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Obstetrics and Gynaecology

Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle Bu Teaching Hospital

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DECLARATION BY CANDIDATE

I do hereby declare that the contents of this dissertation were conceptualized after a problem identification and discussion with my supervisors.

This research was done conscientiously, and data analysis and the final report were done to the best of my ability.

I confirm that this work I have submitted for review is mine and that references/citations made within the works of other authors in any form are properly acknowledged at the point of their use.

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SUPERVISORS ATTESTATION PAGE

We hereby declare that the contents of this dissertation were conceptualized and developed after a problem identification and discussion with us by the candidate.

We supervised the content of the study, analysis of the data, and write-up of the final report.

We are certain that the candidate undertook the study conscientiously.

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DEDICATION

I dedicate this work firstly to the Almighty God by whose grace I have been able to make it this far. Secondly, I dedicate this to my amazing wife, Yaa, and wonderful children, Laurent, Maxine, and Josué. You are my inspiration and my motivation. Everything I do, I do for you.

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ABSTRACT

Introduction

Diabetic ketoacidosis (DKA) is a state of relative or absolute insulin deficiency that results in major metabolic changes including increased glucose production accompanied by decreased peripheral uptake and enhanced protein catabolism and lipolysis. It affects 1 to 3% of diabetic pregnancies. It most commonly complicates type 1 diabetes mellitus (DM) but also affects type 2 DM and more occasionally gestational DM. The incidence is higher in the second and third trimesters of pregnancy when insulin resistance peaks. Diagnosis is based on a triad of hyperglycaemia, ketonaemia or ketonuria, and metabolic acidosis. In pregnancy, DKA tends to occur at lower blood glucose levels. Euglycaemic DKA is a rare condition in which ketoacidosis occurs at normal blood glucose levels. This occurs more commonly in pregnancy. DKA in pregnancy significantly increases the risk of maternal and fetal morbidity and mortality. Management can be very challenging and must involve a multidisciplinary team in a high-dependency or intensive care unit. Maternal complications include acute kidney injury, adult respiratory distress syndrome, cerebral oedema, coma, and death. Fetal complications include fetal heart rate abnormalities, fetal demise, prematurity, and long-term neurodevelopmental delay. The objective of this study was to determine the incidence of DKA in pregnancy in KBTH and maternal and fetal outcomes.

Methods

This was a prospective cohort study. The study population was pregnant women with diabetes admitted at KBTH. Pregnant women who met the eligibility criteria were screened for ketonuria every time they were seen at the obstetrics emergency room or admitted to the maternity ward or labour ward. Women with urine ketones ≥2+ were tested for bicarbonate and/or pH. Women with pH<7.3 or bicarbonate <15mmol/l became the DKA cases. All the women were followed up for maternal and fetal outcomes including maternal mortality, fetal demise, preterm birth, etc. The association between DKA and maternal and fetal outcomes was determined with logistic regression using a confidence interval (CI) of 95%. Odds ratios were obtained and measurements with p-value <0.05 were deemed statistically significant. Multivariate analysis was done to control for confounders and adjusted odds ratios were determined.

Results

We screened 234 women, representing 91% of pregnant women with diabetes who were admitted at KBTH from 1st September 2021 to 28th February 2022. Forty-four of them had significant ketonuria and six had DKA, giving an incidence of 2.6%. Two-thirds of the cases occurred in the second and third trimesters. Half occurred in women with GDM. A third had euglycaemic DKA. All the cases were managed according to the KBTH management protocol for DKA in pregnancy. They all recovered. There was no maternal mortality among the DKA cases. We found no significant effect of DKA on maternal and fetal outcomes.

Conclusions

The incidence of DKA in pregnancy in KBTH is similar to what has been reported in other parts of the world. Universal screening of all pregnant women with diabetes for DKA led to early diagnosis and prompt treatment. The pregnancy outcomes in pregnant women with DKA were comparable to those without DKA.

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LIST OF ABBREVIATIONS

AOR	Adjusted odds ratio
AVPU	Alert, Verbal, Pain, Unresponsive
BMI	body mass index
BUN	blood urea nitrogen
BW	birth weight
CBC	complete blood count
CNS	central nervous system
DKA	diabetic ketoacidosis
DM	diabetes mellitus
ER	emergency room
GCS	Glasgow coma scale
GDM	gestational diabetes mellitus
GIT	gastrointestinal tract
GLUT-1	glucose transporter 1
ICU	intensive care unit
IUFD	intrauterine fetal death
IUGR	intrauterine grwoth restriction
K-S	Kolmogorov-Smirnov
KBTH	Korle Bu Teaching Hospital
MOE	margin of error
NICU	neonatal intensive care unit
OGTT	oral glucose tolerance test
OR	odds ratio
PDA	patent ductus arteriosus

RBS random blood sugar

SD standard deviation

SGLT-2 sodium-glucose cotransporter 2

SIRS systemic inflammatory response syndrome

SPSS statistical package for social sciences

vs versus

VSD ventricular septal defect

CHAPTER 1

1.1 INTRODUCTION

The prevalence of diabetes mellitus (DM) including DM in pregnancy is increasing worldwide and in Sub-Saharan Africa. Accompanying this is increasing DM-related complications, both acute and chronic [1].

Diabetic ketoacidosis (DKA), an acute complication of DM, is a state of relative or absolute insulin deficiency that results in major metabolic changes including increased glucose production accompanied by decreased peripheral uptake, and enhanced protein catabolism and lipolysis [2]. It is characterized by a biochemical triad of hyperglycaemia, ketonaemia, and metabolic acidosis (Figure 1) [3]. DKA is a medical emergency that can have dire effects on both the mother and the baby. It was consistently fatal before the discovery of insulin [4]. Getting the best pregnancy outcomes requires a high index of suspicion, rapid treatment, and multidisciplinary management.

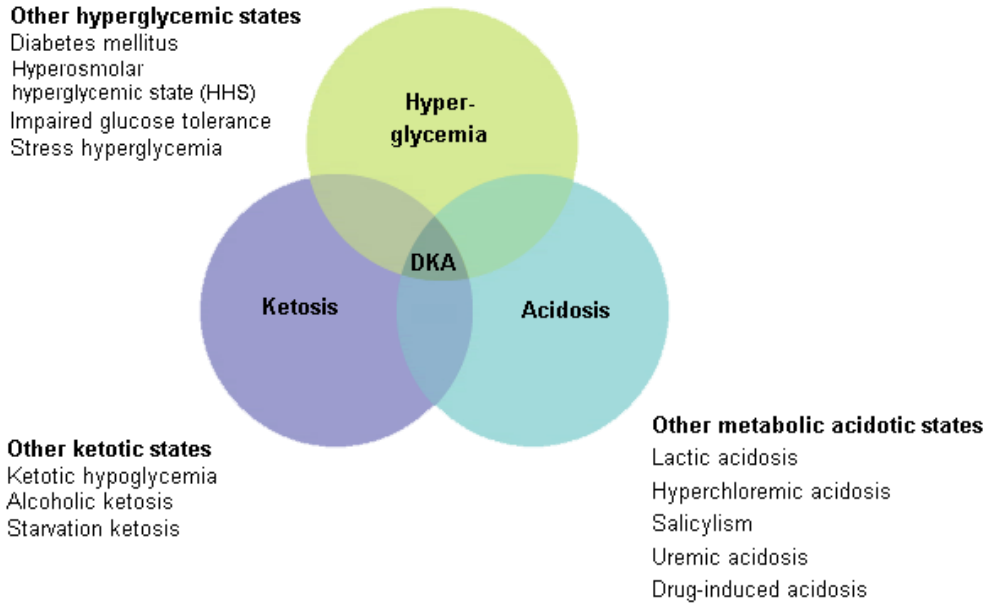


Figure 1: Metabolic triad of DKA [5]

About 5-10% of pregnancies are complicated by diabetes mellitus [6]. Diabetes mellitus (DM) in pregnancy can be subclassified into pregestational and gestational diabetes. Of all diabetes in pregnancy, only 10% are diagnosed before pregnancy (pregestational) [6]. A study by Oppong *et al* found the prevalence of gestational diabetes mellitus (GDM) in Accra, Ghana to be 10% [7]. In Nigeria, Oputa *et al* recorded the prevalence of diabetes in pregnancy as low

as 1.7%, with 61% being gestational DM [8]. The incidence of diabetes in pregnancy is rising, especially with increasing obesity [7].

Good antenatal care, frequent self-monitoring of blood glucose, and medical diet therapy in pregnant women with diabetes have been found to improve glycaemic control. This decreases the risk of adverse outcomes for both mother and baby [9].

Physiological changes in pregnancy predispose pregnant women with diabetes to DKA [10]. Case reports, retrospective studies with small numbers, and review articles form the main basis of epidemiologic data on DKA in pregnancy. This makes the true incidence difficult to determine [11]. DKA occurs in 1 to 3% of diabetes in pregnancy [12]. This is a massive drop from 10 to 20% in the 1970s, and this is owed to early recognition and intensive multidisciplinary management of diabetes in pregnancy [4]. It is more commonly associated with type 1 DM but can also occur in type 2 DM and GDM [10]. It tends to occur later in pregnancy, typically second or third trimester [12]. Seventy-eight to ninety percent of cases occurs in the second and third trimesters. In pregnancy, it more commonly occurs at lower blood glucose levels and progresses at a faster rate compared to non-pregnant women [13]. The diagnosis, management, and prevention of DKA in pregnancy can be very challenging. Monitoring during treatment has shifted from solely relying on blood glucose to incorporating blood ketone levels, which gives a more accurate indication of resolution [14]. DKA in pregnancy poses significant threats of morbidity and mortality to both mother and fetus.

