 6 hours in order to ensure that ketone levels decrease at the required rate of at least 0.5 mmol/l. Other biochemical parameters such as pH, bicarbonate and serum potassium can be monitored using venous gas samples every 2 hours in the first 6 hours,[4] provided that a concomitant laboratory sample is taken at baseline to confirm the accuracy of serum potassium levels. If a ketone meter is not available, the calculated anion gap (Box 6) helps in monitoring the patient response.[1] Measurement of arterial pH is not required (unless the patient is hypoxic or has an impaired level of consciousness), as it is only 0.03 units higher than the venous pH.[14]

The bicarbonate level can be reliably used to evaluate the treatment response in the first 6 hours of management, as, subsequently, aggressive hydration using 0.9% sodium chloride could lead to the development of hyperchloraemic acidosis associated with a normal anion gap, which tends to lower the bicarbonate level.[4] Ketoacidosis and hyperchloraemic acidosis are two different types of metabolic acidosis associated with low serum bicarbonate levels. In ketoacidosis, the primary process is the increased production of keto acids. The body uses bicarbonate to neutralise these keto acids; therefore, serum bicarbonate level decreases and, subsequently, the anion gap increases. Hyperchloraemic acidosis results from the administration of large volumes of normal saline with high chloride content to the patient, which dilutes plasma bicarbonate, leading to increased chloride with low bicarbonate, and, subsequently, metabolic acidosis associated with a normal anion gap.[2,4,15]

Urinary ketones take time to clear, as the body excretes ketones through metabolising the major ketone of DKP (3-beta-hydroxybutyrate [3BHB]), which can be measured on a bedside capillary sample, to acetoacetate, which is semi-quantitatively measured in urine. Thus, ketonuria can persist for a significant period after 3BHB has cleared and the metabolic acidosis has resolved.[16]

Fetal response

DKP may result in severe maternal complications such as acute renal failure, adult respiratory distress syndrome, cerebral oedema, coma and even death.[2,11,17] The fetal mortality associated with DKP ranges between 9% and 36%;[1,18,19] however, considerably higher perinatal morbidity is observed with DKP, including hypoxia-related complications, which are attributable to an increased rate of preterm delivery. During DKP, the fetal brain is susceptible to increased maternal 3BHB and lactate concentration, which lead to decreased glucose uptake by the fetal brain.[20] These events may increase the chance of fetal brain injury and may have a long-term developmental impact.[20,21] Future research may assist in understanding the complete effect of DKP on the fetus.

Box 6. Anion gap calculation

Anion gap = $(NA^+ + K^+) - (Cl^- + HCO_3^-)$

Fetal monitoring and delivery in diabetic ketoacidosis in pregnancy (DKP)

The fetal effects in DKP involve a combination of severe maternal dehydration with acidosis, which may be caused by reduced uteroplacental perfusion in an acidotic environment. In addition to this combined insult, severe maternal electrolyte disturbances (particularly potassium) could result not only in maternal cardiac arrhythmias but also fetal cardiac arrhythmias, which may lead to fetal death.[22] Fetal heart tracing performed in DKP may often demonstrate fetal acidotic changes, representing the effect of maternal metabolic acidosis on the fetus. This is often corrected with maternal hydration and correction of metabolic acidosis. Normalisation of fetal heart tracing after correction of DKP may require 4–8 hours. Fetal biophysical profile and Doppler studies may also reflect the fetal acidotic status. However, the decision to deliver should be individualised and should be primarily based on evaluation of the maternal clinical status to ensure a safe labour and delivery, fetal gestational age[23,24] and the results of fetal investigations such as fetal heart tracing. All these factors should be considered together with a multidisciplinary approach while making a decision regarding delivery. However, in the majority of cases of DKP, the aim should be to monitor the fetus until the maternal metabolic state is stabilised, without any immediate plans for delivery, and to continue the pregnancy with complete resolution of DKP. There is no consensus on further fetal monitoring after complete resolution of DKP, especially when the fetus is preterm. The best practice, however, is aimed at educating the patient to avoid further recurrence of DKP, and an increased surveillance to ensure adequate diabetic control and compliance with treatment. The frequency of fetal monitoring is unknown and no definite recommendations are currently available. Therefore, individualised care with a multidisciplinary approach is recommended as a best practice option.

