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Retrospective Analysis of Diabetic Ketoacidosis in Pregnant Women over a Period of 3 Years

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Abstract

Objective: The incidence of diabetic ketoacidosis in pregnancy (DKP) varies from 0.5%, the lowest reported rate in western countries, to 8.9% in a study conducted in China. The associated fetal mortality is 9-36%. This study aimed to assess the current incidence, causes, and outcomes of diabetic ketoacidosis in pregnancy and identify factors associated with favorable outcomes.

Methods: A retrospective chart review of 20 diabetic ketoacidosis hospital admissions of 19 pregnant women from 3,679 diabetic pregnancies delivered between June 2012 and May 2015 was conducted. Those with successful DKP management (group A) or with intrauterine fetal death or urgent delivery during diabetic ketoacidosis management (group B) were compared.

Results: Thirteen cases had type 1 diabetes, and 6 cases had type 2 diabetes, including 2 new diagnoses. The most common precipitating factors were vomiting (55%) and insulin non-compliance (45%). Plasma glucose was <200 mg/dl in 50% of the patients. There was no maternal mortality, but there was one fetal death (5%). Only mean gestational age (21.8 ± 11.0 versus 33.7 ± 4.6 weeks, P=0.005) was significantly different between groups A (14 admissions) and B (6 admissions).

Conclusion: The incidence of diabetic ketoacidosis was 0.5%, similar to the lowest incidence previously reported. Fetal mortality was 5%, lower than previously reported. The only factor associated with a favorable outcome was early gestational age at presentation. We recommend antenatal screening for diabetes, patient education, and compliance with insulin treatment as preventive measures against DKP.

Keywords: Ketoacidosis; Diabetes in pregnancy; Euglycemic diabetic ketoacidosis

Introduction

Diabetic ketoacidosis (DKA) is a state of relative or absolute insulin deficiency leading to major shifts in metabolism and increased glucose production with decreased peripheral uptake, protein catabolism, and lipolysis [1]. It is classically characterized by high blood glucose levels, ketosis, and high anion gap metabolic acidosis [2,3].

DKA in pregnancy (DKP) can complicate type 1 diabetes, type 2 diabetes, or gestational diabetes mellitus (GDM) [4]. The incidence of DKP varies greatly according to the place and period of the concerned study; it ranges from 0.5% [5], the lowest reported rate in western countries, to 8.9% in a study conducted in China [6]. The difference is due to the local patient demography, level of physicians' awareness and patient education regarding DKP. Despite advances in diabetes management, the incidence is expected to increase because of the growing incidence of type 2 diabetes and GDM as a result of changes in pregnant women's demographics and the rising rate of pregnancies in women 35 years old or older [5].

Compared with DKA in non-pregnant patients, DKP is unique in a number of different aspects; it usually happens at lower (or even normal) blood glucose levels [7] and progresses rapidly, requiring prompt diagnosis and management. Deleterious morbidities and mortality may affect both the woman and fetus. Several reports have attempted to determine the characteristics of the clinical presentation of patients with DKP [6,8-11]. However, most of these reports are relatively old, with no recent studies from our region in the Middle East. Although one study compared the characteristics of those with fetal mortality at presentation against those with live fetuses [9], the exact risk factors for fetal demise remain unknown.

DKP-associated fetal mortality ranges from 9% to 35%, while maternal mortality is <1% [5]. However, the reported incidence of DKP and associated maternal and fetal outcomes, especially fetal mortality, are improving [4,12]. This likely reflects the improvement in medical care provided for pregnant women with diabetes. Management should occur in an intensive care setting by a multidisciplinary team including an obstetrician, a diabetologist, an anesthesiologist, and nursing staff experienced in DKP management [5]. The advent of new insulin analogues and their popularity for pregnant women may have changed the outlook for DKP; in addition,

doctors and patients are more aware of the recommended blood glucose targets.

