A 10-year audit of pregnancies affected by diabetic ketoacidosis at the Pretoria Academic Complex

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Abstract

Background: Diabetic ketoacidosis (DKA) during pregnancy is associated with increased rates of maternal and perinatal mortality and morbidity. DKA management guidelines are designed to ensure optimal management and minimize adverse outcomes.

Objective: To determine the level of adherence to DKA management guidelines at a tertiary center in Pretoria, South Africa and report on maternal and perinatal outcomes of the pregnancies complicated by DKA.

Methods: This was a retrospective clinical record audit using the Society for Endocrinology, Metabolism and Diabetes of South Africa guidelines against documented management. Adherence to three cornerstones of therapy was measured: intravenous fluids, insulin therapy, and management of electrolytes.

Results: Fifty-six records of pregnancies that were complicated with DKA over a 10-year period were reviewed. Mean age was 29.6 years (range 20–43 years). Thirty-six (64.3%) women had type 1 diabetes mellitus. DKA was categorized into mild (n = 26, 46.4%), moderate (n = 22, 39.3%), and severe (n = 8, 14.3%). The study demonstrated lack of adherence to the three cornerstones of therapy. Of the 49 (85.7%) women with recorded perinatal outcomes, 30.6% had stillbirths. Severe maternal DKA (pH <7.0) demonstrated adverse perinatal outcomes (P = 0.005).

Conclusion: Despite the availability of guidelines, DKA is sub-optimally managed in pregnancy, which may contribute to adverse maternal and perinatal outcomes.

Keywords: diabetic ketoacidosis, perinatal outcome, pregnancy

1 INTRODUCTION

In the general population, 46–50 per 10 000 patients per year will experience diabetic ketoacidosis (DKA).[1] In the pregnant population, the incidence of DKA is estimated to be even lower, at 0.3 to 5 per 10 000 patients per annum.[2] DKA occurring in pregnancy is a medical emergency and is associated with increased rates of maternal and perinatal mortality and morbidity. It is a complication that is commonly seen in patients with type 1 diabetes mellitus, although it has also been reported in up to 25% of patients with type 2 diabetes mellitus and rarely in patients with gestational diabetes mellitus.[1, 2]

Diabetes mellitus may present with DKA for the first time in pregnant women with undiagnosed diabetes mellitus. Pregnancy is a potent risk factor for DKA because of the normal physiologic changes and increased metabolic demands.[2-5] It is therefore important to understand the physiologic changes associated with pregnancy to assist in the diagnosis and optimal management of DKA in pregnancy. DKA usually occurs in the second and third trimesters of pregnancy as the result of a relative or absolute insulin deficiency. Non-adherence to insulin therapy and infections are established precipitants of DKA. Obstetrically related conditions known to precipitate DKA include hyperemesis gravidarum and medications used in the prenatal period for tocolysis or to improve fetal lung maturity (e.g. beta sympathomimetic agents and steroids).[3]

DKA evolves over hours to days and the symptoms may be nonspecific, which may lead to the diagnosis being missed, especially in pregnancy.[6] Patients with DKA classically present with a triad of abnormalities—dehydration, ketosis, and metabolic acidosis.[7] The diagnosis can be more challenging in pregnancy because DKA does not always present with the classical symptoms or laboratory findings, and often progress more rapidly than in non-pregnant patients, therefore a high index of suspicion is required in pregnancy.[3, 6, 8] Non-specific symptoms include nausea or vomiting, fatigue, abdominal pains, and polyuria, which are also common in normal pregnancy.[2, 9] DKA in pregnancy may occur even with normal, or mildly elevated serum glucose levels (euglycemic diabetic ketoacidosis).[9-11] Euglycemic DKA should be considered in pregnancy in the presence of ketoacidosis plus a serum glucose level less than 11.1 mmol/L.[11]

According to the American Diabetes Association[12] and the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) 2017 guideline[13] the criteria for DKA diagnosis is: serum pH less than 7.3, serum bicarbonate less than 18 mmol/L, and the presence of serum or urine ketones. In 2003, the American Diabetes Association classified the severity of DKA by serum pH into mild (pH 7.25–7.3), moderate (pH 7.0–7.24), and severe (pH <7.0).[12] Prompt diagnosis and early initiation of therapy are mandatory because of the risks of adverse maternal and fetal outcomes (Table 1).