1.2 PROBLEM STATEMENT

Diabetes in pregnancy is associated with adverse pregnancy outcomes. Pregnancy outcomes associated with DKA are even worse. In Korle Bu Teaching Hospital (KBTH) and the subregion at large, there is poor laboratory support for accurate diagnosis and management of DKA. This leads to underdiagnosis and suboptimal management. In our current practice at the department of Obstetrics and Gynaecology in KBTH, pregnant women are not universally screened for diabetes. We do selective screening which leads to underdiagnosis because women without obvious risk factors are missed. Women with undiagnosed diabetes in pregnancy are at a high risk of developing DKA, with poor outcomes. Also, we do not routinely screen pregnant women with diabetes for ketones. Urine ketones are only checked when the blood glucose is very high or the pregnant woman with diabetes has classic clinical features of DKA. This leads to underdiagnosis and delay in instituting appropriate management, leading to poor

outcomes. Some cases are also managed as DKA once they have significant ketonuria without confirming acidosis with measurement of blood gases. This way, there is room for misdiagnosis which affects hospital data for research purposes.

1.3 RATIONALE FOR THE STUDY

There is insufficient data on diabetes in pregnancy in Africa. Macaulay *et al* did a systematic review of gestational diabetes in Africa and found that only six countries were represented in this study [15]. Also, there is no data on the incidence of DKA in pregnancy and associated pregnancy outcomes in our subregion. This highlights the need for research in this area.

This study would add to the body of knowledge on the subject and generate data that would provide baseline information on the burden of DKA in pregnancy in Korle Bu Teaching Hospital (KBTH), Ghana. It would conscientize clinicians to screen for DKA in pregnant women with diabetes routinely to diagnose and treat early to reduce complications. It would investigate the maternal and fetal outcomes of the disease, as well as management gaps due to limited resources in comparison to standard guidelines. This would justify the mobilization of resources from policymakers and stakeholders for the effective management of DKA in pregnancy. Ultimately, improved screening, diagnosis, and management of DKA would reduce maternal and perinatal mortality contributed by DKA in pregnancy.

1.4 STUDY OBJECTIVES

1.4.1 General objective

To determine the incidence of DKA among diabetic pregnant women admitted to KBTH and pregnancy outcomes.

1.4.2 Specific objectives

1. To determine the incidence of DKA in pregnancy in KBTH.
2. To determine the maternal outcomes of DKA in pregnancy. These outcomes include admission to the intensive care unit (ICU), mode of delivery, length of hospital stay, pre-eclampsia, and maternal mortality.
3. To determine the fetal outcomes of DKA in pregnancy. These outcomes include polyhydramnios, macrosomia, congenital anomalies, abnormal fetal heart tracing, fetal demise, preterm birth, etc.

CHAPTER 2: LITERATURE REVIEW

2.1 EPIDEMIOLOGY

Globally the prevalence of diabetes mellitus is now 10.5%, more than a two-fold increase over the past two decades. It is projected to rise to 11.3% by the year 2030 [16]. In Africa, it is estimated that less than half of the people living with diabetes have been diagnosed and the prevalence is 4.5%. Asamoah-Boaheng *et al* conducted a systematic review and meta-analysis to determine the prevalence of DM in Ghana and found it to be 6.5% [17].

The rising prevalence of lifestyle-related diseases including obesity and type 2 diabetes mellitus is partly due to lifestyle changes, especially diet and physical inactivity. Other factors include longer life expectancy as well as more quality data in recent times. There is a clear association between obesity and diabetes (Figure 2). Obese women are three times more likely to develop gestational diabetes mellitus (GDM) [7]. About 80% of women with diabetes during pregnancy are overweight or obese.

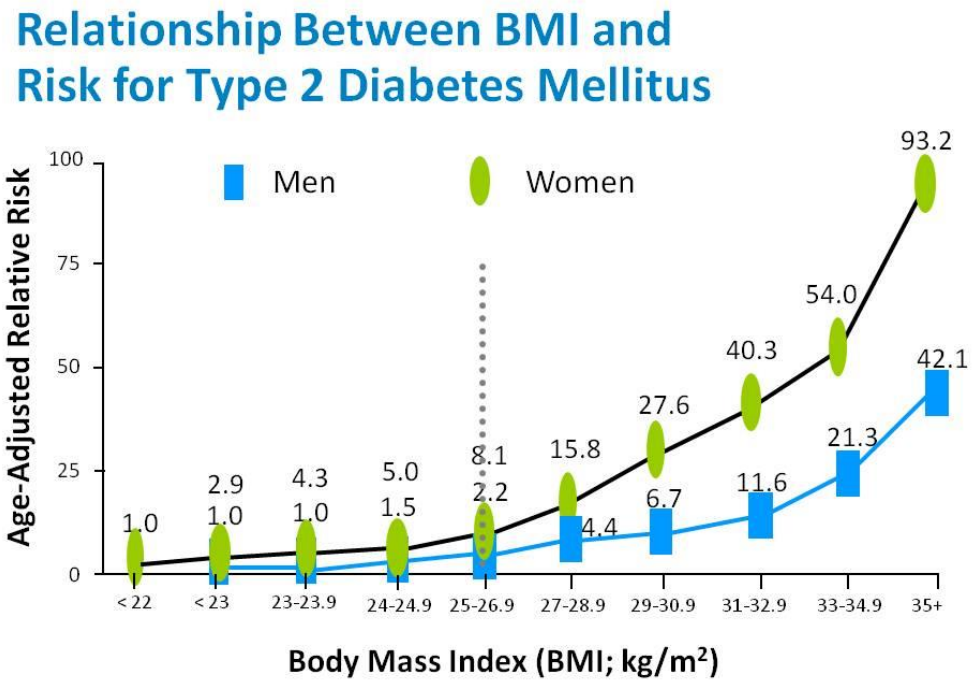


Figure 2: Relationship between BMI and risk of type 2 DM [18] [19]

In 2021, over 21 million live births were to women with diabetes during pregnancy. Of these, 80.3% had gestational DM, 10.6% had pregestational DM, and 9.1% had type 1 or type 2 DM diagnosed for the first time during pregnancy [16]. Increasing maternal age is one of the reasons why the prevalence of diabetes in pregnancy is on the increase globally [20]. A lot

more women are now educated, and they advance in their careers before starting a family. Also, modern effective ways of managing infertility allow more women to achieve pregnancy, even later in life. Macaulay *et al* did a systematic review of GDM in Africa and found incidence ranging from as low as 0% in rural Tanzania to 13.9% in urban Nigeria [15]. In Tanzania, Lutale *et al* found that 76% of diabetes in pregnancy was detected in the second and third trimesters.

Robinson *et al* found the prevalence of ketonuria in pregnancy to be 22%. The ketonuria was variable with most of the women only recording trace ketonuria. Only 2% had ketonuria ≥2+. The study population was overweight and obese pregnant women, not pregnant women with diabetes [21]. Ketonuria or ketosis is much more prevalent among pregnant women with diabetes owing to abnormal insulin secretion or utilization [22]. Huang *et al* did a retrospective study of 570 women with GDM to assess an association between ketonuria and pregnancy outcome. They found that ketosis occurred in 26.6%, while 31.6% had moderate ketonuria, and 41.8% had no ketonuria. In their study, a family history of diabetes positively correlated with increasing levels of ketonuria. [23].

DKA complicates 5 to 10% of pregestational diabetes mellitus [24]. In a study by Restrepo-Monero *et al* looking at maternal and fetal outcomes in pregnant women with type 1 diabetes, the incidence of DKA was 7% [25]. Guo *et al* compared the occurrence of DKA in pregnant and non-pregnant women and found that the incidence of DKA was higher in pregnancy (8.9% vs 3.1%), 88% of DKA in pregnancy occurred in the second or third trimester, and DKA occurred at a lower mean blood glucose level (16.3mmol/l vs 27.5mmol/l) [26].

DKA occurs more commonly in type 1 DM. A study by Baagar *et al* found that 68% of DKA in pregnancy occurred in type 1 diabetics, and 32% in type 2 [2]. Bryant *et al* had a similar finding of 69% of DKA in pregnancy occurring in type 1 diabetics [27]. It has a higher incidence in the second and third trimesters (78 to 90% of cases) due to increasing insulin resistance. It occurs less commonly in gestational diabetes. Himuro *et al* presented a case report of a woman who had a normal oral glucose tolerance test (OGTT) in early pregnancy but developed DKA in the third trimester [13]. Many of the women with gestational diabetes who had DKA in case series were found to be obese, had risk factors for overt diabetes, or had specific precipitating factors [9].

