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Clinical Management of Diabetic Ketoacidosis in Pregnancy: A Review of Current Literature

Noël Niyondiko

The School of Medicine, Hope Africa University, Bujumbura, Burundi
Email: niynoel2015@gmail.com

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Abstract

Background: Diabetic ketoacidosis (DKA) in pregnancy is a life-threatening condition for both the mother and the fetus. This condition is often associated with type 1 diabetes, but it can also complicate type 2 diabetes and rarely complicates gestational diabetes. DKA in pregnancy often occurs in the 3rd trimester of pregnancy and its prevalence is worryingly increasing. Timely diagnosis and appropriate management of DKA are crucial to decreasing the maternal-fetal complications associated with that condition. As DKA in pregnancy is still poorly understood, it is important to increase awareness of healthcare professionals on this condition for its quick diagnosis and appropriate management. This narrative overview aimed to highlight the cornerstones of the management of DKA in pregnancy. **Objective:** The objective of this research was to review and report the current literature on the management of DKA in pregnancy. **Methods:** A search of the literature on the management of DKA in pregnancy was conducted through PubMed, Google Scholar, and HINARI. This narrative overview included only abstracts and articles written in English, and published between January 2003 and January 2023. This study focused on the review of the general measures, the use of fluids, the use of electrolytes, and the use of insulin in the management of DKA in pregnancy. **Results:** Appropriate management of pregnant women with DKA should include their admission to high dependency unit, IV fluids, electrolyte replacement, insulin therapy, management of precipitating factors, and monitoring of maternal-fetal response to treatment. Supplemental oxygen and bicarbonate may be indicated and placement of the pregnant patient in the left lateral position is crucial to avoid aortocaval compression. **Conclusions:** The timely diagnosis of DKA in pregnancy requires a high index of suspicion of that condition. Appropriate management of DKA in pregnancy includes fluid replacement, correction of electrolyte abnormalities, insulin therapy, management of triggers, and monitoring of maternal-fetal response to treatment.

Subject Areas

Diabetes & Endocrinology, Emergency & Critical Care

Keywords

Management, Diabetes, Diabetic Ketoacidosis, Pregnancy

1. Research Background

Diabetic ketoacidosis (DKA) in pregnancy is an uncommon but potentially life-threatening condition for both the mother and the fetus [1] [2]. Actually, DKA in pregnancy has been associated with an increased rate of maternofetal morbidity and fetal loss [3]. In fact, this condition has been mentioned as a cause of severe maternal complications such as acute renal failure, acute cerebral oedema, adult respiratory distress syndrome, coma and even death [2]. On the other side, the perinatal morbidity rate associated with DKA is considerably higher [2]. For instance, the fetus may suffer from a combination of severe maternal dehydration with acidosis, as there is reduced uteroplacental perfusion in an acidotic environment [2]. Also, severe maternal electrolyte abnormalities are likely to cause not only maternal cardiac arrhythmias but also fetal cardiac arrhythmias, with potential fetal death [2]. Additionally, preterm delivery often results in hypoxia-related complications [2]. Furthermore, during DKA, raised maternal 3-beta-hydroxybutyrate (3BHB) and lactate concentration lead to low glucose uptake by the fetal brain, which is a high risk of fetal brain injury and a long-term developmental impact [2]. Literature mentions that, in the context of DKA during pregnancy, fetal mortality rate has been estimated between 15% and 90% [4]-[6], but maternal deaths are not common [7].

DKA in pregnancy is often associated with type 1 diabetes [8] and mostly occurs in the 3rd trimester of pregnancy [7]. Indeed, DKA can also occur in pregnant women with type 2 diabetes [9], but this condition is an extremely rare complication of gestational diabetes [8], [10]. The incidence of DKA in pregnancy has been reported between 0.5 and 10% of all diabetic gestations [4]. Globally, the prevalence of diabetes is worryingly rising [11], and the rate of pregnancy associated with diabetes is increasing accordingly [2].

1.1. Increase in Diabetes Prevalence

Globally, it has been estimated that 463 million adults aged 20-79 years (representing 9.3% of the world's population in this age group) were living with diabetes in 2019 [12]. This number is expected to increase to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045 [12]. Moreover, the number of deaths caused by diabetes and its complications has been estimated to be 4.2 million in 2019 [12]. Furthermore, it has been estimated that, in 2019, 15.8% (20.4 million) of live births were affected by hyperglycemia in pregnancy, and annual global health expenditure

on diabetes has been estimated to be USD 760 billion [12]. In addition, it is expected that annual global health expenditure on diabetes will reach USD 825 billion by 2030 and USD 845 billion by 2045 [12].

1.2. Increase in DKA Hospitalization Rates

In a study conducted in the USA and which analyzed DKA rates in four age groups (<45, 45 - 64, 65 - 74, and ≥75 years), DKA hospitalization rates among people with diabetes increased at a rate of 54.9% from 2009 to 2014 [13]. In fact, it has been stated that, from 2009 to 2014, all age groups experienced an annual increase of ≥6.0% in DKA hospitalization rates, with the highest rates among patients aged <45 years [13]. However, although there was an increase in DKA hospitalization rates, in-hospital mortality among patients with DKA continued to decrease during the study period [13]. Importantly, the decline in DKA in-hospital mortality rates would have resulted from a better comprehension of the pathophysiology of DKA and an adoption of DKA management guidelines, both of which might have influenced better management of patients [13]. Also, the lower in-hospital mortality rates would have been influenced by hospital admission of less severe cases resulting in increased admission rates [13].

1.3. Pathophysiology of DKA

Compared to non-pregnant people, pregnant women are likely to develop insidious DKA which may become severe more quickly, even with lower glucose levels [14]. Commonly, triggers of DKA in pregnancy include refractory vomiting, infectious disease, inappropriate insulin use or cessation, administration of steroids for fetal lung maturation, and β-sympathomimetic use [14]. Also, there is an increased risk of euglycemic diabetic ketoacidosis (EDKA) with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors in insulin-deficient patients with chronic type 2 diabetes, latent autoimmune diabetes, or type 1 diabetes [15]. Actually, SGLT2 inhibitors such as empagliflozin, dapagliflozin, and canagliflozin have demonstrated similar or improved efficacy in reducing serum glucose, hemoglobin A1C levels, body weight, blood pressure, cardiovascular and all-cause mortality. Nevertheless, this class of medications increases the risk of EDKA by a factor of 7 [15].

Regarding its pathophysiology, DKA develops when there is insulin deficiency and/or an increase in counterregulatory hormones (such as catecholamines, cortisol, and glucagon) causing the body to metabolize amino acids and triglycerides instead of glucose for energy. As a result, because of unrestrained lipolysis, serum levels of glycerol and free fatty acids increase. In addition, because of muscle catabolism, alanine levels increase. Furthermore, glycerol and alanine provide substrates for hepatic gluconeogenesis, which is induced by the excess of glucagon that follows insulin deficiency [16].