TABLE 1. Summary of management of diabetic ketoacidosis in adults[13]

Timing	IV fluids	Insulin	Electrolytes
Admission	*0.9% NaCl or Ringer's lactate:* • 1–1.5 L in the first hour (infusion rate: 15–20 mL/kg)	*IV bolus:* • Regular insulin 0.1–0.15 IU/kg followed by a continuous infusion at a rate of 0.1 IU/kg per hour *Usually prepared as follows:* • 200 IU in 200 mL 0.9% saline (1 IU/mL) *Reassess blood glucose:* • Increase the insulin infusion rate by 1 mL/hr if the blood glucose concentration does not decrease by 3–4 mmol/h • sGluc <5.6 mmol/L—decrease by 1 mL/h; give 25 mL of 50% dextrose IV • sGluc >15.6 mmol/L—increase by 1mL/h; give a bolus of regular insulin of 8 U IV *When the patient is able to eat:* • meal-related boluses of regular insulin in addition to the IV insulin infusion	*Bicarbonate (controversial):* • If pH <7.0 50 mmol/L $NaHCO_3$ in 200 mL of 0.45% NaCl over 1 h • If pH <6.9: 100 mmol/L $NaHCO_3$ in 400 mL 0.45% saline over 1 h • This can be repeated 2-hourly *Potassium (not >20 mmol/h)* Always check the K^+ concentration before commencing with insulin administration. • If sK^+ >5.5 mmol/L—no K^+ supplement but check K^+ 2-hourly • If sK^+ 4.1–5.5 mmol/L—add 20 mmol in each litre of IV fluid • If sK^+ 3.1–4.0 mmol/L—add 30 mmol in each litre of IV fluid • If sK^+ <3.0 mmol/L—add 40 mmol to the initial IV fluid (withhold insulin until K^+ >30 mmol/L) *Phosphate:* • Replacement only necessary if PO_4 is <0.33 mmol/L • Replace with potassium phosphate solution IV 14 mmol (10 mL) in 1 L rehydration fluid
After 1 h	*Reassess:* Hydration status hourly – sNa^+ concentration *If sNa^+ is normal or low:* • 0.9% NaCl/Ringer's lactate 250–500 mL/h (4–14 mL/kg depending on hydration status) *If sNa^+ is elevated:* • change to 0.45% NaCl Replace half the fluid deficit in the first 12 h (serum osmolality should not change >0.3 osmol/kg)		
Blood glucose <14 mmol/L	Change to 5% dextrose or 5% dextrose in 0.45% NaCl solution		

Abbreviations: IV, intravenous; sGluc, serum glucose; sK^+, serum potassium; sNa^+, serum sodium.

The management of DKA in pregnancy is similar to that in non-pregnant patients with the exception of fetal monitoring.[9, 13] The management includes prompt and effective maternal resuscitation, which entails aggressive administration of intravenous fluids, soluble insulin therapy, correction of electrolytes, and identification and management of precipitating factors. It is essential to prioritize maternal resuscitation and monitor maternal response above that of the fetus. Although the principles of management of DKA in low- to middle-income countries is the same, the mortality associated with DKA associated with preventable factors is higher.[14-16] Challenges in managing DKA in low- to middle-income countries include the lack of resources for close monitoring of electrolytes and glycemic control leading to insulin-related hypoglycemia and hypokalemia.[14-16]

The aim of the study was to audit the management of DKA in pregnancy and report on perinatal and maternal outcomes.

2 MATERIALS AND METHODS

This study was a clinical record audit of all pregnancies complicated by at least one episode of DKA, managed from 1 January 2008 to 31 December 2019 at the Pretoria Academic Complex, which comprises the Steve Biko Academic Hospital (SBAH) and the Kalafong Provincial Tertiary Hospital (KPTH). These two tertiary hospitals serve the greater Tshwane area in Gauteng Province, South Africa. The study was conducted in high-risk obstetrical units that have dedicated diabetic prenatal clinics managed by feto-maternal medicine specialists and diabetologists. A multidisciplinary team, which consists of obstetrical and internal medicine registrars (supervised by feto-maternal medicine specialists and physicians/diabetologists), midwives, dieticians, and onsite laboratories in both hospitals.