2.2 PRECIPITATING FACTORS OF DKA IN PREGNANCY

Precipitating factors of diabetic ketoacidosis in pregnancy include protracted vomiting, infections, insulin non-compliance, medications (including corticosteroids and betamimetics), insulin pump failure, and conditions such as gastroparesis [10]. Montoro *et al* found that DKA in pregnancy was precipitated by insulin non-compliance in 40% of cases, and infection in 20%. For 30% of cases, diabetes was diagnosed for the first time when they presented with DKA. In this group, ketoacidosis was more advanced compared to known diabetics. Melville *et al* presented a case report on a Ghanaian woman who presented with DKA as the first sign of undiagnosed diabetes. At presentation, she had intrauterine fetal death (IUFD) at 30 weeks [28]. In a retrospective study by Rodgers and Rodgers, refractory vomiting and the use of beta-sympathomimetics were found to be the commonest precipitating factors of DKA [9].

2.3 PATHOPHYSIOLOGY

Pregnancy does not alter the basic pathophysiology of DKA. DKA results from the relative or absolute deficiency of insulin and concomitant increase in counter-regulatory hormones including cortisol, catecholamines, glucagon, and growth hormone (Figure 3).

Also, the secretion of hormones including human placental lactogen, progesterone, and cortisol tends to decrease insulin sensitivity in pregnancy. By 36 weeks of pregnancy, insulin sensitivity is estimated to drop by 50% from non-pregnant levels [29]. Due to these factors, insulin requirement increases with gestational age. In reaction to this, insulin production is boosted as gestation advances. In early pregnancy, baseline insulin production increases by 1.5 to 2-fold compared to non-pregnant controls. In late pregnancy, insulin production increases 3-fold [9]. However, if this is unable to match the increased requirement, diabetes ensues. In a known diabetic it is even less likely the increasing demand would be met. This explains why DKA is more common in the second and third trimesters [26].

The fetoplacental unit has a high glucose demand, approximately 150g/day in the third trimester. Placental glucose transporter 1 (GLUT-1) increases the flux of glucose across the placenta five-fold. In the third trimester, maternal basal metabolism increases by 300kcal/day. These factors explain why DKA occurs at lower blood glucose levels in pregnancy [26]. Also, the placenta secretes insulinase, which diminishes maternal insulin even more.

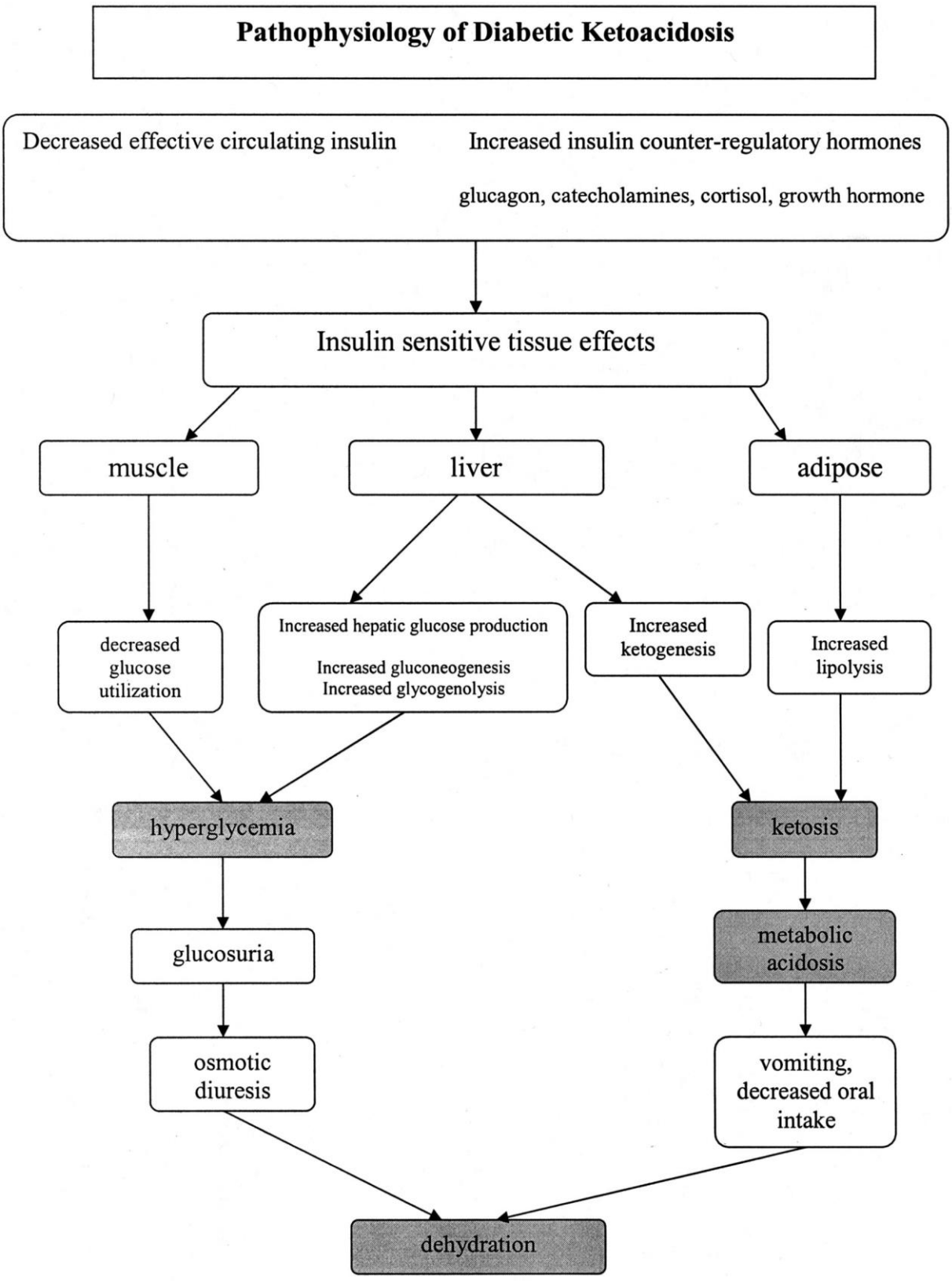


Figure 3: Pathophysiology of DKA [30]

The diminished effect of insulin causes major shifts in metabolism in three main target tissues: muscle, liver, and adipose tissue. The decreased insulin production or sensitivity causes perceived hypoglycaemia in these target tissues, and an exaggerated counterregulatory response leads to these metabolic shifts. In the muscle there is reduced peripheral uptake of glucose, leading to hyperglycaemia. In the liver, there is increased gluconeogenesis and glycogenolysis, which further compounds hyperglycaemia. In the adipose tissue, enhanced lipolysis leads to increased fatty acid levels. These fatty acids are presented to the liver where they are oxidized into ketone bodies or ketoacids (3-beta-hydroxybutyrate, acetoacetate, and acetone), leading to ketoacidosis (Figure 4).

Acidosis results because these ketone bodies contribute a large pool of hydrogen ions which overwhelm the buffering capacity of the body. There is preferential production of 3-beta-hydroxybutyrate, such that its ratio to acetoacetate is 10:1. Acetone is produced from the decarboxylation of acetoacetate and is in a much lower concentration. It is excreted through the lungs and is responsible for the fruity breath in ketosis. Osmotic diuresis from hyperglycaemia, and nausea and vomiting induced by ketoacidosis together result in severe volume depletion and electrolyte imbalance [14]. The electrolyte imbalance is further worsened due to the binding of ketoacids to sodium and potassium, which are excreted in the urine [4]. If left untreated, patients can develop cardiac dysfunction, decreased tissue perfusion, and declining renal function. These can lead to shock, coma, and death.