Resolution of diabetic ketoacidosis in pregnancy (DKP)

Recovery from DKP is defined by a blood ketone level less than 0.6 mmol/l, a pH more than 7.3 and a serum bicarbonate more than 15 mmol/l (however, after 6 hours, bicarbonate may not be a reliable indicator, as mentioned above).[4] Moreover, normalisation of the anion gap (less than or equal to 12 mEq/l) helps to ensure that the patient has recovered from DKP

(Box 6).[1] Insulin infusion has no role in the management of hyperchloraemic acidosis. This condition is usually corrected by the kidney, and no intervention is required.

Euglycaemic diabetic ketoacidosis in pregnancy (DKP)

Euglycaemic (normoglycaemic) DKP is a rare situation where the patient presents with normal or below normal, rather than high, blood glucose levels with diabetic ketoacidosis.[25] This can affect patients with type I diabetes, type II diabetes or gestational diabetes.[2,26] The likely mechanisms are as follows:[26]

- the use of glucose by the fetoplacental unit, with decreased maternal glycogenolysis and gluconeogenesis
- increased renal loss of glucose as the renal blood flow increases with increased glomerular filtration of glucose without a corresponding increase in tubular glucose reabsorption
- increase in estrogen and progesterone in pregnancy accompanied by increased maternal usage of blood glucose
- dilutional effect on blood glucose because of the increased plasma volume during pregnancy

Moreover, starvation, which is associated with increased ketone production, is also accompanied by depletion of glycogen stores and normoglycaemic DKP.[27]

It is notable that the management of euglycaemic DKP follows the same principles. However, IV fluid therapy should involve the concomitant administration of 5% dextrose with IV saline via a separate line from the start of treatment to avoid hypoglycaemia caused by IV insulin administration, which is necessary to stop the production of ketoacids.[28,29]

Prevention of diabetic ketoacidosis in pregnancy (DKP)

Several strategies should be adopted during the preconception period and during pregnancy to prevent DKP.

Prepregnancy

- Education: As per National Institute for Health and Care Excellence (NICE) guidlines,[30] a woman with diabetes should plan her pregnancy with support from her team of diabetes experts; she should receive structured education with explanation of the facts regarding the risks associated with uncontrolled blood glucose in pregnancy. This can reduce complications such as DKP as well as the maternal and fetal risk associated with diabetes in pregnancy.
- Self-monitoring: A woman with diabetes should be offered a glucose meter to check her blood glucose levels at home. Women with type I diabetes should be provided a capillary ketone meter to check for blood ketonaemia, (or) at least urine ketone test strips to check for urine ketonuria when she has hyperglycaemia or feels unwell. Patients should be educated regarding sick day rules. Ideally, a woman with diabetes should be in touch with her diabetes medical team to check her prepregnancy HbA1c level and to keep it below 6.5% (48 mmol/mol).[30] Pregnancy should be avoided if HbA1c level is above 10% (86 mmol/mol).[30]
- Prepregnancy counselling: A woman with diabetes should receive counselling from her primary care physician or at her diabetes clinic. Effective contraception to avoid unplanned pregnancy should be discussed.