SBAH has approximately 3500 deliveries per year, of which approximately 150 (4.3%) are women with diabetes in pregnancy. KPTH has approximately 5000 deliveries per year, of which approximately 150 (3%) are women with diabetes in pregnancy.

All the women were hospitalized; admission and discharge registers in the obstetrics high care and intensive care units (ICU) from the two hospitals were perused. Patients were identified from the International Classification of Diseases 10th revision code for DKA in pregnancy, perusal of maternity admission registers, the diabetes clinic database, and maternal near-miss records for the period January 2008 until December 2019. The files of identified patients were retrieved for the audit. Repeated admissions for DKA of the same patient were treated as separate episodes as long as the inclusion criteria were met at each presentation. All the retrieved clinical records were allocated study numbers.

All the women included in the study were confirmed to be pregnant (biochemically or clinically) and met the inclusion criteria for DKA, i.e. serum pH <7.3, serum bicarbonate <18 mmol/L, and the presence of serum or urine ketones. Patients were excluded from the study if they were diagnosed with metabolic acidosis in pregnancy with other causes, hyperosmolar non-ketotic state, or uncontrolled diabetes mellitus without DKA in pregnancy or the puerperium. The reference standard for care against which the care of patients for this audit was measured was adapted from the SEMDSA guidelines of 2017.[13]

Maternal demographic data and information regarding diabetes mellitus, i.e. type of diabetes mellitus, details of medication used, and glycemic control, and pregnancy-related information such as gestational age at time of diagnosis or presence of other pregnancy-associated conditions were collected. The presenting symptoms, the patient's initial bedside biochemical or laboratory investigations (pH, serum glucose, potassium, bicarbonate, urea and electrolytes, urine ketones) before the initiation of DKA management were captured. The trends of the bedside biochemical or laboratory values over time were recorded, and times to resolution of hyperglycemia, metabolic acidosis, and ketonuria were calculated.

The clinical records and nursing charts were reviewed and adherence to the SEMDSA 2017 guideline[13] were assessed. Key parameters included the quantity and type of intravenous fluids administered in the first hour of management and over time thereafter, insulin therapy (route of administration and amount) administered, the appropriate correction of electrolytes and the management of DKA precipitants. Recorded evidence for clinical monitoring was reviewed. Information on infection screening, investigations, results, and management of the DKA precipitant were collected. The time (in hours) from the time of admission to resolution of DKA was recorded. Perinatal outcomes of interest included live births or stillbirths, preterm births, cesarean section rate, congenital malformations, birth weights at delivery, requirement and reasons for neonatal intensive care unit admissions (NICU) and early neonatal deaths. Information on perinatal outcomes were obtained from maternity case records, department of obstetrics daily deliveries electronic database and birth registers dated January 2008 to December 31, 2019.

Resolution of DKA was defined as venous/arterial blood pH >7.3/7.32, serum bicarbonate >18 mmol/L, and ketonemia (<1 mmol/L) or urine ketones (1+ or 0). The absence of documented interventions and treatment in patient clinical records was considered as not done.

Data were analyzed with IBM SPSS statistics version 26 (IBM Corp., Armonk, NY, USA). Categorical data were summarized using frequencies and percentages and continuous data were summarized in terms of means, standard deviations (SD), and medians and interquartile ranges (IQR) where appropriate. Student's *t* test was used to compare groups for normally distributed data variables and the Mann–Whitney *U* test was used for skew or ordinal data variables. The χ^2 test was used to compare nominal variables. Analysis of variance was applied for comparisons between continuous data variables with more than two categories. Statistical significance was set at an alpha threshold of less than 0.05.

The study was approved by the University of Pretoria Human Research Ethics Committee (Protocol no. 624/2019). It was an audit of DKA management so patient consent was waived.