Because the incidence of DKP, maternal and fetal characteristics, and maternal and fetal outcomes have not been accurately described in our region, the present study sought to identify the current outcomes of DKA in pregnancy based on analyses of the incidence, characteristics of the affected patients, and associated pregnancy outcomes. Also, identification of factors for favorable maternal and fetal clinical outcomes was attempted.

Methods

Subjects

Patients were included if they were 1) pregnant women with type 1 diabetes, type 2 diabetes, or GDM; 2) had DKA fully managed at our facility; and 3) fulfilled the diagnostic criteria for DKA (plasma glucose >250 mg/dl, serum bicarbonate ≤ 18 mEq/L or arterial pH <7.3, and positive urinary or serum ketones) [3] or euglycemic DKA [13,14], i.e., patients who met all the criteria to diagnose DKA but with plasma glucose levels lower than the usual threshold to diagnose DKA and no other reason for high anion gap metabolic acidosis with a normal serum lactate.

Research design and statistical analysis

In this retrospective study, we reviewed the characteristics and pregnancy outcomes of all patients with DKP admitted to our tertiary care center (Hamad Medical Corporation, Qatar) between June 2012 and May 2015. The study protocol was reviewed and approved by our local ethics committee and waiver of informed consents was obtained. Using our institution's electronic medical record system, we searched for all pregnant women admitted with DKA during the study period. Two investigators worked separately with each patient record to ensure the required criteria were met and to extract the required characteristics and associated pregnancy outcomes.

Statistical analysis was conducted using SPSS 17.0 (SPSS Inc., Chicago, IL). Quantitative variables are expressed as means ± standard deviations, and categorical variables are described as number (percentage).

Secondary analyses were performed with 2 groups of patients with DKA in pregnancy; group (A) included patients who were successfully managed without fetal compromise and group (B) included patients that underwent emergency delivery or experienced intrauterine fetal death (IUFD) during management of DKP. Fisher's exact test was used to compare the possible risk factors and characteristics at presentation between the 2 groups. Results were considered significant if the P-value was <0.05.

Results

Based on the coding system at our medical records department, we identified 20 admissions with DKA from the total 134,856 admissions during the study period, which included 3,679 pregnant women with diabetes. Two patients had 2 admissions for different pregnancies, and one patient had 2 admissions during the same pregnancy. We considered those with a recurrence of DKA in different pregnancies as separate patients, resulting in 19 patients in the study.

The baseline demographic characteristics of the 19 patients are described in Table 1. Thirteen patients (68%) had type 1 diabetes, based on treatment with only insulin since the diagnosis of diabetes and a history of positive glutamic acid decarboxylase antibodies with low C-peptide; 6 patients (32%) had type 2 diabetes. DKP was the first presentation of type 2 diabetes in 2 patients, based on HbA1C levels >6.5% (48 mmol/mol)][14], 8% (64 mmol/mol) and 12.6% (108 mmol/mol). Pre-pregnancy HbA1C was 9.1 ± 1.6% (76 ± 17 mmol/mol); only 10% had HbA1C ≤ 7% (53 mmol/mol), and none of the patients had HbA1C ≤ 6.5% (48 mmol/mol). The first HbA1C measurement during pregnancy was 8.7 ± 1.7% (72 ± 19 mmol/mol); one patient had an HbA1C of 6.5% (48 mmol/mol), and none of the patients had HbA1C ≤ 6% (42 mmol/mol). The treatment regimen for diabetes in the first trimester of 11 patients (58%) included modern insulin analogues, including one patient who used a continuous subcutaneous insulin infusion pump. Three patients were not on insulin therapy for diabetes; one was being managed with dietary strategies, and the other two had undiagnosed diabetes.