During pregnancy

- Team: During pregnancy, the diabetes specialist nurse/midwife, diabetes specialist dietician and/or joint obstetric-diabetes consultations will form a group of service providers for effective management.
- Screening: Diabetes screening of the general obstetric population should be offered to exclude diabetes in pregnancy as per the local diabetic guidelines, if available; otherwise, efforts should be made to formulate an effective diabetic local screening policy.
- Education: Women diagnosed with diabetes should be educated in a structured and impartial manner and in simple language about the precipitating factors and manifestations of DKP.
- Self-monitoring: Patients should continue to have a glucose meter for self-monitoring, and those with type I diabetes should have a ketone meter to be used as previously described.[30]
- Suspected DKP: Pregnant women with any type of diabetes should be advised to seek prompt attention at a medical facility if their blood glucose level is persistently above 11.1 mmol/l (200 mg/dl), or if they have any signs of infection or any other problems, as outlined in Box 1.[2] They should be assessed for hospital admission.
- Corticosteroid treatment: If a woman with diabetes requires antenatal corticosteroid therapy for the fetus, e.g. for fetal lung maturation in a suspected preterm birth, her insulin dose should be gradually adjusted (usually, insulin dose is increased by 25–40%).[31]
- Tocolysis treatment: If tocolysis is required, it is preferable to avoid betamimetics (they increase susceptibility for DKP) and use a different class of tocolytics. Tocolytics that are safer to use are the oxytocin receptor antagonist atosiban or a calcium channel blocker e.g. nifedipine.[32]

To prevent the recurrence of DKP, prior to discharge, it is necessary to:[4]

- educate the patient about how to identify and rectify the precipitating factors;
- review the pre-admission diabetes control, injection technique, injection sites, glucometer reliability, and storage of insulin with the patient; and

- provide the patient with the contact information of the diabetes team and a written plan of care.

In addition, future fetal monitoring should also be planned prior to discharge and a follow-up should be organised to review both maternal and fetal antenatal progress, and to ensure continuation of care.

Conclusion

DKP is a life-threatening condition; therefore, prompt diagnosis along with rapid initiation of acute care management involving an experienced multidisciplinary team could help to reduce maternal and fetal mortality, and morbidity. Patient education will form the main framework to reduce the risks associated with DKP. This study intends to spread awareness regarding DKP among caregivers and to improve the quality of care in pregnancy.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

MM instigated, designed, drafted, and critically revised the intellectual content of the manuscript, and contributed to the obstetric management of the study in the manuscript. KB contributed to the medical management of the study, and assisted in drafting and revising the intellectual content of the manuscript. SL contributed to drafting and revising the intellectual content of the manuscript. All authors approved the final version of the manuscript.

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Supporting Information

Additional supporting information may be found in the online version of this article at http://wileyonlinelibrary.com/journal/tog

Infographic S1: Prevention of diabetic ketoacidosis in pregnancy.