In normal conditions, insulin prevents ketogenesis by inhibiting the transport of free fatty acid derivatives into the mitochondrial matrix [16]. However, in the

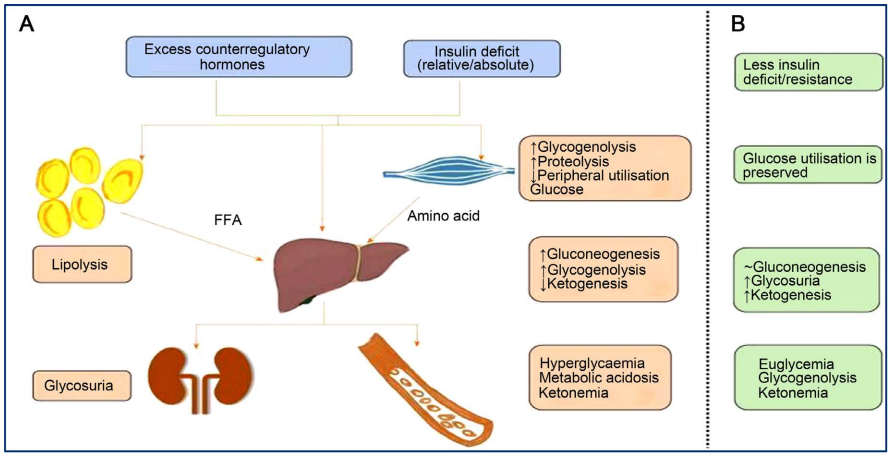
absence of insulin, ketogenesis takes place. In fact, glucagon stimulates mitochondrial conversion of free fatty acids into ketones [16]. Actually, acetoacetic acid and beta-hydroxybutyric acid are the main ketoacids produced, and these ketoacids create metabolic acidosis. Moreover, acetone produced from the metabolism of acetoacetic acid accumulates in serum and is slowly eliminated by respiration [16].

In the context of insulin deficiency, hyperglycemia causes an osmotic diuresis, leading to important urinary losses of water and electrolytes. In addition, urinary excretion of ketones causes additional losses of sodium and potassium. Also, serum sodium levels can decrease because of natriuresis or increase in case of excretion of large volumes of free water [16]. Despite an important loss of potassium, initial serum potassium levels appear normal or increased due to the extracellular migration of potassium in response to acidosis. However, during treatment, insulin therapy drives potassium into cells, and potassium levels usually fall, leading to a potential life-threatening hypokalemia [16].

Emesis in pregnant women contributes to the development of ketoacidosis. Actually, nausea and vomiting are commonly observed because of elevated human chorionic gonadotrophin in early stages of pregnancy and increased esophageal reflux in later stages. The resulting stress and fasting state induce raised insulin antagonistic hormones. This, combined with the ensuing dehydration, leads to the development of ketoacidosis [17].

In addition, premature onset of labor in diabetic pregnancies increases the risk for DKA due to the need for tocolysis and systemic steroids for fetal lung maturation. In fact, β2-Agonists, which are administered to suppress premature uterine contractions, induce an increase of blood glucose, free fatty acids and ketones by stimulating gluconeogenesis, glycogenolysis, and by activating lipolysis resulting in hyperglycemia and ketosis. Also, corticosteroids administered in diabetic pregnancies for fetal lung maturation can worsen hyperglycemia and insulin resistance resulting in ketosis [17].

On the other hand, euglycemic diabetic ketoacidosis (EDKA) is an acute life-threatening metabolic emergency characterized by ketoacidosis in a context of relatively lower blood glucose (less than 11 mmol/L) [18]. Indeed, the absence of hyperglycemia is a real challenge for healthcare professionals in the intensive care units and emergency department, as it may cause worse outcomes by delaying diagnosis and treatment [18]. EDKA has different etiologies which include the use of SGLT-2 inhibitors for the management of diabetes mellitus, fasting, pregnancy, gastroparesis, bariatric surgery, chronic liver disease, glycogen storage disease, cocaine intoxication, and insulin pump failure [18]. Possible complications of EDKA are persistent vomiting, dehydration, hypoglycemia, hypovolemic shock, respiratory failure, cerebral edema, seizures, coma, infection, thrombosis, myocardial infarction, and death [19]. Definitely, EDKA in pregnant women may result in an increased rate of fetal demise (up to 9%) and maternal mortality [19]. **Figure 1** [18] summarizes both the pathophysiology of DKA and the pathophysiology of EDKA.



FFA: Free fatty acids; ↑: Increase; ↓: Decrease; ~: No change.

Figure 1. A: Pathophysiology of diabetic ketoacidosis; B: Pathophysiology of euglycemic diabetic ketoacidosis.

1.4. DKA Presentation and Diagnosis

Both healthcare professionals and patients should have a high index of suspicion for DKA in all pregnant women presenting with symptoms that could be associated with this condition [3]. Clinically, DKA in pregnancy is generally characterized by the same symptoms as those in non-pregnant patients, but the onset of symptoms is more rapid in pregnant women [9]. In fact, symptoms of DKA include nausea, vomiting, polyuria, polydipsia, and altered mental status [9]. Moreover, laboratory evaluation includes venous blood gas for serum pH, bicarbonate, and ketones [15]. Briefly, DKA is characterized by the triad of hyperglycemia, ketosis, and anion gap metabolic acidosis [20]. In DKA patients, the anion gap is usually greater than 12 [16], and the diagnostic criteria are the following: 1) blood glucose level > 200 mg/dL or known diabetes mellitus; 2) venous pH < 7.3 and/or bicarbonate level < 15.0 mEq/L, and 3) blood ketone level ≥ 3.0 mmol/L or urine ketone level > 2+ [21].

1.5. Classification of DKA

The classification of DKA in general is the following [22]:

- ***Mild DKA*** is characterized by a plasma glucose concentration of greater than 250 mg/dl, an arterial pH of 7.25 - 7.30, a serum bicarbonate concentration of 15 - 18 mEq/l, a positive test for urine ketone, a positive test for serum ketone, a variable serum osmolality, an anion gap of more than 10, and an alert patient.

- ***Moderate DKA*** is characterized by a plasma glucose concentration of greater than 250 mg/dl, an arterial pH of 7.00 to <7.24, a serum bicarbonate concentration of 10 to <15 mEq/l, a positive test for urine ketone, a positive test for serum ketone, a variable serum osmolality, an anion gap of more than 12, and an alert or drowsy patient.

- ***Severe DKA*** is characterized by a plasma glucose concentration of greater than 250 mg/dl, an arterial pH of less than 7.00, a serum bicarbonate concentration of

less than 10 mEq/l, a positive test for urine ketone, a positive test for serum ketone, a variable serum osmolality, an anion gap of more than 12, and stupor or coma.

1.6. Management of DKA

Prompt and appropriate treatment of DKA might decrease the maternal-fetal complications associated with that condition [6]. Accordingly, the management of DKA in pregnancy should mainly focus on timely diagnosis, followed by the correction of hypovolemia in order to improve renal and uteroplacental perfusion, the insulin therapy to reduce serum glucose, the correction of acidosis and electrolyte aberrations, the identification and treatment of any underlying causes and the monitoring of maternal-fetal response to treatment [4].

2. Research Objectives

There is limited published evidence of risk factors and outcomes of DKA in pregnancy, and this condition is still poorly understood [23]. Therefore, for improved pregnancy outcomes, it is crucial to increase awareness on DKA with a particular focus on its swift recognition and appropriate management [24] [25]. This review aimed to highlight the cornerstones of the management of DKA in pregnancy. In fact, the general aim of this research was to review and report the current literature on the management of DKA in pregnancy. The specific aims of the review were the following:

- To review the general measures for the management of DKA in pregnancy;
- To review the use of fluids for the management of DKA in pregnancy;
- To review the use of electrolytes for the management of DKA in pregnancy;
- To review the use of insulin for the management of DKA in pregnancy.