Characteristics (n=19)	Value
Age (years)	32.3 ± 5.2
Ethnicity	
Qatari	8 patients (42%)
Arab (excluding Qatari)	7 patients (37%)
Asian	4 patients (21%)
Gravidity	3.7 ± 2.3
Parity	2.1 ± 1.8
History of abortion	7 patients (37%)
Type of diabetes	
Type1	13 patients (68%)
Type 2	6 patients (32%)

Duration of diabetes (years)	10.0 ± 7.02
HbA1C (last pre-pregnancy value available); [% (mm)]	9.1 ± 1.6 (76 ± 17)
HbA1C (first value during pregnancy); [% (mmol/mol)]	8.7 ± 1.7 (72 ± 19)
Diabetes medications during first trimester	
Insulin pump (aspart)	1 patient (5%)
Detemir+Aspart	5 patients (26%)
Glargine+Aspart	1 patient (5%)
NPH+Aspart	4 patients (22%)
NPH+Regular	3 patients (16%)
Mixtard 30/70	1 patient (5%)
Gliclazide+Sitagliptin	1 patient (5%)
Nil	3 patients (16%)
Data are presented as mean ± standard deviation or number (percentage).Abbreviation: HbA1C=hemoglobin A1C	

Table 1: Baseline maternal characteristics of 19 pregnant women who presented with diabetic ketoacidosis.

Maternal and fetal characteristics at the time of presentation are summarized in Table 2. Mean ± SD HbA1C at presentation was 8.2 ± 2.0% (66 ± 22 mmol/mol); only 15% of the patients had HbA1C ≤ 6% (42 mmol/mol), 20% had HbA1C ≤ 6.5% (48 mmol/mol), and 30% had HbA1C ≤ 7% (53 mmol/mol). At the time of presentation with DKP, 13 patients (65%) were using insulin analogues, 3 patients were using NPH and regular insulin, and one patient was on oral anti-diabetes medications at 6 weeks of pregnancy. Patients reported the following symptoms: vomiting (55%), nausea (50%), abdominal pain (50%), generalized weakness (25%), and fever (20%). The most common signs were tachycardia (45%), dry mouth (45%), and tachypnea (25%). Plasma glucose levels at presentation were <200 mg/dl (11.1 mmol/L) in 10 (50%) admissions and <140 mg/dl (7.8 mmol/L) in 4 (20%) admissions. Fetal abdominal circumference (AC) was at the 63.7 ± 33.4th percentile. Four (19%) fetuses had an AC ≥ 95th percentile.

Characteristic (20 presentations)	**Value**
Gestational Age (weeks)	25.2 ± 11.0
1st trimester	4 patients (20%)
2nd trimester	5 patients (25%)
3rd trimester	5 patients (25%)
During labor	6 patients (30%)
HbA1C [% (mmol/mol)]	8.2 ± 2.0 (66 ± 22)
Weight (kg)	75.4 ± 16.9
Body mass index (kg/m^2)	31.2 ± 6.5
Use of insulin analogues including insulin pump	13 patients (65%)
Precipitating factors	
Excessive vomiting	11 patients (55%)
Non-compliance with insulin	9 patients (45%)
Poor glycemic control	5 patients (25%)
Corticosteroids	3 patients (15%)
Viral infection	3 patients (15%)

Bacterial infection	2 patients (10%)
Undiagnosed diabetes	2 patients (10%)
Stress of labor	2 patients (10%)
β-Sympathomimetic drugs	1 patient (5%)
Duration of symptoms before DKA diagnosis (days)	2.8 ± 3.1
Investigations	
Plasma glucose (mg/dl)	232 ± 115
Plasma glucose <200 mg/dl (11.1 mmol/L)	10 (50%)
Plasma glucose <140 mg/dl (7.8 mmol/L)	4 (20%)
Sodium (mEq/L)	135.2 ± 2.3
Potassium (mEq/L)	4.4 ± 0.6
Bicarbonate (mEq/L)	13.8 ± 4.6
Urea (mg/dl)	8.68 ± 3.64
Creatinine (mg/dl)	0.64 ± 0.17
Arterial PH	7.3 ± 0.1
PCO_2 (mmHg)	22.3 ± 9.4
Anion gap (mEq/L)	19.3 ± 7.1
White blood cell count (× 10^3 cells/µl)	11.2 ± 4.0
DKA severity based on HCO_3 level	
Mild (15 to 18 mEq/L)	12 patients (60%)
Moderate (10-14 mEq/L)	4 patients (20%)
Severe (<10 mEq/L)	4 patients (20%)
Fetal measurements at presentation	
Abdominal circumference percentile	63.7 ± 33.4
Head circumference percentile	37.1 ± 34.3
Amniotic fluid index	18.6 ± 8.9
Initial Cardiotocography (CTG) for 11 fetuses	
Normal	9 (82%)
Abnormal	1 (9%)
Suspicious	0
Not suitable to interpret	1 (9%)
Fetal mortality at presentation	1 (5%)
Maternal mortality	0
Data are presented as mean ± standard deviation or number (percentage). Abbreviations: HbA1C=hemoglobin A1C, P_{CO2}=partial pressure of carbon dioxide in the blood.	