References

1 Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;**32**:1335–43.
2 Sibai BM, Viteri OA. Diabetic ketoacidosis in pregnancy. *Obstet Gynecol* 2014;**123**:167–78.
3 Carroll MA, Yeomans ER. Diabetic ketoacidosis in pregnancy. *Crit Care Med* 2005;**33**:S347–53.
4 Joint British Diabetes Societies Inpatient Care Group. *The Management of Diabetic Ketoacidosis in Adults*. Sept 2013. [http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_DKA_Adults_Revised.pdf].
5 Department of Health. *Comprehensive Critical care: A Review of Adult Critical Care Services*. UK: Department of Health; 2000 [http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4082872.pdf].
6 Wass J, Owen K. Diabetic hyperglycaemic emergencies. *Oxford Handbook of Endocrinology and Diabetes*. 3rd ed. Oxford: Oxford University Press; 2014.
7 Barrett EJ, DeFronzo RA. Diabetic ketoacidosis: diagnosis and treatment. *Hosp Pract* (Off Ed) 1984;**19**(89–95):99–104.
8 Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A, et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. *Diabetes Care* 2009;**32**:1164–9.
9 National Patient Safety Agency. *Potassium Solutions: Risks to Patients from Errors Occurring during Intravenous administration*. London: National Patient Safety Agency; 2002 [http://www.nrls.npsa.nhs.uk/resources/?entryid45=59882].
10 Irish Medication Safety Network. *Best Practice Guidelines for the Safe Use of Intravenous Potassium in Irish Hospitals*. Dublin: Irish Medication Safety Network; 2013 [http://www.imsn.ie/images/guidelines/imns-july-2013-best-practice-guidance-for-iv-potassium-use.pdf].
11 Parker JA, Conway DL. Diabetic ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am* 2007;**34**:533–43, xii.
12 Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. *Ann Intern Med* 1986;**105**:836–40.
13 Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrinol Metab* 1996;**81**:314–20.
14 Middleton P, Kelly AM, Brown J, Robertson M. Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J* 2006;**23**:622–4.
15 Yeung SJ, Agraharkar M, Sarlis NJ, Fahlen MT, Baweja K. *Hyperchloremic Acidosis*. *Medscape*; 2014 [http://emedicine.medscape.com/article/240809-overview#a5].
16 Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev* 1999;**15**:412–26.
17 Kamalakannan D, Baskar V, Barton DM, Abdu TA. Diabetic ketoacidosis in pregnancy. *Postgrad Med J* 2003;**79**:454–7.
18 Cullen MT, Reece EA, Homko CJ, Sivan E. The changing presentations of diabetic ketoacidosis during pregnancy. *Am J Perinatol* 1996;**13**:449–51.
19 Schneider MB, Umpierrez G, Ramsey RD, Mabie WC, Bennett KA. Pregnancy complicated by diabetic ketoacidosis: maternal and fetal outcomes. *Diabetes Care* 2003;**26**:958–9.
20 Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics* 2012;**129**:e1121–8.
21 Stenerson MB, Collura CA, Rose CH, Lteif AN, Carey WA. Bilateral basal ganglia infarctions in a neonate born during maternal diabetic ketoacidosis. *Pediatrics* 2011;**128**:e707–10.
22 de Veciana M. Diabetes ketoacidosis in pregnancy. *Semin Perinatol* 2013;**37**:267–73.
23 Royal College of Obstetricians & Gynaecologists. *Perinatal Management of Pregnant Women at the Threshold of Infant Viability—the Obstetric Perspective* (Scientific Impact Paper No. 41). UK: RCOG; 2014.
24 Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. *Arch Dis Child Fetal Neonatal Ed* 2014;**99**:F181–8.
25 Munro JF, Campbell IW, McCuish AC, Duncan LJP. Euglycaemic diabetic ketoacidosis. *Br Med J* 1973;**2**:578–80.
26 Guo RX, Yang LZ, Li LX, Zhao XP. Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: case-control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. *J Obstet Gynaecol Res* 2008;**34**:324–30.
27 Chico M, Levine SN, Lewis DF. Normoglycemic diabetic ketoacidosis in pregnancy. *J Perinatol* 2008;**28**:310–2.

28 Montoro MN, Myers VP, Mestman JH, Xu Y, Anderson BG, Golde SH. Outcome of pregnancy in diabetic ketoacidosis. *Am J Perinatol* 1993;**10**:17–20.
29 Franke B, Carr D, Hatem MH. A case of euglycaemic diabetic ketoacidosis in pregnancy. *Diabet Med* 2001;**18**:858–9.
30 National Institute for Health and Care Excellence. *Diabetes in Pregnancy: Management from Preconception to the Postnatal Period*. UK: NG3; 2015 [https://www.nice.org.uk/guidance/ng3].
31 Gabbe SG, Carpenter LB, Garrison EA. New strategies for glucose control in patients with type 1 and type 2 diabetes mellitus in pregnancy. *Clin Obstet Gynecol* 2007;**50**:1014–24.
32 Royal College of Obstetricians and Gynaecologists. *Tocolysis for Women in Preterm Labour*. RCOG Green-top Guideline No. 1B. London: RCOG; 2011.