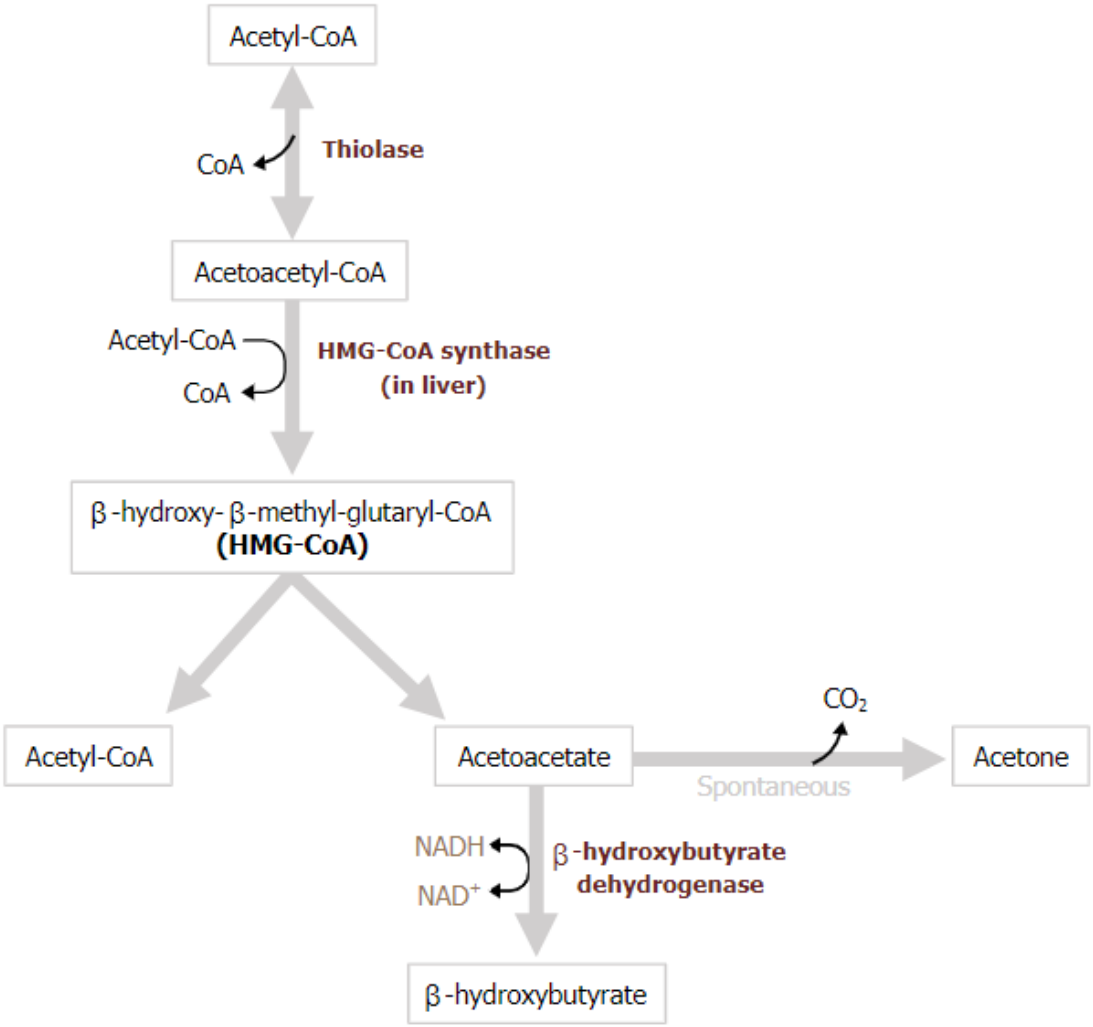


Figure 4: Ketogenesis [31]

During pregnancy, minute alveolar ventilation increases, creating a state of respiratory alkalosis. To compensate for this, renal excretion of bicarbonate increases, depleting the buffering capacity. This increases susceptibility to DKA in pregnancy [10].

2.4 DIAGNOSIS

The clinical features of DKA in pregnancy are similar to DKA in non-pregnant women (Figure 5). They include nausea or vomiting, abdominal pain, polyuria, polydipsia, blurred vision, muscle weakness, drowsiness, lethargy, change in mental status, hyperventilation (Kussmaul breathing), pear drop odour, tachypnoea, hypotension, tachycardia, coma, and shock [10]. The altered mental status results from worsening acidosis. The abdominal pain could be explained by many mechanisms including acute hyperglycaemia-mediated impaired gastrointestinal motility, the rapid expansion of the hepatic capsule, and mesenteric ischaemia due to volume depletion from dehydration and acidosis. It may also be from pancreatitis. In pregnancy, however, attention must be paid to fetal well-being as well. The main clinical feature seen with the fetus during DKA is abnormal fetal heart tracing.

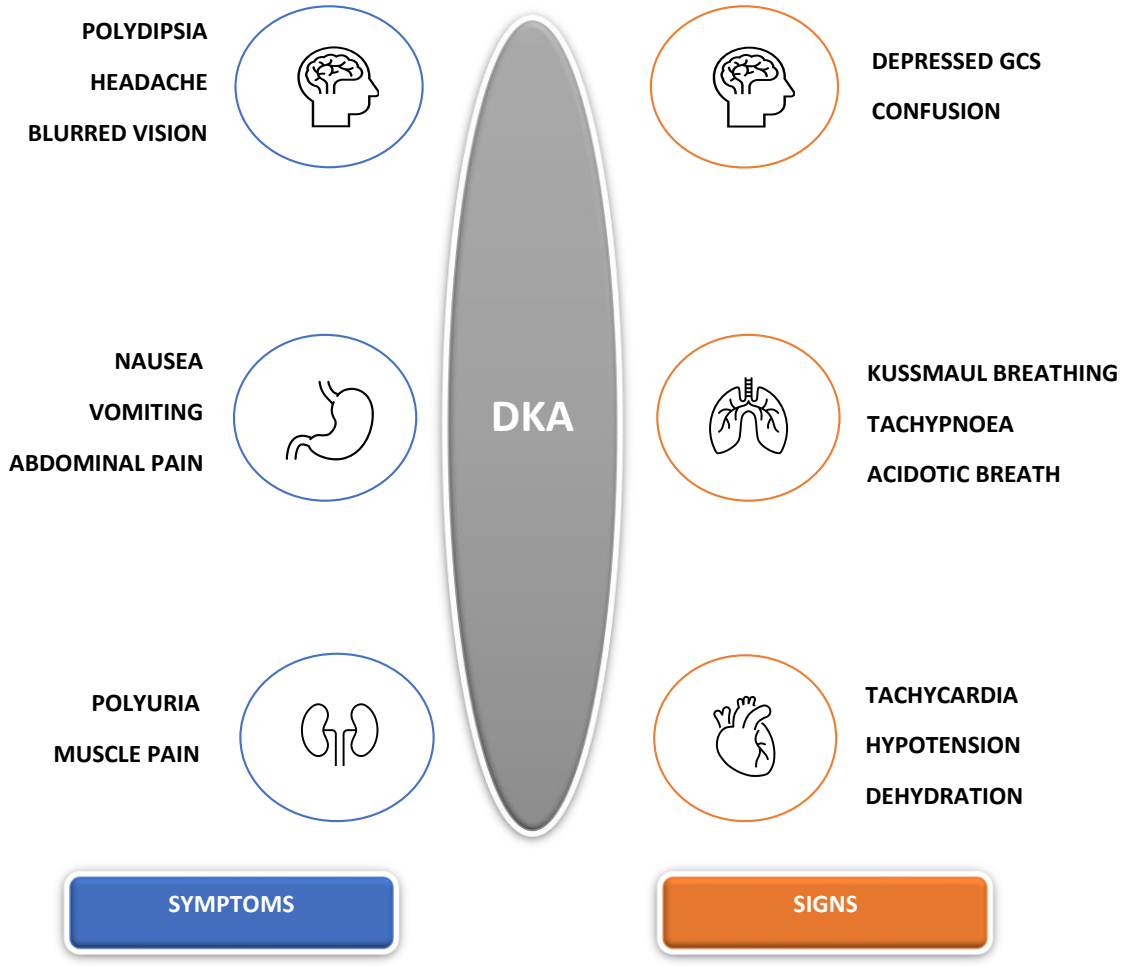


Figure 5: Clinical features of DKA

Precipitating factors of DKA in pregnancy include protracted vomiting, hyperemesis gravidarum, infections, insulin non-compliance, medications precipitating diabetic ketoacidosis in pregnancy including beta sympathomimetic agents and corticosteroids, insulin pump failure, and conditions such as gastroparesis. In pregnant women with diabetes requiring tocolysis, beta sympathomimetic agents such as terbutaline should be used very cautiously, if ever. In those requiring corticosteroids for fetal lung maturation, their insulin doses must be increased to match the increased insulin demand. There are varying recommendations in various guidelines concerning the amount of increment. Here is a typical example. Following the first dose of corticosteroid, the night insulin is increased by 25%. All insulin doses are increased by 40% on days 2 and 3. On day 4, the increment is stepped down to 20%, then to 10-20% on day 5. Insulin is gradually tapered down to pre-corticosteroid doses on days 6 and 7 [32]. A blood glucose profile is instituted throughout the corticosteroid administration. Alternatively, the original regimen can be maintained while adding on a sliding scale to cater to the additional insulin requirement.

The diagnostic criteria according to the Joint British Diabetes Societies guideline [14] for the management of diabetic ketoacidosis are:

1. Blood ketone level ≥ 3.0mmol/l or urine ketone level ≥ 2+
2. Blood glucose level > 11.0mmol/l or known diabetes mellitus
3. Venous bicarbonate < 15.0mmol/l and/or venous pH < 7.3mmol/l

The urine test that semi-quantitatively determines ketonuria uses nitroprusside which reacts with acetoacetate or acetone to give a purple colour. This nitroprusside, however, does not react with 3-beta-hydroxybutyrate which is the main ketone body in DKA. For this reason, DKA may not always be detected with urine ketones. Blood ketone is a superior test for the diagnosis of DKA. However, where a blood ketone test is not available, urine ketone is the next best test for diagnosis.

Other investigations include anion gap >12 and elevated base deficit ≥4mEq/l. Potassium levels may be falsely normal or elevated.

A close differential is hyperglycaemic hyperosmolar state (HHS) (Tables 1 and 2). This is however characterized by insidious onset at an older age, making it rare in pregnancy. It is rather more common in type 2 DM. Laboratory features include plasma glucose > 33.3mmol/l, pH >7.3, bicarbonate > 18mmol/l, serum ketones < 3.0mmol/l, osmolality > 320mOsm/kg, and variable anion gap. It is also associated with stupor or coma [34].