Table 2: Characteristics at diabetic ketoacidosis (DKA) presentation in 19 pregnant women with 20 presentations

Initial cardiotocography (CTG) was suitable for 11 fetuses; the results were normal in 9 (82%) fetuses, abnormal in 1 (9%) fetus, and could not be interpreted in 1 (9%) fetus. One fetus (5%) died during treatment, and there was no maternal mortality.

During treatment, the median total insulin dose was 50 units (range: 19-325 units). The median duration of DKA treatment until recovery was 21 hours (range: 6-120 hours). Bicarbonate therapy was not administered for any patient.

Outcomes of the pregnancies are provided in Table 3. Three pregnancies were lost (16%), one (5%) during the DKA management at 25 weeks of pregnancy and 2 (11%) several weeks after DKA management: one at 11 weeks of pregnancy, 5 weeks after the DKA, and the other at 29 weeks of pregnancy, after 2 episodes of DKA at 15 and 18 weeks. For the patient with 2 DKA episodes, both episodes were associated with excessive vomiting, an inability to eat, and omission of insulin.

Neonatal outcomes are shown in Table 3. There were 15 live births (12 boys and 3 girls) from 14 women (one set of twins). Six babies (40%) were admitted to the neonatal intensive care unit for observation and were discharged with no early neonatal death.

Variable	Value
Duration from DKA presentation till delivery (days)	47.1 ± 75.1
Gestational age at delivery (weeks)	33.1 ± 9.8
Induction of labor	4 patients (21%)
Mode of delivery	
Emergency caesarean section	7 patients (37%)
Elective caesarean section	
Assisted vaginal	2 patients (10%)
Normal vaginal	4 patients (22%)
Pregnancy lost	3 patients (16%)
No data	2 patients (10%)
Still birth	3 (16%) patients
	(1 at presentation and 2 later in pregnancy)
Live birth	15 (75%)
1st week neonatal death	0
No data	2 (10%)
Neonate sex	
Male	12 (80%)
Female	3 (20%)
Birth weight (g)	3049.5 ± 855
Normal birth weight	12 (80%)
Macrosomia (≥ 4500 g)	0
Low birth weight (≤ 2500 g)	3 (20%)
APGAR 1 min<7	4 newborns (27%)
APGAR 5 min<7	0 newborn
Neonatal seizures	0 newborn
Neonatal intensive care unit admission	6 newborns (40%)
Data are presented as mean ± standard deviation or number (percentage).	

Table 3: Summary of pregnancy and neonatal outcomes following diabetic ketoacidosis (DKA).

Table 4 shows the comparisons between the patients who were successfully treated (group A: 14 presentations, 70%) versus those who required emergent delivery or experienced IUFD (group B: 6 presentations, 30%); 1 patient experienced IUFD, 4 patients were delivered emergently because of the DKP, and 1 patient was delivered emergently because of DKP and antepartum hemorrhage. In group A, 9 presentations were of patients with type 1 diabetes, and 5 presentations were of patients with type 2 diabetes; in group B, 5 presentations were of patients with type 1 diabetes, and 1 presentation was of a patient with type 2 diabetes. The only statistically significant difference between the groups was gestational age at presentation, 21.8 ± 11 versus 33.7 ± 4.6 weeks, respectively (P=0.005).