3 RESULTS

Fifty-six pregnant women were admitted with DKA during the study period. This equates to an incidence of about 1.5%–2%. Forty-one (73.2%) women were managed at SBAH, of which 37 (90.2%) received prenatal care at a specialized clinic. Fifteen (26.8%) women were managed at KPTH, of which 11 (73.3%) received prenatal care at a specialized clinic. Selected maternal demographics at presentation with DKA are presented in Table 2. The mean age of women at the time of DKA episode was 29.6 years (range 20–43 years) with 12 (21.1%) women aged 35 years or older. Twenty-three (41.1%) women were nulliparous. Eight (14%) women did not receive prenatal care before presentation with DKA in pregnancy. More than half (58.9%) of the women presented with DKA in the third trimester of pregnancy. The mean glycated hemoglobin (HbA1c) at presentation was 9.7% (SD 2.1; IQR 8.2–10.7). DKA severity was mild in 26 (46.4%), moderate in 22 (39.3%), and severe in 8 (14.3%) women. All 56 women had a confirmed singleton intrauterine pregnancy. Eighteen (32%) women had an identifiable infectious cause precipitating the DKA episode. Urinary tract infection was the most common infection. Eight (14.3%) women were diagnosed with diabetes mellitus for the first time at presentation with DKA. Non-compliance was cited as the cause in 27 (48.2%) women. No precipitant cause for DKA was identified in 3 (5%) women.

TABLE 2. Maternal variables in pregnant women with diabetic ketoacidosis (n = 56)[a]

Demographic variables	
Maternal age, years	29.6 [20–43]
Body mass index[b]	
Underweight (<18.5)	0 (0.00)
Normal weight (18.5–24.9)	7 (12.5)
Overweight (25.0–29.9)	21 (37.5)
Obese (30.1–39.9)	25 (44.6)
Morbidly obese (>40)	3 (5.4)
Chronic hypertension	10 (19.2)
Pre-eclampsia	4 (8.2)
DM type	
Type 1 DM	36 (64.3)
Type 2 DM	13 (23.2)
Gestational DM	2 (3.6)
Newly diagnosed DM at presentation	5 (8.9)
HbA1c	9.7 (8.2–10.7)
>7% (n = 52)	47 (92.2)
Treatment	
No treatment	4 (7.1)
Metformin only	12 (21.5)
Insulin only	35 (62.5)
Insulin + metformin	5 (8.9)
Admission per trimester	
First trimester (≤14 weeks)	4 (7.1)
Second trimester (15–27 weeks)	19 (33.9)
Third trimester (≥28 weeks)	33 (58.9)
DKA severity	
Mild (pH 7.25–7.3)	26 (46.4)
Moderate (pH 7.0–7.24)	22 (39.3)
Severe (pH <7.0)	8 (14.3)

Abbreviations: DKA, diabetic ketoacidosis; DM, diabetes mellitus; HbA1c, glycated hemoglobin.

[a] Values are presented as mean [range], mean (interquartile range), or as number (percentage).

[b] Body mass index is calculated as weight in kilograms divided by the square of height in meters

Table 3 displays selected admission information and laboratory values at initial presentation. Of the 56 women, 14 (25%) were admitted and managed in an ICU, 2 (3.5%) required acute hemodialysis during ICU admission. All 56 women had their vital signs monitored as well as blood glucose, urine dipsticks, and blood gases performed before initiation of DKA management. The median pH was 7.25 (IQR 7.10–7.30), median bicarbonate was 10.8 mmol/L (IQR 7.8–14.2), median potassium of 3.7 mmol/L (3.4–4.7), and median initial blood glucose was 18.1 mmo/L (IQR 14.8–23.1 mmol/L). Eight (14.2%) patients had blood glucose <11.1 mmol/L, i.e. euglycemic DKA. Ketonuria was confirmed in all patients at initial presentation, but no measurement of blood β-hydroxybutyrate tests were performed because of unavailability.

TABLE 3. Initial biochemistry at diagnosis on diabetic ketoacidosis (n = 56)

Biochemical variable	Median (IQR)	Reference range[13]
Glucose, mmol/L	18.1 (14.8–23.1)	3.6–11.1
pH	7.25 (7.10–7.30)	7.35–7.45
Bicarbonate, mmol/L	10.8 (7.8–14.2)	21–28
Potassium, mmol/L	3.7 (3.4–4.7)	3.5–5.1
Anion gap	19.65 (15–23)	−2 to +2

Abbreviation: IQR, interquartile range.