3. Methods

A search of the current literature on the clinical management of DKA in pregnancy was conducted through the PubMed, Google Scholar, and HINARI databases. In this search process, the keywords included "management", "diabetes", "diabetic ketoacidosis", and "pregnancy". Then a narrative overview included only abstracts and articles written in English, and published between January 2003 and January 2023.

a) *Inclusion Criteria*

- The abstract or article provides information on the management of DKA in pregnancy,
- The abstract or article was written in English,
- The abstract or article was published between January 2003 and January 2023.

b) *Exclusion Criteria*

- The abstract or article does not provide information on the management of DKA in pregnancy.
- The abstract or article was written in a language other than English.
- The abstract or article was published before January 2003 or after January 2023.

c) *Data Analysis and Reporting*

In this study, data related to the general measures, the use of fluids, the use of electrolytes, and the use of insulin in the management of DKA in pregnancy were carefully analyzed and critically summarized. Conclusions were drawn regarding the management of DKA in pregnancy.

d) *Ethical Considerations*

The researcher ensured that ethical protocols were followed as prescribed by the guidelines of the University of South Wales. In fact, the researcher's project proposal was approved by the ethical committee of the university before the commencement of the study. In addition, the sources of literature that were found during the study got full recognition and were reported.

4. Results

The cornerstones of the management of DKA in pregnancy include prevention, early diagnosis, prompt hospitalization, and appropriate treatment using intravenous fluids, insulin and electrolyte replacement [4]. Also, the management of DKA should include the treatment of the underlying etiology [14] [15] [25] and the monitoring of maternal-fetal response to therapy [14] (See **Figure 2**).

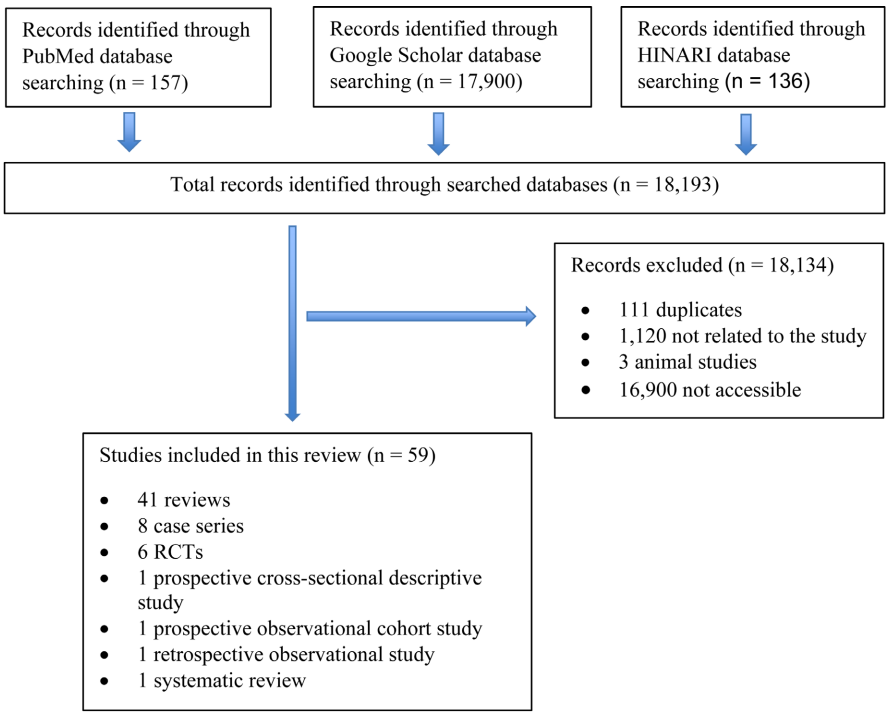


Figure 2. PRISMA flowchart of the search procedure for this narrative review on the management of DKA in pregnancy.

Importantly, in patients with DKA, metabolic management targets include a reduction of the blood ketone concentration by 0.5 mmol/L/hour; a reduction of capillary blood glucose by 3.0 mmol/L/hour, an increase of the venous bicarbonate by

3.0 mmol/L/hour, and a kalemia level maintained between 4.0 and 5.5 mmol/L [26]. A pH >7.3 units, a bicarbonate level > 15.0 mmol/L, and a blood ketone level < 0.6 mmol/L are the characteristics of a resolved DKA [26]. Although clinical studies involving pregnant women are not common, it has been stated that the treatment of DKA in pregnant patients is the same as in non-pregnant persons [27].

4.1. General Measures for the Management of DKA in Pregnancy

4.1.1. Prevention and Timely Diagnosis

Prevention is one of the cornerstones of DKA management during pregnancy [4]. Actually, pregnant women with diabetes mellitus should be provided with prenatal education focusing on DKA prevention strategies. In addition, prenatal education offered to pregnant patients with diabetes would contribute to timely diagnosis of DKA among these people who should also have a high index of suspicion for this condition [3].

One of the prevention strategies consists of educating diabetic pregnant women regarding the risks of DKA, the triggers for this condition, and the importance of reporting its signs and symptoms in a timely way [14]. For the prevention strategies, it is ideal to use whenever possible a team approach which includes the patient herself, a diabetes nurse educator, a nutritionist, and a social worker [28]. Also, patients treated for DKA should get appropriate diabetes education before being discharged. For example, the selected insulin regimen should be well understood by and affordable for the patient. Moreover, supplies for the initial insulin administration at home should be prepared. Additionally, patients being discharged should be provided with specific information regarding when to seek help from healthcare providers, the blood glucose goals, the use of supplemental short-acting insulin during illness, the use of insulin during infection and fever, initiation of an easily digestible liquid, diet containing carbohydrates and electrolytes, the need to never discontinue insulin therapy and to look for professional advice early in the course of the disease [29]. Furthermore, family members or caregivers likely to be involved in patient's care should be educated about the insulin regimen and how to measure blood glucose and β-OHB using point-of-care devices. Also, the patient and/or caregiver should be given a written care plan, as this improves their understanding of the importance and the procedure of self-management of diabetes **[29]**.

4.1.2. Management of Precipitating Factors

The management of DKA in pregnancy requires the management of precipitating factors, and the monitoring of maternal-fetal response to therapy, in addition to fluid replacement, insulin therapy and electrolyte replacement [14].

Actually, principles of the management of DKA during pregnancy include the admission of the patient to high dependency unit, supplemental oxygen for respiratory disorders, placement of the pregnant patient in the left lateral position to avoid aortocaval compression, management of triggers, monitoring of fetal heart rate, and monitoring of urine output [17] [30]. Treatable precipitating factors

(such as infection, trauma, cerebrovascular accident, or myocardial infarction) should be managed to prevent worsened prognosis and recurrence [31]. Therefore, a detailed history and physical examination are of great importance in the choice of investigations for the targeted management of triggers [2].

4.1.3. Monitoring of Maternal Response to Treatment

Monitoring of maternal response to treatment is crucial, as DKA can cause severe maternal complications such as acute renal failure, acute cerebral oedema, adult respiratory distress syndrome, coma and even death [2]. Thus, during insulin infusion, capillary glucose should be assessed every hour [2]. Also, to ensure that ketone levels are diminished at the recommended rate of at least 0.5 mmol/l, monitoring of blood ketones should be performed every hour for the first 6 hours [2]. Monitoring of bicarbonate, pH, and serum potassium can be performed by using venous gas samples every 2 hours during the first 6 hours, but a concomitant laboratory sample should be taken at baseline to confirm the accuracy of serum potassium levels [2]. In case a ketone meter is not available, the calculated anion gap [Anion gap $= \left(N^+ + K^+\right) - \left(Cl^- + HCO_3^-\right)$] has an important role in monitoring the patient's response [2]. Although the measurement of arterial pH is not required, it can be performed when the patient is hypoxic or has a compromised consciousness, as arterial pH is only 0.03 units higher than the venous pH [2]. It is reliable to use the bicarbonate level for evaluation of the treatment response during the first 6 hours of management, because, thereafter, fluid resuscitation using 0.9% normal saline could result in the development of hyperchloremic acidosis associated with a normal anion gap, which tends to decrease the bicarbonate level [2].