Variable	Group A (n=14)	Group B (n=6)	P value
Gestational age (weeks)	21.8 ± 11.0	33.7 ± 4.6	0.005
Body mass index (kg/m^2)	31.1 ± 6.2	31.5 ± 7.8	0.9
Duration Diabetes (years)	10 ± 7.4	9.8 ± 6.6	0.96
HbA1c [% (mmol/mol)]	8.8 ± 1.7 (73 ± 19)	8.4 ± 1.8 (68 ± 20)	0.68
Systolic blood pressure (mmHg)	119.9 ± 12.9	109.5 ± 6.7	0.08
Diastolic blood pressure (mmHg)	65.9 ± 9.6	71 ± 7.6	0.27
Heart rate (bpm)	97.9 ± 10.9	105 ± 11.5	0.21
Oxygen saturation (%)	99.1 ± 0.9	97.6 ± 3.7	0.23
Laboratory at presentation			
Glucose (mg/dl)	231 ± 126	238 ± 92	0.9
Sodium (mg/dl)	134.9 ± 2.2	135.8 ± 2.5	0.43
Potassium (mg/dl)	4.3 ± 0.5	4.6 ± 0.8	0.43
Chloride (mg/dl)	101.9 ± 4.7	103.8 ± 1.9	0.34
Bicarbonate (mg/dl)	14.8 ± 3.9	11.3 ± 5.5	0.12
Urea (mg/dl)	8.68 ± 4.20	8.40 ± 2.52	0.81
B-Hydroxybutric acid (mg/dl)	0.032 ± 0.017	0.050 ± 0.008	0.05
Haemoglobin (g/dl)	11.9 ± 1.5	11.6 ± 1.4	0.64
White blood cells (x10^3 cells/µl)	10.5 ± 4.4	12.9 ± 2.6	0.25
Severe DKA assessment	2 (14.3%)	2 (33%)	0.55
Data are presented as mean ± standard deviation or number (percentage). Abbreviations: NS: not significant, HbA1C=hemoglobin A1C, bmp=beat per minute			

Table 4: Comparison of characteristics of pregnant women with diabetic ketoacidosis (DKA) between those successfully treated (normal outcome for mother and fetus; Group A) and those requiring emergent delivery and/or experienced intrauterine fetal death (Group B)

Discussion

The incidence of DKP in the present study was 0.5%, which is one of the lowest reported incidences in the literature [5]. At the time of presentation, the mean HbA1C for the patients with DKP in the present study was 8.2 ± 2.0% (66 ± 22 mmol/mol). To our knowledge, this is the first reported series of DKP cases in the era of approved insulin analogue use during pregnancy; 13 (58%) patients were using insulin analogues including use of an insulin pump for one patient. Our cohort had the lowest reported fetal mortality rate (5%), and there was no maternal mortality.

The incidence of DKA in women with diabetes is higher during pregnancy [6], owing to several pregnancy-specific physiological changes [5,12]. Buffering capacity is impaired, with a decrease in bicarbonate to compensate for the pregnancy-associated hyperventilation and respiratory alkalosis. Second, the excess levels of human placental lactogen, cortisol, progesterone, and prolactin decrease insulin sensitivity. Finally, enhanced lipolysis and increased fatty acids decrease the threshold for ketogenesis. In the present study, we recorded 20 DKP episodes from 3,679 diabetic pregnancies, resulting in an incidence of almost 0.5%, reflecting the recent good care provided for the large number of diabetic pregnancies.

DKP affects not only patients with type 1 diabetes but also those with type 2 diabetes or GDM. While all of the patients in older case series [9,10] had type 1 diabetes, six (32%) of the patients in the present study had type 2 diabetes, reflecting the increasing number of women who develop type 2 diabetes at a young age.

It is recommended that women with diabetes interested in conceiving achieve good diabetes control (HbA1C<6.5%; 48 mmol/

mol) prior to conception, to lower the risk of congenital anomalies [15]. However, none of the DKP cases in the present study met this target. The American Diabetes Association (ADA) previously recommended a preconception HbA1C<7% (53 mmol/mol) [16-19], and only 10% of the present cohort achieved this target, suggesting that poor diabetes control before pregnancy was a major contributor to DKP.