All the women had intravenous access and transurethral Foley's catheter inserted to monitor urine output. Intravenous fluids and insulin therapy were administered to all women shortly after diagnosis of DKA was confirmed. Crystalloid solutions (0.9% NaCl or Ringer's lactate) were prescribed as the initial resuscitation fluids. Thirty-six (64.3%) women received 0.9% NaCl solution and 20 (35.7%) received Ringer's lactate as initial resuscitation fluid. However, adherence to intravenous fluid bolus administration was observed in 32 (57.1%) women, who received 1–1.5 L of intravenous fluid bolus, which is equivalent to 15–20 mL/kg in the first hour. The mean volume of intravenous fluid in the first 24 h was 4.4 L (SD 6.1), which is inadequate according to the guideline.

Insulin therapy was administered as a continuous intravenous infusion or as intravenous bolus in 22 (33%) women and 34 (61%) women received subcutaneous insulin boluses. Adherence to insulin therapy according to the SEMDSA guideline was in 22 (39.3%) patients. Adherence to correction of electrolytes was also reviewed, potassium correction according to the SEMDSA guideline was inadequate in 31 (55.4%) women and in 19 (33.9%) women adherence to magnesium and phosphate was inadequate for those patients whose serum phosphate was less than 0.33 mmol/L.

Ongoing monitoring of the patient and clinical parameters is mandatory because of the risk of relapse.[1] Time-based monitoring of blood gases, which are advised to be done 4- to 6-hourly, was appropriately adhered to in 36 (66%) women and urine ketone testing, which should be every 2–4 h, was appropriately adhered to in 34 (62%) women. Fifty-three women had a known precipitant identified for the DKA episode, which was appropriately managed. In three DKA episodes no precipitant could be identified. DKA resolution was measured in hours from the time of admission to the time of resolution and was categorized as less than 24 h or more than 24 h. Three (5%) women had resolution of DKA in less than 24 h from time of admission.

Table 4 highlights selected perinatal outcomes after DKA in pregnancy. Data on perinatal outcomes were available for 49 women. The main reason for missing data was the seven women (12.5%) who were lost to follow up after discharge from the hospital after DKA resolution, but who did not deliver in any of the hospitals in the Pretoria Academic Complex. All women (n = 49) had singleton pregnancies. The median gestational age at delivery was 36 weeks (IQR 30–37 weeks) and the median birth weight 2618 g (IQR 1280–3210 g) with 6 (12.2%) neonates weighing 4 kg or more. There were 8 (16.3%) major congenital abnormalities, which included neurologic, cardiovascular, and gastrointestinal defects. Six fetuses with congenital anomalies had an prenatal diagnosis, but two were diagnosed in the postnatal period. Among the 49 pregnancies, live births, stillbirth, preterm birth, and NICU admission occurred in 30 (61%), 15 (30.6%), 24 (49%), and 23 (47%) of pregnancies, respectively. All patients with a stillbirth (n = 15, 26.8%) delivered via normal vaginal

delivery. Nine (60%) patients with a stillbirth underwent an induction of labor and 6 (40%) had a spontaneous vaginal delivery. Cesarean section was the route of delivery in almost half the women (24, 49%). The most common reasons for NICU admissions were neonatal respiratory distress syndrome and neonatal hypoglycemia. Severe maternal DKA (pH <7.0) was associated with an increased risk of stillbirth (mild 4/25, moderate 7/17, and severe 5/8, $P = 0.005$). Among the eight patients with severe maternal DKA, all were admitted to the adult ICU wards but were associated with poorer perinatal outcome, 5 (62.5%) stillbirths, 2 (25%) miscarriages, and 1 (12.5%) NICU admission. There were 2 (4.1%) early neonatal deaths; both women had chorioamnionitis and preterm delivery complicated by neonatal sepsis. One (2%) birth injury occurred as the result of shoulder dystocia. No maternal deaths due to DKA were recorded in the study period.

TABLE 4. Perinatal outcomes after diabetic ketoacidosis in pregnancy ($n = 49$)[a]

Perinatal outcomes[b]	
Gestational age at presentation, weeks	27 (23–32)
Mean gestational age at delivery, weeks	36 (30–37)
Live births	30 (61.1)
Cesarean section	22 (49)
Stillbirths	15 (30.6)
Major congenital malformations	8 (16.3)
Median birth weight at delivery, g	2618 (1280–3210)
Neonatal intensive care unit admissions	23 (47)
neonatal hypoglycemia	7 (30.4)
neonatal respiratory distress syndrome	7 (30.4)
hyperbilirubinemia requiring phototherapy	2 (4.2)
Early neonatal deaths	2 (4.2)

[a] Values are presented as mean (interquartile range) or as number (percentage).