Actually, hyperchloremic acidosis and ketoacidosis are two different types of metabolic acidosis associated with low serum bicarbonate levels [2]. Hyperchloremic acidosis is caused by the administration of large volumes of normal saline with high chloride content to the patient, resulting in dilution of plasma bicarbonate, leading to low bicarbonate and raised chloride, and, thereafter, metabolic acidosis associated with a normal anion gap [2]. In ketoacidosis, the primary mechanism is the raised production of ketoacids [2]. The body uses bicarbonate to neutralize these ketoacids; thus, there is a decreased serum bicarbonate level and, thereafter, an increased anion gap [2]. The body eliminates ketones by metabolizing the major ketone of DKA (i. e. 3-beta-hydroxybutyrate [3BHB]), which is measurable on a bedside capillary sample, to acetoacetate, which is semiquantitatively measured in urine [2]. Therefore, ketonuria may persist for a long period after 3BHB has cleared and the metabolic acidosis has resolved [2].

4.1.4. Monitoring of Fetal Response to Treatment

Fetal response to treatment should also be monitored [2]. In fact, it has been estimated that the fetal mortality rate associated with DKA is between 9% and 36% [2]. Nevertheless, the perinatal morbidity rate associated with DKA is considerably higher; there are hypoxia-related complications, which are associated with a

high rate of preterm delivery [2]. During DKA, the fetal brain is susceptible to raised maternal 3BHB and lactate concentration, leading to a low glucose uptake by the fetal brain, a high risk of fetal brain injury and a long-term developmental impact [2]. When DKA happens after 24 weeks of gestation, fetal status should be continuously monitored as there is an association between acidosis and fetal hypoxemia [14].

The decision for delivery should be based on gestational age as well as maternal-fetal response to treatment [14]. A combination of severe maternal dehydration with acidosis may harm the fetus, as there is reduced uteroplacental perfusion in an acidotic environment [2]. Furthermore, severe maternal electrolyte abnormalities (potassium in a particular way) can induce not only maternal cardiac arrhythmias but also fetal cardiac arrhythmias, with potential fetal death [2]. It is therefore crucial to perform fetal heart tracing to assess fetal acidotic changes induced by maternal metabolic acidosis [2]. The fetal acidotic status may also be reflected by fetal biophysical profile and Doppler studies [2]. Fetal acidotic issues are commonly corrected with maternal hydration and correction of metabolic acidosis and the normalization of fetal heart tracing may be achieved within 4 - 8 hours after correction of DKA [2]. In a multidisciplinary context, the decision to deliver should be individualized, based on evaluation of the maternal clinical status to ensure a safe labor and delivery, fetal gestational age and the results of fetal investigations such as fetal heart tracing [2]. Commonly, the aim should be to monitor the fetus until the maternal metabolic state is stabilized, without any immediate plans for delivery, and to continue the pregnancy with complete resolution of DKA [2].

4.1.5. Management of EDKA

Management of EDKA follows the same principles as those for treatment of DKA. These principles include fluid resuscitation, correction of electrolyte abnormalities and insulin therapy, with the precaution that dextrose-containing fluids should accompany IV insulin for the correction of ketonemia and metabolic acidosis, while preventing hypoglycemia [18].

4.2. Use of Fluids for the Management of DKA in Pregnancy

In the context of absolute or relative insulin deficiency, hyperglycemia causes an osmotic diuresis, leading to important urinary losses of water [16]. Therefore, intravenous (IV) fluids should be provided for correction of dehydration [18]. IV fluids are required to quickly restore the intravascular volume; this rapidly raises blood pressure and ensures glomerular perfusion while the remaining total body water deficits are corrected slowly over about 24 hours [16].

IV fluids used for resuscitation include both crystalloid and colloid solutions [32]. Whereas crystalloid solutions consist of isotonic saline (e.g., 0.9% saline, also called normal saline) or balanced electrolyte solutions (e.g., Ringer's lactate, Plasmalyte) which largely diffuse across extracellular fluid compartments, colloid solutions (e.g., hydroxyethyl starch, gelatins, albumin) contain high-molecular-

weight molecules which are suspended in crystalloid carrier solution and which do not easily diffuse across the extracellular fluid compartments [32]. Crystalloid solutions are the first choice for fluid resuscitation in patients presenting with hypovolemia, sepsis, hemorrhage, and dehydration [33]. Furthermore, crystalloids are also used as solutions for IV medication delivery, maintenance fluids in persons with deficient or absent enteral nutrition, solutions for blood pressure management, and for improving diuresis in order to prevent nephrotoxic drug or toxin-mediated end-organ injury [33]. Colloid solutions have been commonly used as volume-sparing agents with some advantages such as a reduced overall volume required for resuscitation and restoration of intravascular volume, a reduced risk of interstitial edema and a decreased risk of hemodilution for patients [32].

For resuscitation of DKA patients, crystalloids rather than colloid solutions were recommended, and "normal saline" (i.e. 0.9% sodium chloride solution) was considered the fluid of choice in this context [34]. However, in 2012, a multicenter retrospective comparative study by Chua *et al.* aimed to evaluate the effects of Plasma-Lyte 148 (PL) versus normal saline (NS) in DKA [35]. The study included 23 non-pregnant adults admitted for DKA to the intensive care unit and who received almost exclusively PL or NS infusion up until 12 hours [35]. Among these patients, 9 had received PL and 14 patients had been given NS [35]. The conclusion was that PL is an excellent fluid to be used in the management of DKA, as it induced a quick initial resolution of metabolic acidosis and less hyperchloremia [35]. Additionally, PL momentarily improved the blood pressure profile and urine output [35].

Moreover, it has been stated that the administration of normal saline (0.9% sodium chloride) for fluid resuscitation commonly results in hyperchloremic acidosis as a side effect of its high content of chloride ions [22]. To overcome this side effect, it is a good option to use balanced fluids as an alternative, because their different composition could physiologically result in a quick resolution of acidosis [22]. A prospective, randomized, double-blind study was undertaken to determine if balanced electrolyte solution (BES) prevents hyperchloremic metabolic acidosis in patients with DKA [36]. They recruited 45 non-pregnant DKA patients aged 18 to 65 years and who had presented to the Emergency Department with a serum bicarbonate level less than or equal to 15 mmol/L and an anion gap greater than or equal to 16 mEq/L [36]. They randomized these patients to receive BES or normal saline (NS) (22 in BES group and 23 in NS group) and found that the use of BES for the management of DKA patients results in lower serum chloride and higher bicarbonate levels than the administration of NS, which is consistent with prevention of hyperchloremic metabolic acidosis [36].

Furthermore, in 2012, a parallel double blind randomized controlled trial by Van Zyl, Rheeder, and Delport was undertaken to determine if Ringer's lactate solution (RL) is superior to normal saline (NS) for resolution of acidosis in the management of DKA [37]. They recruited 57 non-pregnant patients over 18 years

old who presented to the emergency department with a venous pH > 6.9 and ≤7.2, a blood glucose of >13 mmol/l and a urine ketone level of ≥2+ [37]. They randomized these patients to receive NS or RL (29 allocated to receive NS and 28 to receive RL), and found that there was no benefit from administering RL compared to NS (unadjusted: P = 0.934, adjusted: P = 0.758) [37]. Also, the normalization of blood glucose level tended to take longer with the RL [37].