At the time of DKP presentation, the mean HbA1C was 8.2 ± 2.0% (66 ± 22 mmol/mol), which overlaps with the range (7.2 ± 3.1%; 55 ± 10 mmol/mol) reported by Cullen et al. [8]. The ADA recommendations for the HbA1C target in pregnancy has evolved from reaching the lowest possible HbA1C while avoiding frequent hypoglycemic episodes [16-18] to <6% (42 mmol/mol) in 2015 [19] and to personalized targets in 2016 and 2017 (6-6.5%, 42-48 mmol/mol; more strict, <6%, 42 mmol/mol; or more relaxed, <7%, 53 mmol/mol) based on the frequency of hypoglycemia [20,21]. In the present cohort, HbA1C was <6% (42 mmol/mol) in 15%, <6.5% (48 mmol/mol) in 20%, and <7% (53 mmol/mol) in 30%.

In the present study, 50% of the cases presented with plasma glucose levels <200 mg/dL (11.1 mmol/L), and the plasma glucose level was <140 mg/dL (7.8 mmol/L) in 20% of the patients. Munro et al. [13] first described euglycemic DKA, which is defined as a plasma glucose level at presentation that is lower than the usually high level associated with DKA. Euglycemic DKP is related with multiple physiological processes that occur during pregnancy [6]: the striking glucose usage by the fetoplacental unit, glycosuria due to an increased glomerular filtration rate, enhanced glucose utilization by estrogen and progesterone effects, and expanded plasma volume, which dilutes the circulating glucose. Additionally, the accelerated starvation state associated with pregnancy leads to lipolysis and ketosis accompanied with depleted glycogen stores and impaired glucose production that predisposes the person to euglycemic DKP [22-24].

Given that the majority of infants were boys (12 boys *vs.* 3 girls), a male fetus might be associated with a higher risk of DKP. Future research could help to explain the mechanism. Interestingly, Retnakaran et al. [25] studied a cohort of 1,074 pregnant women without diabetes, and mothers of a male fetus had worse β-cell function than their counterparts with a female fetus; however, insulin resistance did not differ between the groups. However, this mechanism might not explain the occurrence of DKP in patients with type 1 diabetes or type 2 diabetes; in the present cohort, the 6 patients with type 2 diabetes gave birth to 2 singleton boys, 2 singleton girls, and a set of twin boys, while the final patient delivered outside our institution and we did not have access to the data for her newborn.

This is the first reported series investigating DKP in the era of approved insulin analogues during pregnancy; 13 (58%) patients were on insulin analogues, including an insulin pump, while the remaining patients were on the conventional types of insulin (regular and NPH) or not on any medication as DKP was the first presentation of diabetes mellitus in them. The two most common precipitating factors of DKP in our cohort were excessive vomiting (55%) and insulin non-compliance i.e. the patient completely or partly skipped her insulin doses on purpose where she should not do that (45%). During vomiting, patients tend to inappropriately stop or decrease their insulin; this reflects the lack of proper diabetes education, particularly regarding the "sick day" rule. The most common underlying cause in previous studies also include emesis (90% and 42%, respectively) [8,10], poor compliance (35%) [9], infection (27%) [11], and missed insulin doses (18%) [11]. Poor compliance was the second most common cause in the studies by Cullen et al. [8] and Rodgers et al. [10] (64% and 17%, respectively). DKP for the patient using an insulin pump was precipitated by a viral infection, not pump failure. It was reported that insulin pump use during pregnancy in patients with type 1 diabetes is associated with more DKP episodes, compared with multiple daily injections of insulin [26]. However, in a recent larger multicenter trial, there was no difference in the risk of DKP between the use of an insulin pump and multiple daily insulin injections; however, the use of an insulin pump was associated with lower HbA1C values [27]. In a meta-analysis, more DKP events occurred in the group of patients using an insulin pump; however, the difference was not statistically significant. The authors attributed the difference to a lack of education and motivation to use the pump technology [28].