Table 1: Clinical features of DKA versus HHS [34]

Clinical features of hyperglycaemic emergencies			
Condition	**Symptoms**	**Signs**	**Presentation**
DKA	Polydipsia Polyuria Weakness Weight loss Nausea Vomiting Abdominal pain	Hypothermia Tachycardia Tachypnea Kussmaul breathing Ileus Acetone breath Altered sensorium	Acute onset (hours-days) More common in type 1 DM than type 2 DM
HHS	Polydipsia Polyuria Weakness Weight loss	Hypothermia Tachycardia Tachypnea Altered sensorium	Insidious onset (days-weeks) Older age More common in type 2 DM than type 1 DM

Table 2: Diagnostic criteria for DKA versus HHS [34]

Diagnostic criteria for DKA and HHS				
Measure	**DKA**			**HHS**
	Mild	**Moderate**	**Severe**	
Plasma glucose (mmol/l)	>13.9	>13.9	>13.9	>33.3
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mmol/l)	15 to 18	10 to <15	<10	>18
Urine or serum ketones	Positive	Positive	Positive	Small
Serum β-hydroxybutyrate (mmol/l)	>3.0	>3.0	>3.0	<3.0
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/ drowsy	Stupor/ coma	Stupr/ coma

2.5 MANAGEMENT

DKA in pregnancy is a medical emergency and must be managed by a multidisciplinary team including a maternal-fetal medicine specialist, a diabetologist/ endocrinologist, an obstetric anaesthesiologist/ critical care specialist, and well-trained nursing staff/ midwives [4]. The presence of one or more of the following is an indication for high dependency unit admission and consideration for central line insertion and immediate senior review [14]:

1. blood ketones > 6 mmol/l
2. bicarbonate level < 5 mmol/l
3. venous/arterial pH < 7.1
4. hypokalaemia on admission (potassium < 3.5 mmol/l)
5. Glasgow Coma Scale (GCS) < 12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale
6. oxygen saturation < 92% on room air (assuming normal baseline respiratory function);
7. systolic blood pressure < 90 mmHg
8. pulse > 100 or < 60 bpm
9. anion gap > 16

The goals of management are to improve circulating blood volume and tissue perfusion, decrease serum glucose, correct ketoacidosis, correct electrolyte imbalance, treat precipitating factors, and monitor therapeutic response in the mother and fetus. The components of management are fashioned to meet these goals and include intravenous fluid therapy, intravenous insulin therapy, electrolyte correction, identification and treatment of precipitating factors, and monitoring of maternal and fetal response (Figure 6). Thromboprophylaxis with low molecular weight heparin is indicated. Treatment requires adequate intravenous access and an indwelling urinary catheter. During the treatment, fluid balance and vital signs need to be monitored regularly and documented well.

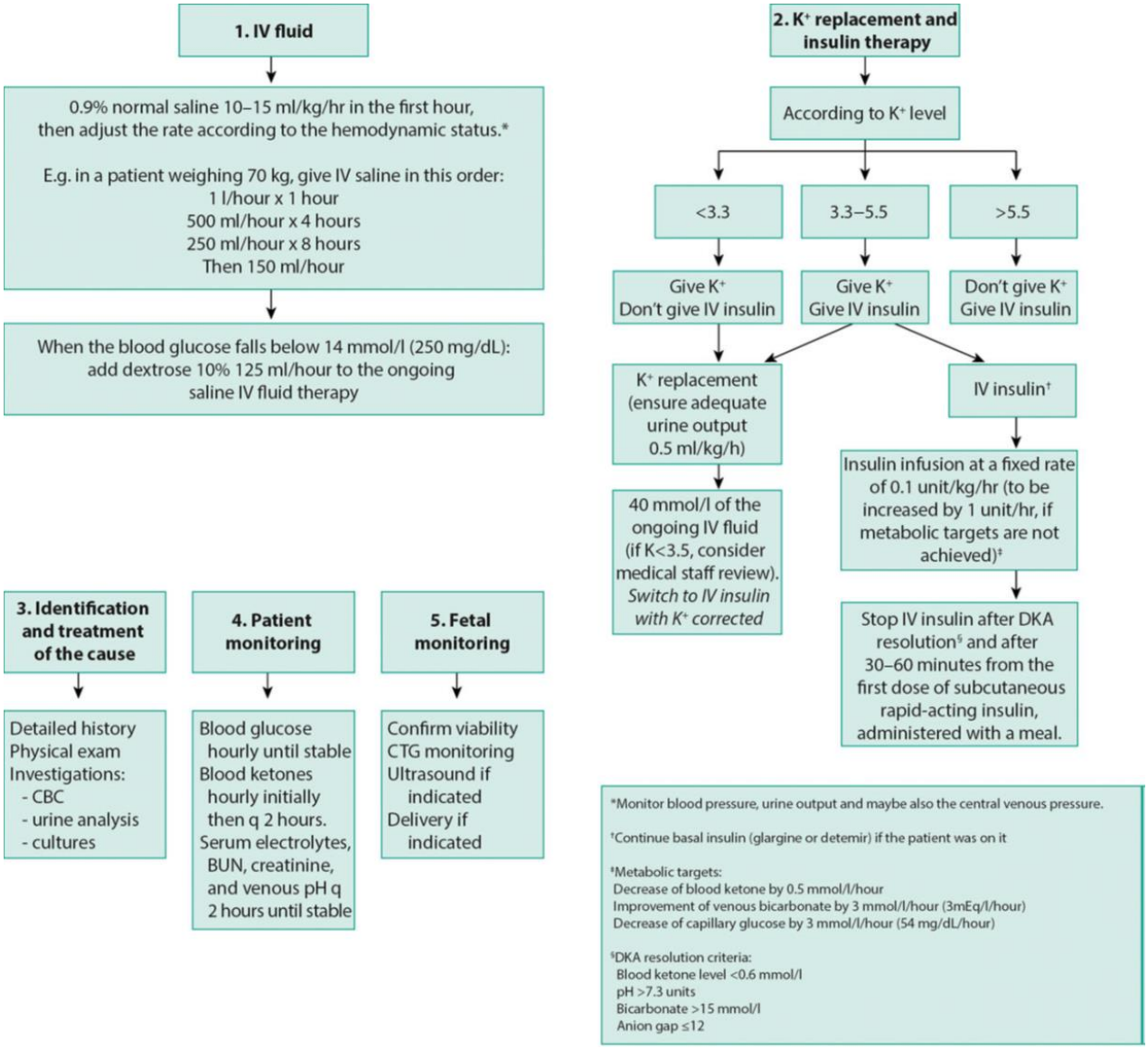


Figure 6: DKA management algorithm [10]

DKA is associated with a fluid deficit of 100ml/kg body weight [10]. Intravenous fluid therapy is done with 0.9% normal saline. If the patient presents with hypotension (systolic blood pressure < 90mmHg), resuscitation is done with 500ml of normal saline infused over 10 to 15 minutes. This is repeated if there is no improvement. Once systolic blood pressure stabilizes above 90mmHg, maintenance fluid is commenced with normal saline at a rate of 10-15ml/kg/hr for the first hour, and then adjusted according to the haemodynamic status. The haemodynamic status is monitored with blood pressure, urine output, and central venous pressure where indicated. An average 70kg woman would receive normal saline at 1l/h for the first hour, 500ml/h for the next 4 hours, 250ml/h for the next 8 hours, and thereafter 150ml/h

[10]. Intravenous fluid therapy should aim at replacing about 75% of the overall fluid deficit in the first 24 hours, and the rest in the next 24 hours [29]. Fluid therapy improves tissue perfusion and decreases stress hormones. It also causes haemodilution, which lowers hyperglycaemia and consequently improves the response to insulin therapy. Hypotonic fluids such as lactated ringers and 0.45% saline should be avoided in the initial stages since they can decrease plasma osmolarity and cause cerebral oedema. Fluid therapy must be continued until all the calculated fluid deficit is replaced.

Insulin therapy and potassium replacement depend on the initial serum potassium. There is usually a potassium deficit of 3-5mmol/kg. If potassium is < 3.3mmol/l initially, insulin therapy must be delayed until hypokalaemia is corrected. This is because insulin would drive more potassium from the extracellular to the intracellular compartment. This would aggravate hypokalaemia, which can lead to fatal cardiac arrhythmias. Potassium correction is achieved with 40mmol potassium chloride in every litre of infused normal saline. Adequate urine output is ensured before potassium replacement since potassium is excreted in the urine. This measure safeguards against hyperkalaemia, which can also lead to fatal cardiac arrhythmia.

Once hypokalaemia is corrected, insulin therapy is started at 0.1U/kg/h via a perfusor. This is increased by 1U/h every hour until metabolic targets are met. The initial dose must not exceed 15U/h. The weight used here is the current body weight. If weighing the woman is not practical at the time of diagnosis, her weight at her last prenatal visit is used. For example, in a 70kg pregnant woman, the initial dose of insulin would come to 7U/h. The constitution of insulin for the perfusor is as follows: 50U of regular insulin is drawn into 50ml of normal saline in a 50ml syringe, giving a concentration of 1U/ml. This is loaded in the perfusor which delivers the insulin at a set rate in ml/h. At a concentration of 1U/ml, every ml the perfusor delivers would contain 1U of insulin. Therefore, in the 70kg woman example, the initial rate on the perfusor would be set at 7ml/h.