Additionally, in 2020, a subgroup analysis of multiple-crossover, cluster, randomized clinical trials was undertaken by Self *et al.* in order to compare the effects of saline versus balanced crystalloid solutions in adult patients with DKA [38]. They recruited 172 non-pregnant adult DKA patients who presented to emergency department and intensive care unit with a plasma glucose greater than 250 mg/dL, a plasma bicarbonate less than or equal to 18 mmol/L, and an anion gap greater than 10 mmol/L [38]. Of these patients, 94 were assigned to balanced crystalloids and 78 to saline [38]. The conclusion was that, compared with the use of saline, the administration of balanced crystalloid solutions results in more quick resolution of DKA in adult patients (adjusted hazard ratio = 1.68; 95% CI, 1.18 - 2.38; P = 0.004) [38]. Therefore, for acute treatment of adult patients with DKA, balanced crystalloid solutions may be preferred over saline [38].

Finally, a cluster, crossover, open-label, randomized, controlled phase 2 trial by Ramanan *et al.* was undertaken in 2021 to determine whether treatment with Plasmalyte-148 (PL) compared to normal saline (NS) results in faster resolution of DKA and whether the acetate in PL potentiates ketosis [39]. They recruited 90 non-pregnant adult patients admitted to intensive care unit with severe DKA [39]. They randomized these patients to receive PL or NS (48 patients assigned to PL group and 42 to NS group), and concluded that, compared to the use of NS, the administration of PL may result in quick resolution of metabolic acidosis in patients with DKA without an increase in ketosis [39].

Based on the discussion above, there is a need for careful planning and monitoring for choosing the adequate fluid replacement for the treatment of DKA. The composition of the commonly used crystalloids is the following [22]:

Lactated Ringer's: pH of 6.5; Na^+ concentration of 130 mEq/L; Cl^- concentration of 109 mEq/L; [Na+]: [Cl^-] ratio = 1.19:1; K^+ concentration of 4 mEq/L; HCO_3^- /Bicarbonate = 28 (lactate); Ca^{2+} concentration of 3 mEq/L; Osmolarity of 275 mOsm/L.

Isolyte solution: pH of 7.4; Na^+ concentration of 140 mEq/L; Cl^- concentration of 98 mEq/L; [Na+]: [Cl^-] ratio = 1.43:1; K^+ concentration of 5 mEq/L; HCO_3^- /Bicarbonate = 27 (acetate) or 23 (gluconate); Ca^{2+} concentration of 0 mEq/L; Osmolarity of 294 mOsm/L.

0.45% *Sodium chloride*: pH of 4.0; Na^+ concentration of 77 mEq/L; Cl^- concentration of 77 mEq/L; [Na+]: [Cl^-] ratio = 1:1; K^+ concentration of 0 mEq/L; HCO_3^- /Bicarbonate =0; Ca^{2+} concentration of 0 mEq/L; Osmolarity of 154 mOsm/L.

0.9% *Sodium chloride*: pH of 5.0; Na^+ concentration of 154 mEq/L; Cl^-

concentration of 154 mEq/L; [Na+]:[Cl^-] ratio = 1:1; K^+ concentration of 0 mEq/L; HCO_3^- /Bicarbonate = 0; Ca^{2+} concentration of 0 mEq/L; Osmolarity of 308 mOsm/L.

Dextrose-containing fluids are to be given with IV insulin to correct metabolic acidosis, ketonemia and to reduce the risk of hypoglycemia [18]. The fluid replacement in pregnant women with DKA should be organized as follows [17]:

- Isotonic saline, 1 - 2 litres in the 1st hour;
- 0.9% or 0.45% saline thereafter, 300 - 500 ml/hour;
- 5% dextrose to be added when serum glucose approaches 12 mmol/l.

When plasma glucose falls to < 11.1 mmol/L (< 200 mg/dL), 5% to 10% dextrose can be added to 0.45% saline [16]. It is required to increase glucose administration using higher percentages of dextrose (10 or 20%) in order to facilitate the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis [40].

4.3. Use of Electrolytes for the Management of DKA in Pregnancy

In patients with DKA, hyperglycemia induces an osmotic diuresis, causing important urinary losses of electrolytes [16]. Moreover, urinary excretion of ketones causes additional losses of sodium and potassium [16]. Hypokalemia may result from any combination of osmotic diuresis, gastrointestinal losses, and poor oral intake [41]. Then, electrolyte replacement in pregnant women with DKA includes the correction of potassium abnormalities, and the correction of possible phosphorus and magnesium abnormalities [17].

As insulin deficiency and acidosis both shift potassium extracellularly, patients with DKA commonly present with a normal serum potassium level before the insulin therapy is started [41]. Serum hypokalemia commonly occurs after insulin is administered, because both insulin and the resulting improvement in acidosis will shift potassium intracellularly [41].

Hence, inadequate administration of IV insulin and bicarbonate therapy may result in a life-threatening and refractory arrhythmia which should be reversed by quick bolus potassium injection [42]. A prospective cross-sectional descriptive study by Arora *et al.* in 2012 was undertaken to estimate the prevalence of hypokalemia in DKA patients before initiation of fluid resuscitation and insulin therapy [43]. They recruited 503 patients with hyperglycemia (capillary blood glucose level of 250 mg/dL or higher) [43]. Of these 503 patients with hyperglycemia, 54 (10.7%) met all criteria for DKA. Of these 54 DKA patients, 3 (5.6%) (95% confidence interval, 1.2% - 15.4%) had hypokalemia (1 patient had a value of 2.8 mmol/L, and 2 had values of 3.0 mmol/L) [43]. The conclusion was that it is crucial to obtain a serum potassium and rule out any life-threatening hypokalemia before starting insulin therapy [43]. It has been indicated that, in patients with DKA, if the initial serum potassium is less than 3.3 mmol/L, IV insulin therapy should not be given until potassium abnormality is corrected [44]. In fact, potassium should be added to the IV fluid to ensure that serum potassium concentration is maintained within the normal

range of 3.3 - 5.5 mmol/L [44]. In case serum potassium is >5 mEq/L (>5 mmol/L), potassium supplementation should be withheld [16]. When serum potassium is <3.3 mEq/L (<3.3 mmol/L), in addition to withholding insulin therapy, one should give potassium at 40 mEq/hour until serum potassium is ≥3.3 mEq/L (≥3.3 mmol/L) [16]. Then hypokalemia should be prevented through replacement of 20 to 30 mEq (20 to 30 mmol) potassium in every liter of IV fluid to maintain serum potassium between 4 and 5 mEq/L (4 and 5 mmol/L) [16].

In DKA patients with severe hypokalemia or when clinical symptoms are present, replacement therapy should quickly be given [45]. In fact, it is preferred to administer potassium chloride of 40 mmol every 3 to 4 hours for 3 doses [45]. Although rapid correction of hypokalemia may be achieved via oral and/or IV formulation, IV administration is the good option in the context of digitalis toxicity, cardiac dysrhythmias and recent or ongoing cardiac ischemia [45]. When peripheral IV infusion rates exceed 10 mmol per hour, common side effects include pain and phlebitis [45]. Furthermore, when the IV infusion rates exceed 20 mmol per hour, there is a risk of rebound hyperkalemia [45]. Actually, the administration of 20 mmol of potassium chloride per hour increases serum potassium levels by an average of 0.25 mmol per hour [45]. In DKA patients with hypokalemia, it is recommended not to administer potassium chloride in dextrose-containing fluids as dextrose induces insulin secretion which then worsens the hypokalemia [45]. During treatment, regardless of severity of hypokalemia, careful monitoring of serum potassium levels is recommended (every 2 to 4 hours) because patients commonly develop hyperkalemia [45].