Bicarbonate was not used to treat any case, although 2 patients presented with a serum bicarbonate of 5 mEq/L, and they successfully responded to the standard therapy; one patient with low serum bicarbonate (4 mEq/L) experienced IUFD before initiating DKP management. Although some experts recommend bicarbonate therapy with a pH<6.9 [29], others do not [30], as there is no evidence of its benefit and it may be associated with harm to the mother and fetus. Bicarbonate hinders the recovery of ketosis, may deteriorate hypokalemia [24], and may increase carbon dioxide (CO_2) partial pressure (PCO_2) because it decreases the compensatory hyperventilation that helps to eliminate CO_2. High PCO_2 impairs fetal oxygen delivery [31] and may lead to paradoxical cerebral acidosis because CO_2 passes through the blood brain barrier faster than bicarbonate [24].

Although DKP is an important cause of fetal mortality [11], our cohort had the lowest reported fetal mortality rate (5%). The only case of fetal loss during DKP management was at 25 weeks of pregnancy for a 32-year-old woman with type 1 diabetes and a history of excessive vomiting for 4 days, medication non-compliance, and poor diabetes control (HbA1C, 11%; 97 mmol/mol). Also, there was a delay in her DKP management, highlighting the importance of prompt management to avoid fetal loss. With delayed DKP management, the reported rate of fetal mortality was 35%, while there were no fetal deaths with optimal management [9]. Similar to the majority of the literature in this area, in which the rate of maternal mortality with DKP is <1% [5], there was no maternal mortality in the present study.

There were no differences between the group of patients with favorable outcome and those who underwent emergent delivery or experienced IUFD during DKP management, except that those with a better outcome had a lower gestational age. The small number of cases is a limitation of this study in the identification of statistically and clinically significant differences between the two groups. However, the present study has one of the largest sample sizes amongst studies on DKP and the previous largest study was conducted by Montoro et al. [9], which included 20 cases. Therefore, we can gather more information about DKP by comparing the outcomes of these studies and combining evidence from all such studies.

In that study, 2 groups of patients with type 1 diabetes patients, one group of 7 patients who experienced IUFD at DKP presentation and one group of 13 patients who did not experience IUFD, the IUFD group had significantly higher plasma glucose levels, osmolality, and blood urea nitrogen levels at presentation and required higher insulin doses and longer treatment durations for DKP [9]. Also, similar to the finding of the present study, the non-IUFD group in Montoro et al. [9] had a lower mean gestational age than the IUFD group (24.2 ± 7.4

versus 30.9 ± 9.1 weeks; P<0.05); however, whether these factors contributed to the fetal deaths is unknown.

Conclusion

One-third of our DKP patients had type 2 diabetes, and DKP was the first presentation of diabetes for 10% of the cases. The most common precipitating factors were vomiting (55%), non-compliance with insulin (45%), and poor glycemic control (25%). Therefore, patient education about sick day rules and compliance to the insulin regimen may prevent many cases of DKP. The low incidence of DKP (0.5%) and low fetal mortality rate (5%) reflect improvements in medical care and represent data that are externally valid for other centers, given the consistent improvement since previously reported case series. However, we could not identify clinically significant differences between the group that was successfully treated and the group with fetal compromise.