[b] Note that more than one perinatal outcome was present in some patients.

4 DISCUSSION

This study audited the adherence to the SEMDSA guidelines in patients presenting with DKA in pregnancy. As expected, the majority of patients in the study population had type 1 diabetes and presented with DKA in the third trimester of pregnancy. This is most likely due to the heightened hormonal response with increased insulin resistance that predisposes pregnant woman with diabetes to the development of DKA. Contrary to the findings of a recent South African audit of DKA in the general population by Thomas et al.,[17] reporting that DKA mostly presented with moderate severity, the study found that the majority of the patients presented with mild DKA in pregnancy and 14.2% patients presented with euglycemic DKA.

The reported incidence of DKA in pregnancy varies from 1.73% to 7.9%.[4] The findings of this 10-year audit are in keeping with these findings. However, as most cases presented with mild DKA we should be aware that some cases of euglycemic DKA may have been missed.[9-11] Furthermore, the elevated HbA1c at presentation with DKA despite the majority of patients being managed at a specialized prenatal clinic highlights the importance of optimal pre-pregnancy control to prevent adverse outcomes in pregnancy. Non-compliance with treatment

was the most common precipitant for DKA. This is in keeping with other studies[4] in which non-compliance was found to be a causative or contributory factor in 17%–25% of women presenting with DKA in pregnancy. Intensive counseling, use of reminders, and dedicated diabetes educators should be considered in the management of women with diabetes mellitus in pregnancy.

The study demonstrated a lack of adherence and compliance to SEMDSA, 2017 guidelines[13] by clinicians, despite the availability of guidelines in the obstetrical units. There was inadequate adherence in administration of adequate amounts of intravenous fluid and the amount of short-acting insulin, and in the frequency of monitoring of clinical parameters of patients with DKA. The reasons for lack of adherence to the guideline were not documented in the clinical records. Possible explanations include over cautiousness of clinicians (doctors and nurses) to administer large volumes of fluids in pregnant patients because of the high incidence of pre-eclampsia and pulmonary edema. Another potential explanation for the lack of adherence to the guideline may be poor record keeping by nursing staff because the majority of patients were managed in labor ward high-care units that are predominantly dealing with other high-risk obstetrical conditions and emergencies, or doctors failing to prescribe appropriate orders.

The lack of adherence to guidelines has been demonstrated in other studies despite the availability of guidelines. A recent study conducted in Kenya[18] demonstrated a delay in the initiation of management, inadequate administration of intravenous fluids, insulin, and potassium, and inadequate monitoring of clinical parameters. The lack of recognition and adherence to guidelines contributed to delayed DKA resolution and high maternal mortality secondary to DKA complications. Another survey by Van Zyl[19] in Kalafong hospital examined the knowledge of hospital care providers regarding management of inpatient diabetes. It was found that knowledge of doctors and nurses caring for diabetic patients was suboptimal, mean score of doctors was 68.3% and of nurses was 53.9%. In the current study, however, knowledge of both doctors and nurses was not assessed. The issue of shortage of human resources could also account for the lack of adherence, where ideally a patient with DKA should be managed at a higher level of care because of the need for intensive monitoring and the complexity of the treatment regimens. A dedicated multidisciplinary team is required.