During the management of DKA, hypophosphatemia often develops, however phosphate repletion is not indicated except in patients with neurologic deterioration, hemolysis, or rhabdomyolysis [16]. When indicated, infusion of potassium phosphate (1 to 2 mmol/kg of phosphate) is given over 6 to 12 hours [16]. The serum calcium level is often decreased due to the infusion of potassium phosphate, and then the level should be monitored [16].

Severe hypophosphatemia rarely occurs, and its replacement should be performed when the concentration is 1.00 - 2.00 mg/dL (0.05 - 0.11 mmol/L) [44]. Moreover, as a quick or over-correction of phosphate can induce hypocalcemia, it is recommended to monitor serum calcium [44].

4.4. Use of Insulin for the Management of DKA in Pregnancy

DKA is characterized by an overproduction of glucose and ketones in the liver with release of free fatty acids from adipose tissues due to an alteration in the balance of glucagon and insulin [46]. When DKA happens, the normal metabolic homeostasis is altered due to an absolute or a relative deficiency in circulating insulin levels in the presence of excess glucose counter-regulatory hormones, such as catecholamines, glucagon, cortisol, growth hormone [46]. IV insulin in patients with DKA is crucial as it promotes glucose utilization by peripheral tissues, decreases glycogenolysis and gluconeogenesis, while suppressing ketogenesis [29].

Insulin therapy should not be started until serum potassium is ≥3.3 mEq/L (≥3.3 mmol/L) [16].

Insulin therapy in pregnant women with DKA is to be administered as follows [17]:

- Regular insulin, loading dose of 0.4 U/kg;
- Continuous insulin infusion at a rate of 6-10 U/hour;
- Infusion rate to be doubled if there is no response in one hour;
- Infusion rate to be decreased to 1 - 2 U/hour when serum glucose comes down to 12 mmol/l;
- Insulin infusion is to be continued 12 - 24 hours after ketosis is resolved.

Although some guidelines for management of DKA indicate that an IV bolus dose of insulin should be administered before starting an insulin infusion, a prospective observational cohort study by Goyal *et al.* in 2010 was undertaken to determine whether the initial bolus dose is of significant benefit to adult patients with DKA and if it results in increased complications [47]. The study included 157 non-pregnant adult patients who presented to the Emergency Department with DKA [47]. Of these patients, 78 formed the insulin bolus group, and 79 the control group [47]. The conclusion was that an initial bolus dose of insulin given before an insulin drip is not associated with significant benefits to adult DKA patients [47]. Additionally, in patients on an initial bolus dose of insulin, there are equivalent changes in clinically relevant endpoints, when compared to patients on an insulin drip only [47].

Also, a prospective randomized study by Kitabchi *et al.* in 2008 was undertaken to evaluate the efficacy of a bolus dose of insulin with a continuous insulin infusion versus two continuous infusions without a bolus dose [48]. They recruited 37 non-pregnant patients aged 17 to 66 years [48]. Of these patients, 12 patients were assigned to the load group (receiving a bolus dose of 0.07 units of regular insulin per kg body weight, followed by an intravenous dose of 0.07 units per kg per hour), 12 were assigned to the no load group (receiving an infusion of regular insulin of 0.07 units per kg body weight per hour, without a loading dose), and 13 were assigned to the twice no-load group (receiving an infusion of regular insulin of 0.14 units per kg per hour, without a bolus dose) [48]. There was no significant difference among the three groups regarding the times to reach glucose ≤ 250 mg/dl, HCO_3^- ≥ 15 mEq/l, and pH ≥7.3 [48]. The conclusion was that a bolus dose of insulin is not required when appropriate dose of regular insulin of 0.14 units per kg body weight per hour (which is about 10 units per hour in a 70-kg patient) is administered [48].

Additionally, a retrospective chart review by Brown, Tran, and Patka in 2018 was undertaken to evaluate the impact of the insulin bolus administration on the resolution of DKA [49]. The study included 145 patients aged 18 and over who were admitted to the emergency department with DKA [49]. All patients received an IV regular insulin infusion at a rate of 0.1 unit per kilogram per hour, but only 58 patients received an IV regular insulin bolus at a rate of 0.1 unit/kg [49]. There

was no difference between the bolus and no bolus groups regarding the time to resolution of DKA (15 vs. 15.9 h; P = 0.24) [49]. The researchers concluded that the insulin bolus administration is not associated with reduced time to resolution of DKA [49].

It has been recommended to provide the *fixed-rate intravenous insulin infusion* (FRIII), at a rate of 0.1 unit/kg/hour (the maximum rate should be 15 unit/hour) of short-acting human soluble insulin (for example: Humulin S®, or Actrapid®) [50]. This therapy will continue until the levels of bedside capillary ketone are less than 0.6 mmol/L, the pH >7.3 and the patient has been put on an alternative insulin [50]. Basal insulin will be administered subcutaneously and this is done to prevent rebound hyperglycemia when the IV insulin is stopped [50]. One can provide long-acting basal insulin analogues (e.g. Lantus®, Levemir®), or human basal insulins (e.g. Insulatard®, Humulin I®, Insuman Basal®) [50].

Furthermore, a controlled multicenter and open-label trial by Umpierrez *et al.* in 2009 was undertaken to compare the safety and efficacy of human insulins and insulin analogs both during acute IV treatment and during the transition to SC insulin in patients with DKA [51]. They recruited 68 non-pregnant adult patients who presented with DKA [51]. They randomized these patients 1:1 to receive IV treatment with regular or glulisine insulin until resolution of DKA [51]. After resolution of DKA, patients treated with IV glulisine insulin were transitioned to SC glargine once daily and glulisine before meals (n = 34), and patients treated with IV regular insulin were transitioned to SC NPH (Neutral Protamine Hagedorn) and regular insulin twice daily (n = 34) [51]. Glulisine and regular insulin were equally effective during the acute treatment of DKA [51]. In fact, there was no difference in the amount of insulin infusion or in the mean duration of treatment until resolution of DKA between IV therapy with glulisine or regular insulin [51]. A transition to SC glargine and glulisine after resolution of DKA resulted in similar glycemic control but in a lower rate of hypoglycemia than with NPH and regular insulin [51]. The conclusion was that, after the resolution of DKA, a basal bolus regimen with glargine and glulisine is safer and should be preferred over NPH and regular insulin [51].

For the management of DKA, insulin therapy remains effective regardless of the route of administration [23]. In fact, insulin may be administered via continuous IV infusion or by frequent SC or IM injections [23]. Additionally, inhaled insulin (Afrezza) has been recently used for treatment of DKA in a patient with SC insulin resistance syndrome [23]. Nevertheless, continuous IV infusion with regular insulin remains the mainstay of therapy because of its short half-life and easy titration compared to other routes of administration [23], [52].

During the insulin therapy, the care provider should perform an hourly monitoring of the capillary blood glucose (CBG), as a perilous hypoglycemia may suddenly result from the FRIII (Intravenous glucose should be provided once the CBG is less than 14 mmol/L) [50]. In fact, hypoglycemia is a major complication of diabetes treatment. Some groups of people have a higher risk of developing

severe hypoglycemia when taking diabetes therapy, and these include elderly persons, patients presenting with other diseases or particular conditions (vascular disease, renal failure), pregnant women and children [53]. Therefore, overzealous management of DKA with insulin and bicarbonate may result in two common complications which are hypoglycemia and hypokalemia respectively [54]. Blood glucose monitoring should be performed hourly or every 2 hours in order to quickly recognize hypoglycemia, as patients with DKA who develop hypoglycemia during treatment do not commonly experience adrenergic manifestations of hunger, sweating, tachycardia, nervousness, and fatigue [54].