Once DKA resolves, insulin is switched from intravenous infusion to a subcutaneous route when the patient can eat and drink. Insulin infusion must continue for 30 minutes to an hour after the first subcutaneous dose. Insulin therapy corrects hyperglycaemia and inhibits ongoing ketogenesis. The overlap between the first subcutaneous insulin and the insulin infusion is to prevent rebound ketogenesis during the period before the onset of action of the former. However, if the subcutaneous insulin is the analogue type with rapid onset of action, the insulin infusion is stopped right after giving the first subcutaneous insulin.

If the initial potassium is between 3.3 and 5.5mmol/l, insulin is started right away alongside potassium replacement. If initial potassium is > 5.5mmol/l, insulin therapy is commenced while potassium is withheld. Patients on long-acting insulin analogue should continue it during the initial management, as this provides background insulin when intravenous insulin is discontinued and avoids rebound hyperglycaemia and ketogenesis [14]. Insulin inhibits lipolysis and ketogenesis. Insulin therapy must not be stopped until the anion gap is closed, and acidosis resolved. It usually takes 12 to 24 hours to achieve this. Continuous intravenous insulin infusion offers several advantages over subcutaneous and intramuscular injections. These include a faster onset of action and better control and regulation of blood glucose levels. Also, it can be administered through a separate intravenous line and regulated independently of intravenous fluid therapy.

The goal of potassium replacement is to maintain serum potassium between 4 and 5mmol/l. potassium chloride is usually added to the maintenance intravenous fluids but can also be given separately.

When blood sugar falls below 14mmol/l, 10% Dextrose is given at a rate of 125ml/h alongside the normal saline infusion. Dextrose infusion should be continued until the patient can eat and drink [14]. This helps to prevent hypoglycaemia, which can stimulate the production of counter-regulatory hormones and cause ketogenesis. Hypoglycaemia can also result in cardiac arrhythmia, acute brain injury, and death.

Bicarbonate replacement is a subject of controversy and is largely not recommended [14]. Metabolism of ketoacids generates bicarbonate spontaneously. Acidosis causes a shift in the oxygen dissociation curve to the right, thereby improving oxygen delivery to the tissues (Figure 7). Acidosis also stimulates hyperventilation, which helps blow off carbon dioxide. Administration of bicarbonate slows down the breakdown of the ketoacids, shifts the oxygen dissociation curve to the left, and causes hypercapnia. Carbon dioxide crosses the blood-brain barrier more readily than bicarbonate, resulting in paradoxical cerebrospinal fluid acidosis. Hypercapnia also interferes with oxygen delivery to the fetus.

Phosphate replacement is not recommended as there is no evidence of benefit [14].

Metabolic targets to be achieved during management include the following:

1. Decrease in blood ketone levels by 0.5mmol/l/h, or

2. Increase in venous bicarbonate by 3mmol/l/h and a decrease in capillary blood glucose by 3mmol/l/h, in the absence of blood ketone monitoring [14]

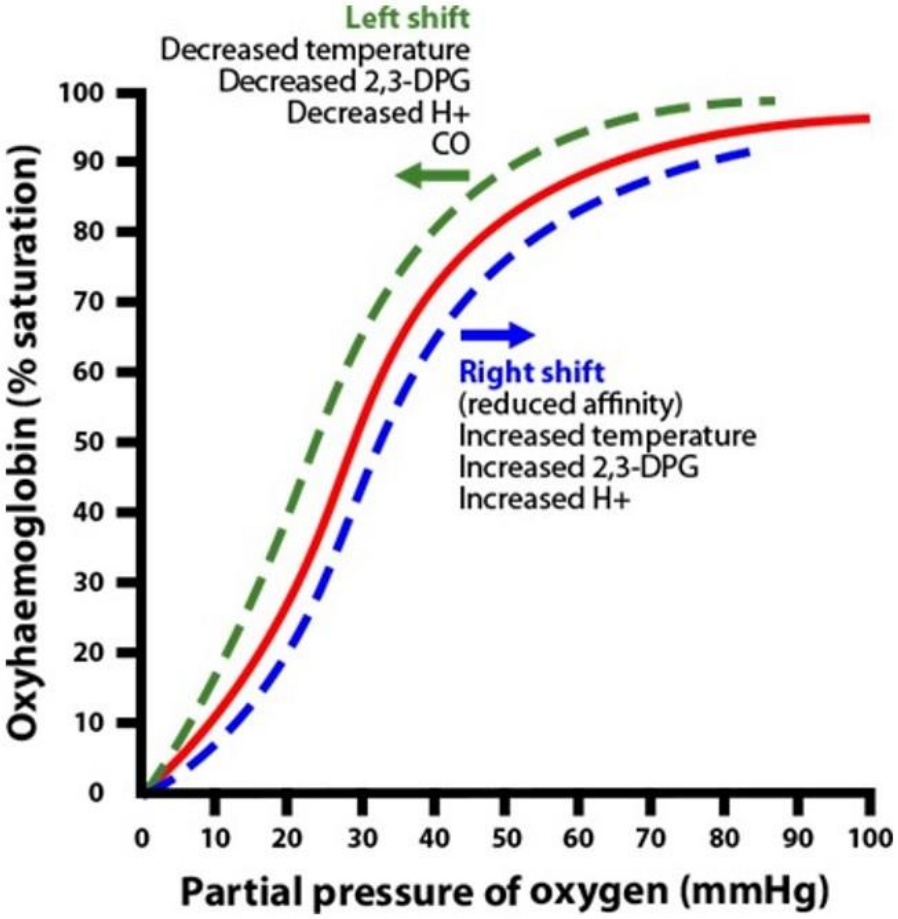


Figure 7: The oxygen dissociation curve [36]

2.6 MATERNAL MONITORING

Capillary blood glucose and blood ketones are monitored hourly for the first 6 hours. The blood ketone meter measures the main ketone body in DKA, 3-beta-hydroxybutyrate. This metabolizes to acetoacetate, which is excreted in urine and is semi-quantitatively measured as urine ketones. Therefore, ketonuria can persist long after 3-beta-hydroxybutyrate has cleared from the blood. For this reason, blood ketone monitoring is recommended over urine ketones [10].

Venous pH, bicarbonate, and serum potassium are monitored every 2 hours for the first 6 hours. After the first 6 hours bicarbonate levels are no longer reliable due to hyperchloraemic acidosis. This results from the large volume infusion of normal saline, which causes haemodilution and consequently lowers bicarbonate. The large dose of chloride however gives a normal anion gap. Potassium must be maintained between 4.0 and 5.0mmol/l [14]. The difference between venous and arterial pH (0.02 – 0.15) and that between venous and arterial bicarbonate (1.8mmol/l) are not significant enough to affect diagnosis or monitoring. Therefore, venous sampling is recommended. Arterial pH measurement is reserved for patients with hypoxia or impaired consciousness [14].

Additional investigations include a complete metabolic panel with magnesium and phosphate, full blood count, and urinalysis. These are basic tests that must be done for all patients with DKA. Other tests including urine culture, blood culture, chest x-ray, etc may be indicated based on clinical suspicion.

Resolution of DKA is defined as:

1. Blood ketone level < 0.6mmol/l
2. pH > 7.3
3. Bicarbonate > 15mmol/l
4. Normalization of anion gap (≤ 12mEq/l) [10]

2.7 MATERNAL OUTCOMES

In general, pregnant women with diabetes have an increased risk of adverse outcomes including hypertension, pre-eclampsia, and an increased rate of caesarean delivery. Women with pregestational diabetes have the added risk of developing or worsening retinopathy and nephropathy [20].

Huang *et al* demonstrated that significant ketonuria is associated with adverse maternal outcomes including postpartum haemorrhage, prolonged labour, forceps delivery, and caesarean section [23].

Maternal complications of DKA include hypokalaemia, adult respiratory distress syndrome, acute myocardial infarction, and sepsis, and these are associated with increased maternal mortality [14]. Mortality due to DKA in non-pregnant adults is <1% but the maternal mortality rate due to DKA is 5-15% [37]. In recent years, however, the maternal mortality rate has reduced to < 1% [11].

Rougerie *et al* did a retrospective study comparing DKA in pregnancy with DKA in non-pregnant women matched by age. They found that the pregnant group had fewer comorbidities including obesity, chronic hypertension, as well as diabetic neuropathy, nephropathy, and retinopathy. They were, however, hospitalized for longer and had more renal failure. The need for ventilation and the occurrence of systemic inflammatory response syndrome (SIRS), seizures, coma, and death were less in the pregnant group [6].

2.8 FETAL MONITORING

If gestational age of viability (28 weeks) has been attained, fetal monitoring must be instituted during DKA. Intrauterine resuscitation is done by placing the mother in the left lateral decubitus position, hydrating adequately, and giving supplemental oxygen. This improves placental perfusion and oxygenation.