In low- to middle-income countries there are patient and healthcare system factors that are associated with a negative impact on management of diabetes, especially DKA.[14-21] Poor compliance with insulin therapy, poor prenatal attendance, and poor recognition of sick days are identifiable patient factors, but these should not influence the emergency inpatient management of DKA.[12-21] Healthcare systems are overburdened with the ever-increasing numbers of women with high-risk pregnancies, including DKA in pregnancy. Poor infrastructure, lack of ICU and high-care facilities, shortages of intravenous fluids and glucose-monitoring equipment and consumables, lack of blood gas machines, and lack of appropriately trained staff may all lead to substandard inpatient DKA management.[12-21] Prevention of DKA in pregnancy should be emphasized to both the patient and clinicians in order to reduce the high fetal mortality rate in low- to middle-income countries, which is currently estimated to be 26%–29%.[1]

Pregnancy outcomes in diabetic patients in the UK estimated the stillbirth rate associated with DKA in pregnancy to be 12.8 per 1000 births. There are few published studies from sub-Saharan Africa, which are mostly limited by small numbers of enrolled patients. A South

African study performed in Cape Town by Rossouw et al.[20] estimated a stillbirth rate for all births over 500 g to be 1.39 per 1000 such births. A study in 2005 in Soweto by Huddle[21] audited outcomes of pregnancy in women with diabetes. The findings were 2.8% stillbirths among women with gestational diabetes mellitus, and 3.9% and 1.8% stillbirths in women with types I and II diabetes, respectively. Pregnant women with diabetes are at an increased risk of fetal loss compared with non-diabetic women for multiple reasons, which include DKA. DKA occurring in pregnancy places the fetus at risk, not only at the time of the DKA episode, but also after the DKA has resolved.[22] Fetal loss after a DKA episode is related to the severity of the DKA and the degree of maternal decompensation during the episode.[22, 23] Severe maternal dehydration and hyperglycemia results in decreased utero-placental perfusion and subsequent fetal acidosis that may lead to myocardial dysfunction and hypoxia, which play a major role in fetal demise. Hyperglycemia is one of the most cited mechanisms of fetal loss, but there are other poorly understood mechanisms of fetal loss in women with diabetes.

This study is limited by the fact that it is a retrospective clinical record audit with a small sample size. Information collected was based on record keeping; if it was not documented, it was considered not performed. The management of these women should be standardized because appropriate guidelines are available. Adherence to the guidelines and frequent training sessions for both doctors and nursing staff coupled with multidisciplinary management of DKA in pregnancy is recommended to improve both maternal and perinatal outcomes. Although patients were included in the study before the publication of the SEMDSA 2017 guidelines, the guidelines followed at the audited facilities before the 2017 guidelines were not significantly different from the guideline used as reference for this study.

The study also demonstrated that patients with severe maternal DKA (pH <7.0) had poorer perinatal outcomes ($P = 0.005$), which included stillbirth, miscarriage, and NICU admission. Ideally all diabetic women should receive preconception counseling and care at a specialized prenatal obstetrical unit to ensure optimal glycemic control before and during the prenatal period to minimize maternal and perinatal morbidity and mortality. Prompt recognition, early institution of appropriate therapy and adherence to the available DKA guidelines are important to optimize maternal and perinatal outcomes in pregnancies complicated by DKA.

In conclusion, regular educational programs in the form of drills for all clinicians taking care of diabetic patients are recommended in order to diagnose DKA promptly, institute appropriate therapy, and adhere to the available DKA guidelines. When the inpatient management of DKA improves, maternal and perinatal outcomes in pregnancies complicated by DKA could improve.

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None.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

SA and DGvZ conceptualized the study. NFM, SA, and DGvZ compiled the research protocol. NFM was responsible for data collection and data management. DGvZ analyzed the data. NFM and SA compiled the manuscript.

REFERENCES

1. Van Zyl DG. Diagnosis and treatment of diabetic ketoacidosis. *SA Fam Pract*. 2008; 50(1): 35- 39.

2. Bryant SN, Herrera CL, Nelson DB, Cunningham FG. Diabetic ketoacidosis complicating pregnancy. *J Neonatal Perinatal Med*. 2017; 10(1): 17- 23. doi:10.3233/NPM-1663

3. Sibai BM, Viteri OA. Diabetic ketoacidosis in pregnancy. *Obstet Gynecol*. 2014; 123(1): 167- 178. doi:10.1097/AOG.0000000000000060

4. Kamalakannan D, Baskar V, Barton DM, Abdu TAM. Diabetic ketoacidosis in pregnancy. *Postgrad Med J*. 2003; 79(934): 454- 457. doi:10.1136/pmj.79.934.454

5. de Veciana M. Diabetes ketoacidosis in pregnancy. *Semin Perinatol*. 2013; 37(4): 267- 273. doi:10.1053/j.semperi.2013.04.005