Hypoglycemia in adults with diabetes in hospital is managed based on the severity level of the condition [55]. Generally, hypoglycemia is characterized by a blood glucose level of less than 4 mmol/L [55]. For mild hypoglycemia, the patient is commonly conscious and orientated [55]. If able to swallow, the patient may be given 15 - 20 g of quick acting carbohydrate, then the blood glucose level should be tested after 10 - 15 minutes [55]. In case the blood glucose level is still less than 4mmol/L, the dose of quick acting carbohydrate may be repeated up to 3 times [55]. If the blood glucose level is not improved, it is good to consider the administration of IV 10% glucose at a rate of 150 - 200 ml over 15 minutes or IM injection of 1 mg of glucagon [55]. As the blood glucose level goes beyond 4mmol/L, the patient may be given 20 g of long-acting carbohydrate (such as 2 biscuits) or a slice of bread or a meal, but if the patient has received IM glucagon, 40 g of long-acting carbohydrate should be given to replenish glycogen stores [55]. Subsequent doses of insulin should not be omitted and regular capillary blood glucose monitoring should be continued for 24 - 48 hours [55].

In moderate hypoglycemia, the patient may be conscious but disorientated or aggressive [55]. If cooperative and able to swallow, the patient with moderate hypoglycemia can be treated as for mild hypoglycemia [55]. Here, 1.5 - 2 tubes of Dextrogel or GlucoGel may be given if the patient is not capable and cooperative but able to swallow [55]. The blood glucose level should be tested after 10 - 15 minutes [55]. In case the blood glucose level is still less than 4mmol/L, the dose of Dextrogel or GlucoGel may be repeated up to 3 times [55]. If the blood glucose level is not improved, it is good to perform an IM injection of 1 mg of glucagon daily [55]. When the blood glucose level is greater than 4mmol/L, the patient may be given 20 g of long-acting carbohydrate (e. g., 2 biscuits) or a slice of bread or a meal, but if the patient has received IM glucagon, 40 g of long-acting carbohydrates should be given to replenish glycogen stores [55]. Also, subsequent doses of insulin should not be omitted and regular capillary blood glucose monitoring should be continued for 24 - 48 hours [55]. Nevertheless, if the patient remains hypoglycemic or deteriorates at any stage, IV glucose should be administered as for severe hypoglycemia [55].

In patients with severe hypoglycemia and who are often unconscious, the healthcare professional should check for airway, breathing and circulation, and any IV insulin should be stopped [55]. If the patient is suitable for IM glucagon

(for instance if enteral feeding is not proscribed and if there is no severe hepatic disease), an IM injection of 1 mg of glucagon is the option [55]. But if the patient is not suitable for IM glucagon, IV glucose is given [55]. Glucose level should then be tested after 10 - 15 minutes [55]. When the blood glucose level is greater than 4 mmol/L, the patient may be given 20 g of long-acting carbohydrate or a slice of bread or a meal, but if the patient has received IM glucagon, 40 g of long-acting carbohydrates should be given to replenish glycogen stores [55]. However as long as enteral feeding is proscribed, the patient receives 10% glucose at a rate of 100 ml per hour [55]. Subsequent doses of insulin should not be omitted and regular capillary blood glucose monitoring should be continued for 24 - 48 hours [55].

Some precautions are to be considered for the insulin therapy in patients with DKA [26]:

- In case DKA is not resolving and the management targets are not being achieved, one should confirm the appropriate rate of IV infusions (i. e., fluids and FRIII [Fixed Rate Intravenous Insulin Infusion]) has been administered, in addition to checking cannula patency and placement.

- The patient's basal (long acting) subcutaneous insulin (such as Tresiba/degludec, Lantus/glargine, Levemir/detemir) should be continued together with the FRIII in order to prevent rebound hyperglycemia when IV insulin therapy is stopped. In patients presenting with DKA and newly diagnosed T1DM, basal insulin should be started as soon as possible, and IV insulin should be continued until there is some basal subcutaneous (SC) insulin on board.

- When DKA has resolved and the patient can eat and drink, SC insulin therapy can be restarted, but the FRIII should not be discontinued until at least 30-60 minutes after the administration of the SC insulin dose taken with a meal. The patient's basal SC insulin should have been continued together with the FRIII. In case the basal SC insulin had been discontinued in error, it is recommended not to stop the insulin infusion until some form of background insulin has been administered, for instance by giving a start dose of Insulatard at half the patient's usual daily dose of basal insulin.

- When stopping the FRIII, depending on the trigger of the DKA episode, it may be appropriate to simply restart the pre-DKA SC insulin regimen. But, if pre-admission glycemic control was suboptimal (for instance if the patient had a high HbA1c, or a recurrent hypoglycemia) then a medication review is required.

- If the pre-DKA SC insulin regimen was a twice daily fixed-mix insulin (e.g. NovoMix 30), it is recommended to restart the patient's usual SC insulin either before breakfast or before the evening meal. IV insulin infusion should be continued until 30 - 60 minutes after the SC insulin was given.

- SC insulin therapy (type and doses of insulin) to be used in a newly diagnosed patient should be based on the advice of the diabetes specialist team.

- When DKA has resolved but the patient cannot eat and drink, it is recommended to switch to a variable rate insulin infusion and IV fluids based on the patient's fluid status.

4.5. Bicarbonate Infusion in the Management of DKA in Pregnancy

A retrospective observational study by Duhon *et al.* in 2013 was undertaken to determine whether the IV bicarbonate therapy was associated with improved outcomes in patients with severe DKA [56]. They recruited 86 DKA patients aged 18 and over, who presented to the emergency department with an initial pH < 7.0 [56]. Of these patients, 44 received IV bicarbonate, and 42 did not [56]. No significant difference was found in time to resolution of acidosis (8 hours vs 8 hours; P = 0.7) or time to hospital discharge (68 hours vs 61 hours; P = 0.3) between patients who received IV bicarbonate therapy compared with those who did not [56]. Therefore, the IV bicarbonate therapy was not associated with a decreased time to resolution of ketoacidosis or time to hospital discharge [56].

Also, a systematic review by Chua, Schneider, and Bellomo in 2011 noted the lack of evidence of improved outcomes or glycemic control with bicarbonate administration in patients with DKA [57]. Bicarbonate administration did not result in any significant benefit in resolution of ketoacidosis, correction of electrolyte abnormalities, tissue oxygenation, cerebrospinal fluid acidosis, hospital stay, or mortality [57].

Although bicarbonate can be used for the correction of acidosis, it should not be administered routinely as it can lead to development of acute cerebral edema [16]. Therefore, bicarbonate should be given only if the pH remains < 7 after 1 hour of therapy, and only modest pH elevation should be attempted with doses of 50 to 100 mEq (50 to 100 mmol) given over 2 hours, followed by repeat measurement of arterial pH and serum potassium [16]. As per the American Diabetes Association, based on the concern of cardiovascular compromise in the setting of severe acidemia, it is recommended to administer 100 mmol sodium bicarbonate in 400 mL sterile water with 20 mEq of KCl (at a rate of 200 ml/h for 2 h) to adult patients with a pH of less than 6.90 until the pH is greater than 7.00 [54]. Moreover, bicarbonate infusion can be justified in the context of life-threatening hyperkalemia, as its administration may shift potassium into cells [58].