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References

1. O'Shaughnessy MJ, Beingesser KR, Khieu WU (1999) Diabetic ketoacidosis in pregnancy with a recent normal screening test. West J Med 170: 115-118.
2. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA (2006) Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care 29: 2739-2748.
3. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, et al. (2004) Hyperglycemic crises in diabetes. Diabetes Care 27: 94-102.
4. Kamalakannan D, Baskar V, Barton DM, Abdu TA (2003) Review Diabetic ketoacidosis in pregnancy. Postgrad Med J 79: 454-457.
5. Sibai BM, Viteri OA (2014) Diabetic Ketoacidosis in Pregnancy. Obstet Gynecol 123: 167-178.
6. Guo RX, Yang LZ, Li LX, Zhao XP (2008) 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 34: 324-330.
7. Tarif N, Al Badr W (2007) Euglycemic diabetic ketoacidosis in pregnancy. Saudi J Kidney Dis Transpl 18: 590-593.
8. Cullen MT, Reece EA, Homko CJ, Sivan E (1996) The changing presentations of diabetic ketoacidosis during pregnancy. Am J Perinatol 13: 449-451.
9. Montoro MN, Myers VP, Mestman JH, Xu Y, Anderson BG, et al. (1993) Outcome of pregnancy in diabetic ketoacidosis. Am J Perinatol 10: 17-20.
10. Rodgers BD, Rodgers DE (1991) Clinical variables associated with diabetic ketoacidosis during pregnancy. J Reprod Med 36: 797-800.
11. Schneider M, Umpierrez G, Ramsey R, Mabie WC, Bennett KA (2003) Pregnancy complicated by diabetic ketoacidosis. Diabetes Care 26: 958-959.
12. Carroll M, Yeomans ER (2005) Diabetic ketoacidosis in pregnancy. Critical Care Medicine 33: 347-353.
13. Munro JF, Campbell IW, McCuish AC, Duncan LJ (1973) Euglycemic diabetic ketoacidosis. Br Med J 2: 578-580.
14. Blumer I, Hadar E, Hadden DR, Jovanovic L, Mestman JH, et al. (2013) Diabetes and pregnancy: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 98: 4227-4249.
15. National Institute for Health and Care Excellence (2015) Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period.
16. American Diabetes Association (2012) Standards of medical care in diabetes-2012. Diabetes Care 35: 42.
17. American Diabetes Association (2013) Standards of medical care in diabetes. Diabetes Care 36: 44.
18. American Diabetes Association (2014) Standards of medical care in diabetes. Diabetes Care 37: 53.
19. American Diabetes Association (2015) Standards of medical care in diabetes. Diabetes Care 38: 77.
20. American Diabetes Association (2016) Standards of medical care in diabetes. Diabetes Care 39: 94.
21. American Diabetes Association (2017) Standards of medical care in diabetes. Diabetes Care 40: 114.
22. Burge MR, Hardy KJ, Schade DS (1993) Short-term fasting is a mechanism for the development of euglycemic keto-acidosis during periods of insulin deficiency. J Clin Endocrinol Metab 76: 1192-1198.
23. Chico M, Levine SN, Lewis DF (2008) Normoglycemic diabetic ketoacidosis in pregnancy. J Perinatol 28: 310-312.
24. Mohan M, Baagar KAM, Lindow S (2017) Management of diabetic ketoacidosis in pregnancy. The Obstetrician and Gynaecologist 19: 55-62.
25. Retnakaran R, Kramer CK, Ye C, Kew S, Hanley AJ, et al. (2015) Fetal sex and maternal risk of gestational diabetes mellitus: The impact of having a boy. Diabetes Care 38: 844-851.
26. Chen R, Ben-Haroush A, Weissmann-Brenner A, Melamed N, Hod M, et al. (2007) Level of glycemic control and pregnancy outcome in type 1 diabetes: A comparison between multiple daily insulin injections and continuous subcutaneous insulin infusions. Am J Obstet Gynecol 197: 404.
27. Kallas-Koeman MM, Kong JM, Klinke JA, Butalia S, Lodha AK, et al. (2014) Insulin pump use in pregnancy is associated with lower HbH without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. Diabetologia 57: 681-689.
28. Mukhopadhyay A, Farrell T, Fraser RB, Ola B (2007) Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: A systematic review and metaanalysis of randomized, controlled trials. Am J Obstet Gynecol 197: 447-456.
29. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (2009) Hyperglycemic crises in adult patients with diabetes. Diabetes Care 32: 1335-1343.
30. Joint British Diabetes Societies Inpatient Care Group (2013) The management of Diabetic Ketoacidosis in Adults.
31. Parker JA, Conway DL (2007) Diabetic ketoacidosis in pregnancy. Obstet Gynecol Clin North Am 34: 533-543.