6. Cullen MT, Reece EA, Homko CJ, Sivan E. The changing presentations of diabetic ketoacidosis during pregnancy. *Am J Perinatol*. 1996; 13(7): 449- 451. doi:10.1055/s-2007-994386

7. Carroll MA, Yeomans ER. Diabetic ketoacidosis in pregnancy. *Crit Care Med*. 2005; 33(10 Suppl): S347- S353. doi:10.1097/01.ccm.0000183164.69315.13

8. Ramin KD. Diabetic ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am*. 1999; 26(3): 481- 488. doi: 10.1016/s0889-8545(05)70092-9

9. Eledrisi MS, Beshyah SA, Malik RA. Management of diabetic ketoacidosis in special populations. *Diabetes Res Clin Pract*. 2021; 174: 108744. doi:10.1016/j.diabres.2021.108744

10. 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(3): 324- 330. doi:10.1111/j.1447-0756.2008.00720.x

11. Soma-Pillay P, Motilall S, Ndaba S, Paruk F, Chausse JM. Starvation ketoacidosis in pregnancy presenting as euglycaemic, high anion gap metabolic acidosis: a case report highlighting the significance of early recognition and prompt intervention. *S Afr Med J*. 2018; 108(8): 636. doi:10.7196/SAMJ.2018.v108i8.13082

12. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care*. 2006; 29(12): 2739- 2748. doi:10.2337/dc06-9916

13. The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. *JEMDSA*. 2017; 21(1)(Supplement 1): S1- S196.

14. Taye GM, Bacha AJ, Taye FA, Bule MH, Tefera GM. Diabetic ketoacidosis management and treatment outcome at medical ward of Shashemene Referral Hospital, Ethiopia: a retrospective study. *Clin Med Insights Endocrinol Diabetes*. 2021; 14: 117955142110049. doi:10.1177/11795514211004957

15. Otieno CF, Kayima JK, Omonge EO, Oyoo GO. Diabetic ketoacidosis: risk factors, mechanisms and management strategies in sub-Saharan Africa: a review. *East Afr Med J*. 2005; 82(12 Suppl): S197- 203. doi:10.4314/eamj.v82i12.9382

16. Ndebele Nontobeko FM, Naidoo M. The management of diabetic ketoacidosis at a rural regional hospital in KwaZulu-Natal. *Afr J Prim Health Care Fam Med*. 2018; 10(1): 1- 6. doi:10.4102/phcfm.v10i1.1612

17. Thomas S, Mohamed NA, Bhana S. Audit of diabetic ketoacidosis management at a tertiary hospital in Johannesburg, South Africa. *S Afr Med J*. 2019; 109(6): 407- 411. doi:10.7196/SAMJ.2019.v109i6.13700

18. Abunga DK. An Audit of the Management of Diabetic Ketoacidosis at the Kenyatta National Hospital. 2018. Accessed March 31, 2021. http://erepository.uonbi.ac.ke/bitstream/handle/11295/104640/Abunga_An%20Audit%20Of%20The%20Management%20Of%20Diabetic%20Ketoacidosis%20At%20The%20Kenyatta%20National%20Hospital.pdf?isAllowed=y&sequence=1

19. Van Zyl DG. Inpatient diabetes care: Evaluation and intervention 2013. Accessed March 16, 2021. https://repository.up.ac.za/handle/2263/24195

20. Rossouw J, Hall D, Mason D, Gebhardt G. An audit of stillborn babies in mothers with diabetes mellitus at a tertiary South African Hospital. *J Endocrinol Metab Diabetes S Afr*. 2017; 22(2): 26- 30. doi:10.1080/16089677.2017.1331652

21. Huddle KR. Audit of the outcome of pregnancy in diabetic women in Soweto, South Africa, 1992–2002. *S Afr Med J*. 2005; 95(10): 789- 794.

22. Morrison FJR, Movassaghian M, Seely EW, et al. Fetal outcomes after diabetic ketoacidosis during pregnancy. *Diabetes Care*. 2017; 40(7): e77- e79. doi:10.2337/dc17-0186

23. Hawthorne G. Maternal complications in diabetic pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011; 25(1): 77- 90. doi:10.1016/j.bpobgyn.2010.10.015