4.6. General Overview of the Management of DKA During Pregnancy

Over the past decade, some principles have been updated regarding the management of DKA [26]:

- It is recommended to rely on measuring *capillary ketones* rather than urinary ketones.

- The treatment of DKA should be guided by the capillary ketone level instead of the capillary glucose. Because clearing ketones is as important as normalizing blood glucose, it is commonly required to administer IV 10% dextrose, to prevent hypoglycemia and allow continued fixed rate intravenous insulin infusion (FRIII) to suppress ketogenesis;

- Measuring venous pH and bicarbonate is sufficient, and it is no longer required to perform measurement of arterial pH and bicarbonate. In fact, venous sampling

is sufficient because the difference between venous and arterial pH/HCO_3 is not significant enough to have an impact on the diagnosis or management of DKA;

- It is recommended to use weight-based FRIII instead of "sliding scales".

- Long-acting basal insulin analogues should be continued together with FRIII in order to prevent rebound hyperglycemia when IV insulin therapy is discontinued.

- It is possible to monitor electrolytes on blood gas analyzer with intermittent laboratory confirmation.

The overview of the management of DKA during pregnancy is presented in Figure 3.

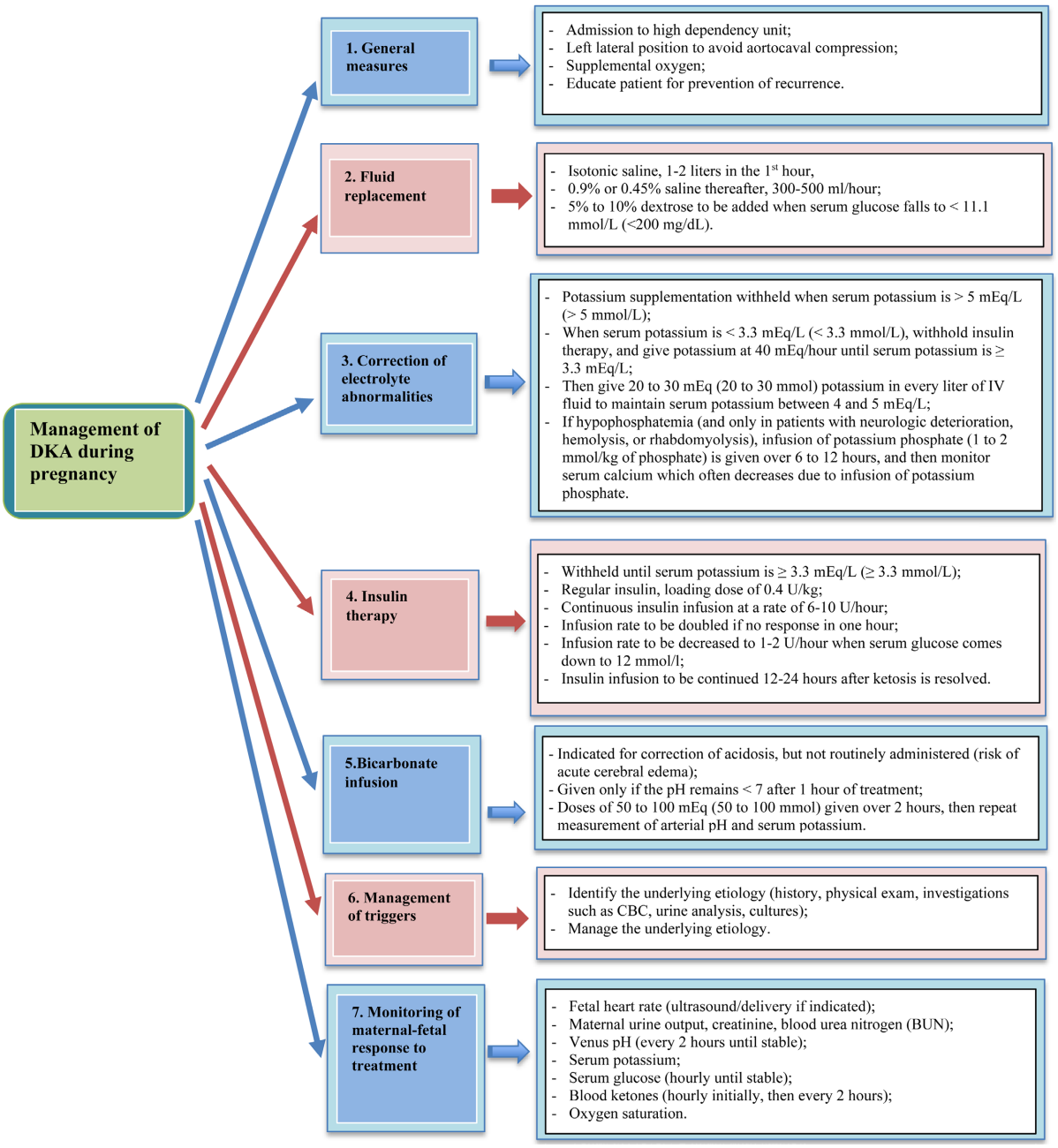


Figure 3. Overview of the management of DKA during pregnancy.

4.7. Strengths and Weaknesses

It is hoped that this narrative overview will be a valuable contribution to the literature. Actually, the narrative overview will bring practitioners up to date with clinical protocols on the management of DKA in pregnancy. Nevertheless, because of the availability of a huge number of online sources, there was a challenge in identifying every quality source regarding the management of DKA in pregnancy. In this review, the researcher could identify only few original studies and the latter were conducted in non-pregnant patients. Regarding the management of DKA in pregnancy, most of the current published sources are reviews.

5. Conclusions

DKA is a life-threatening condition which can occur with lesser degrees of hyperglycemia in pregnant women. Therefore, a high index of suspicion along with prompt diagnosis and appropriate management are crucial for optimal patient outcomes. The management of DKA in pregnancy includes fluid replacement, correction of electrolyte abnormalities, insulin therapy, identification and management of triggers, and the monitoring of maternal-fetal response to treatment.

Actually, DKA patients should be admitted to a high dependency unit, and the left lateral position is recommended to avoid aortocaval compression. Then, dehydration caused by important urinary losses of water should be corrected by IV fluids. The later commonly include crystalloid solutions as the first choice, and colloid solutions alternatively. Also, when the blood glucose level approaches the normal value, dextrose-containing fluids should be administered to reduce the risk of hypoglycemia while facilitating the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis. Moreover, pregnant women with DKA are likely to have potassium abnormalities, and other issues such as phosphorus and magnesium abnormalities. Thus, it is important to obtain serum potassium and rule out any life-threatening hypokalemia before starting insulin therapy. In addition, phosphorus and magnesium abnormalities should be managed as well.

Furthermore, the administration of IV insulin promotes glucose utilization by peripheral tissues, decreases glycogenolysis and gluconeogenesis, while suppressing ketogenesis. However, in order to prevent hypokalemia-induced cardiac arrhythmia, insulin therapy should not be started until serum potassium is ≥ 3.3 mEq/L. Additionally, Bicarbonate infusion is not routinely administered, but the identification and management of triggers, together with the monitoring of maternal-fetal response to treatment, are part of the cornerstones of the management of DKA in pregnancy. After all, as there is a major deficiency in strong evidence for optimal management of DKA in pregnancy, more research on pregnant patients is needed to confirm or adjust treatment and improve patient outcomes.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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