Fetal heart tracing often demonstrates acidotic changes including minimal or absent variability and recurrent late decelerations (Figure 8). The biophysical profile also tends to be nonreassuring. The umbilical artery Doppler may show reduced, absent, or reversed end-diastolic flow while the middle cerebral artery Doppler may show evidence of redistribution. These changes mostly revert to normal after the correction of maternal DKA. It may, however, take 4-8 hours for fetal heart tracing to normalize [11].

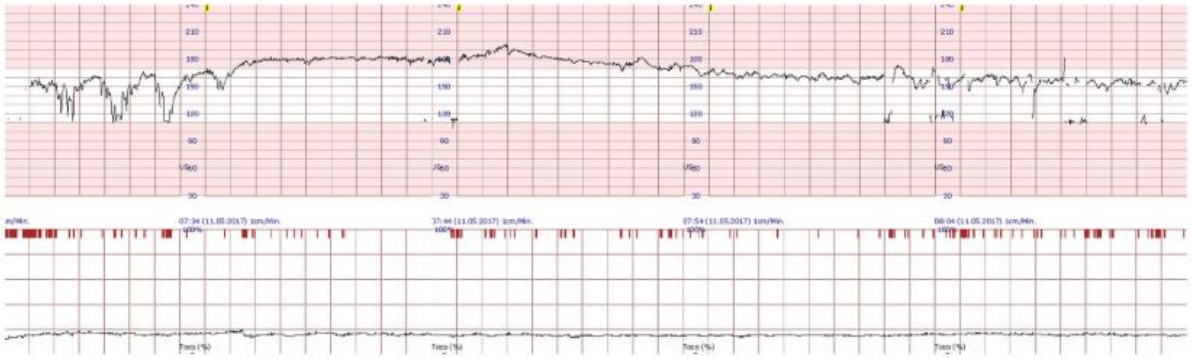


Figure 8: Cardiotocogram showing minimal variability and variable decelerations [38]

2.9 FETAL OUTCOMES

In general, diabetes in pregnancy is associated with an increased risk of developing adverse fetal outcomes including congenital anomalies, macrosomia, polyhydramnios, preterm birth, and unexplained intrauterine fetal demise [20].

In women with pregestational diabetes, the risk of congenital anomalies is especially high, and there is also an increased risk of fetal growth restriction. The commonest congenital anomalies associated with pregestational diabetes are congenital heart disease and central nervous system defects [39]. There is a positive correlation between HbA1C and congenital malformations (Figure 9). Hammouda *et al* explored this correlation and found that the risk of congenital anomalies in women who had HbA1C in the diabetes range, prediabetes range, or normal range was 27.8%, 9.8%, and 3.0% respectively [40]. For this reason, women with pregestational diabetes must have preconception care during which HbA1C is measured. These women must be advised to target HbA1C < 6.5% before embarking on a pregnancy. This is achieved through tighter glycaemic control. Women with HbA1C >10% are advised to avoid pregnancy until their HbA1C is lower. They are offered appropriate contraception while instituting tighter glycaemic control.

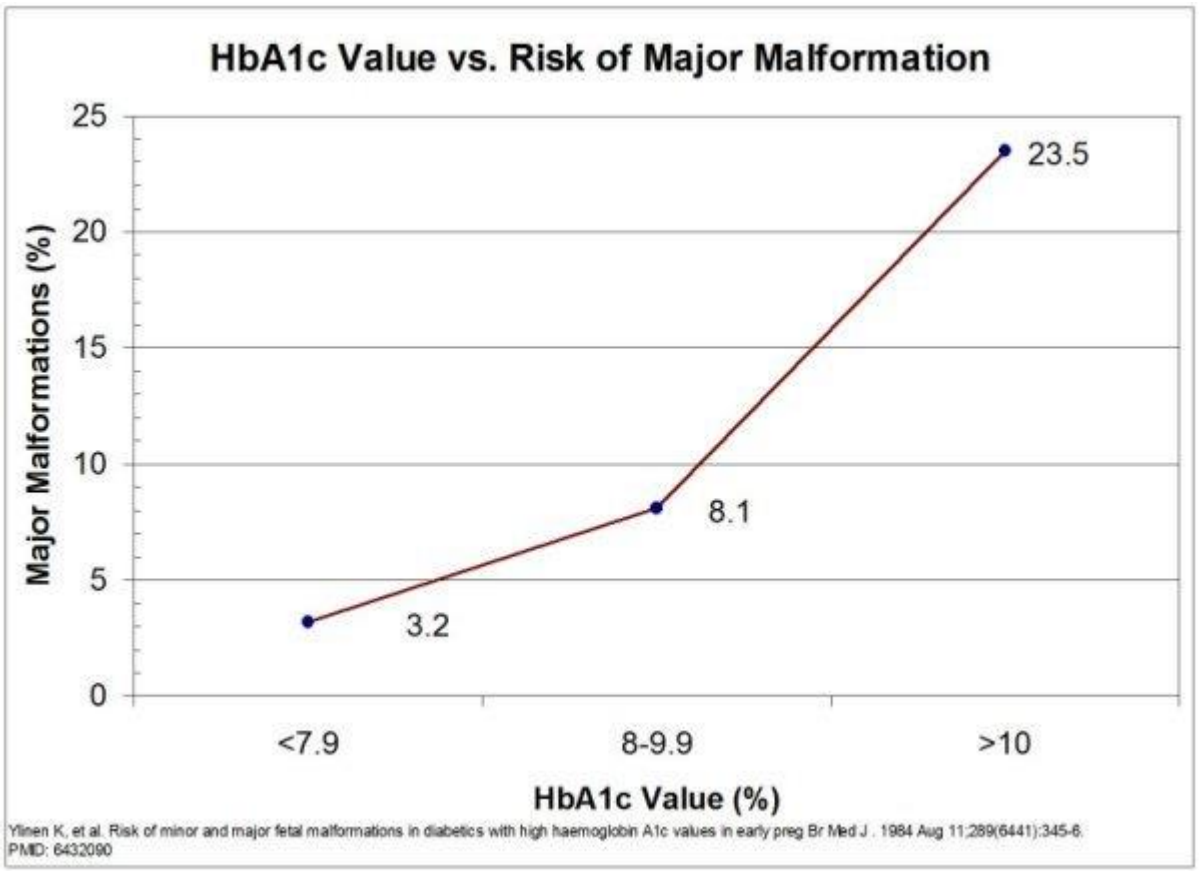


Figure 9: Correlation between HbA1C and congenital malformations [41]

About 50% of neonates born to diabetic mothers have hypoglycaemia at birth. This mostly occurs in neonates with macrosomia and those whose mothers had poor glycaemic control [9]. Throughout pregnancy, glucose, free fatty acids, and ketones are transferred from maternal to fetal circulation across the placenta. Maternal insulin does not cross the placenta. After 20 weeks gestation, fetal pancreatic islet cells produce insulin in response to hyperglycaemia. In-utero hyperglycaemia transferred from maternal circulation causes reactive fetal islet cell hyperplasia. This leads to fetal hyperinsulinaemia. At delivery, when the maternal transfer of glucose stops, the induced hyperinsulinaemia predisposes the neonate to hypoglycaemia. Tight glycaemic control during labour has been shown to decrease but not eliminate the incidence of neonatal hypoglycaemia.

Kgosidialwa *et al* did a consensus developmental study to develop a core outcome set for studies evaluating pregnant women with diabetes. They developed a core outcome set for the fetus which includes birth weight, large for gestational age, small for gestational age, gestational age at birth, preterm birth, mode of birth, shoulder dystocia, neonatal

hypoglycaemia, congenital malformations, stillbirth, and neonatal death [20]. This core outcome set helps to improve trial reporting and enable greater comparison and evidence synthesis across studies.

Some studies have found that ketonuria even without acidosis is associated with adverse fetal outcomes including non-reactive stress tests, fetal heart rate decelerations, oligohydramnios, and reduced childhood intelligence quotient (IQ) [21]. Huang *et al* observed that increasing ketonuria was associated with increasing numbers of category III fetal heart tracing, grade III meconium-stained amniotic fluid, neonatal hypoglycaemia, umbilical artery pH <7.2, low Apgar scores, and increased NICU admissions [23].

DKA predisposes fetal malformation in the first trimester, and fetal distress and fetal demise in the second and third trimesters [26]. Fetal well-being is threatened by maternal acidosis, hyperglycaemia, and hypovolaemia. Maternal dehydration and acidosis result in impaired uteroplacental perfusion. In DKA, osmotic diuresis leads to hypovolaemia and reduces uterine blood flow. The maternal hyperglycaemia reflected in the fetal circulation stimulates fetal hyperinsulinaemia, which increases oxygen consumption by the fetus. Maternal hypophosphataemia results in decreased 2,3-diphosphoglycerate. This shifts the oxygen dissociation curve to the left, increasing maternal oxygen affinity and reducing oxygen delivery to the fetus. Also, maternal ketoacids cross the placenta and cause decreased fetal perfusion and oxygenation. After crossing into the fetal circulation, these ketoacids can also dissociate into anions and cause fetal metabolic acidosis. All these factors contribute to fetal hypoxia. The fetus is very sensitive to maternal acidosis due to its limited ability to buffer significant acidaemia. Also, maternal hypokalaemia is reflected in fetal circulation. This is further aggravated by fetal hyperinsulinaemia and can result in fetal cardiac arrhythmias.

Fetal mortality ranges from 9 to 36% and in recent times has reduced towards the lower end of the spectrum [24]. Earlier reports estimated fetal mortality as high as 50 to 85%. Baagar *et al* recorded 16% fetal loss and 40% NICU admissions in their study [2]. Schneider *et al* recorded fetal mortality of 27% [42]. In a study by Bryant *et al*, there were 55% of preterm deliveries [27]. Preterm delivery is contributed by both spontaneous preterm labour and iatrogenic delivery. In a study by Morrison *et al*, fetal demise occurred in 15.6% of cases. Risk factors for this outcome included maternal ICU admission and higher serum osmolality. Preterm delivery occurred in 43.6%. Risk factors for this outcome included maternal smoking and higher pre-DKA HbA1C. Neonatal intensive care unit (NICU) admissions occurred in

59%. Risk factors included maternal smoking, pre-eclampsia, higher anion gap during the DKA event, and preterm delivery [43]. Glucose uptake by the fetal brain is interfered with by 3-beta-hydroxybutyrate and lactate and can result in brain injury with long-term neurodevelopmental defects [44].

2.10 DELIVERY

An immediate caesarean section before the mother is stabilized increases the risk of maternal mortality, thus delivery is usually avoided until the maternal condition is ameliorated. Stabilization of the maternal metabolic condition usually leads to correction of the fetal heart rate abnormality. Generally, the aim is to correct the DKA and allow the pregnancy to continue. Delivery for fetal indications is reserved for cases with persistent fetal impairment (e.g. persistent bradycardia) even after correcting DKA. In a study by Baagar *et al*, 70% of cases of DKA in pregnancy were managed successfully and the pregnancy continued [2].

2.11 EUGLYCAEMIC DKA

Euglycaemic DKA is ketoacidosis in a diabetic with normal or low blood glucose. It was first described by Munro *et al* as ketoacidosis with plasma bicarbonate ≤ 10mEq/l and blood glucose < 16.7mmol/l. About 0.8 to 1.1% of DKA in pregnancy are euglycaemic [45].

The pathophysiology (Figure 10) is explained by increased glucose consumption by the fetoplacental unit, increased renal excretion of glucose due to increased glomerular filtration without corresponding tubular reabsorption, increased maternal utilization of glucose, haemodilution, and starvation with depletion of glycogen stores [10]. It is observed after 18 hours of starvation in pregnant women, compared to 36 hours for the non-pregnant [46]. Management is the same except for the addition of 5% Dextrose from the beginning to prevent hypoglycaemia since insulin infusion is still required to halt ketogenesis.

Guo *et al* presented a case report on a nulliparous woman at 32 weeks with a poor appetite who presented with a blood glucose of 6.9mmol/l, ketonuria, anion gap 14, pH 7.29, and bicarbonate 9mmol/l [26]. In a study by Baagar *et al*, 50% of cases of DKA in pregnancy presented with blood glucose < 11.1mmol/l, and in 20%, < 7.8mmol/l [2]. Tarif *et al* also reported on a case of DKA with presenting blood glucose of 4.3mmol/l. Suarez *et al* also reported euglycaemic DKA in a patient with presenting blood glucose of 9.2mmol/l [47]. The

common thing about all these cases is that the DKA was precipitated by vomiting, starvation, and omission of insulin doses. Graham *et al* were the first to publish a case report of euglycaemic DKA in a gestational diabetic, with presenting plasma glucose of 3.3mmol/l [48]. Chausse *et al* presented a case report on a woman with euglycaemic DKA whose diagnosis was missed at primary and secondary care hospitals and only picked up at the tertiary hospital. This caused a delay in management, eventually leading to fetal demise at 36 weeks [49]. This underscores the need for a high index of suspicion. The use of sodium-glucose co-transporter-2 (SGLT2) inhibitors among women who have pregestational diabetes must be explored as this is a common cause of euglycaemic DKA.

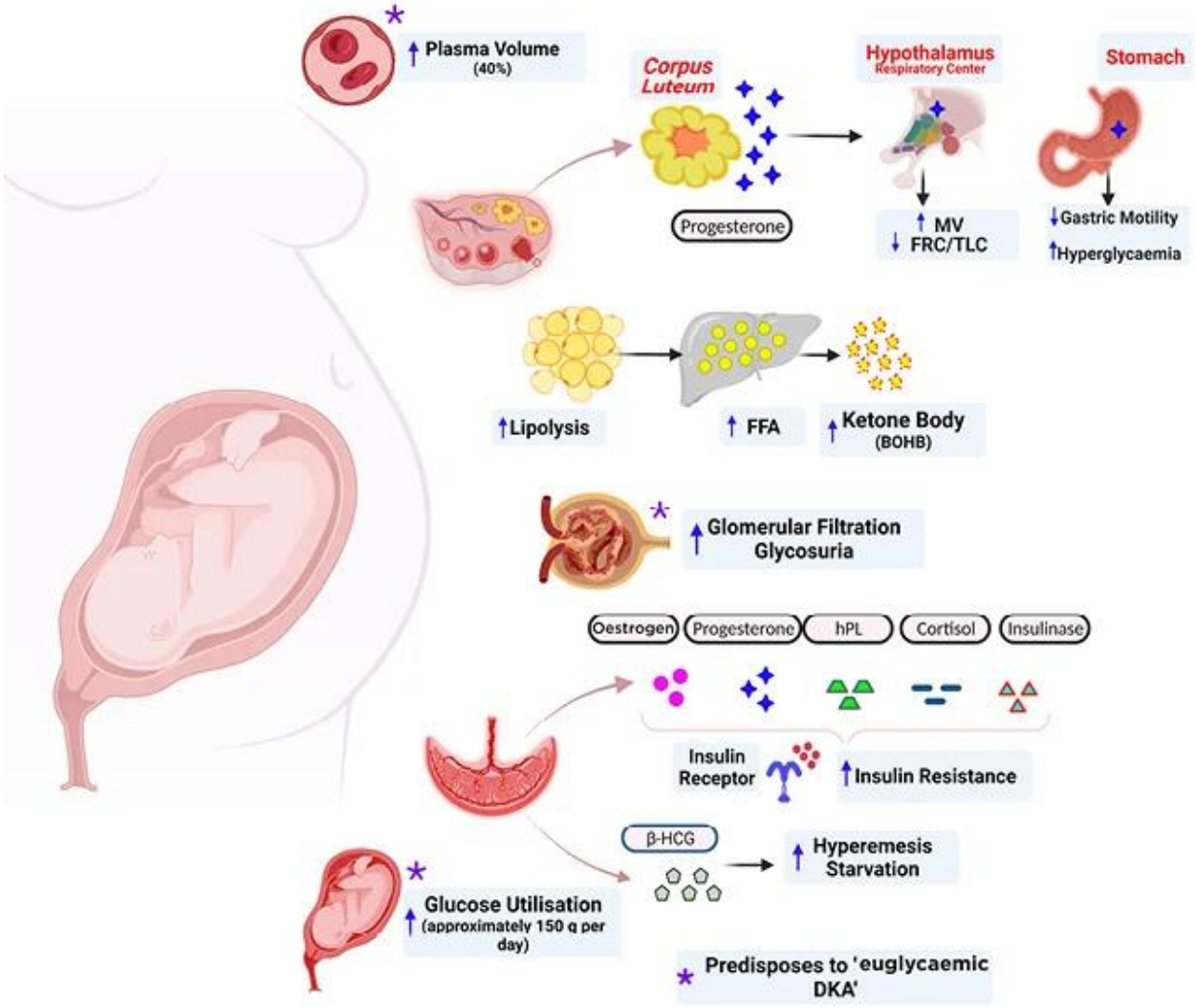


Figure 10: Pathophysiology of euglycaemic DKA [50]

2.12 PREVENTION

Preventive measures during the preconception period include the following:

Diabetic women should be educated on DKA and its complications in pregnancy, as well as the tell-tale signs. Self-monitoring of blood glucose at home should be encouraged. Whenever blood glucose is high or a diabetic woman feels sick, she should test for blood ketones if a meter is available, or at least urine ketones, and then report to the hospital. Preconception care is essential for all diabetics to ensure blood glucose is well-controlled with HbA1C < 6.5% before embarking on pregnancy. Contraception must be offered while awaiting optimization before pregnancy.

Preventive measures during pregnancy include the following:

Diabetes in pregnancy should be managed by a multidisciplinary team. The general obstetric population should be screened for DM. Diabetic pregnant women should be educated on the precipitating factors and clinical features of DKA. Self-monitoring of blood glucose should be encouraged. There should be a high index of suspicion for DKA in pregnancy. Corticosteroid treatment should be accompanied by an adjusted insulin dose or sliding scale. Agents other than betamimetics should be used for tocolysis.

CHAPTER 3: MATERIALS AND METHODS

3.1 STUDY DESIGN

This was a prospective cohort study.

3.2 STUDY SITE

The study was conducted in the Department of Obstetrics and Gynaecology, Korle Bu Teaching Hospital (KBTH).

Korle Bu Teaching Hospital

The Korle Bu Teaching Hospital is in Accra, Ghana. It is within the Ablekuma Sub-district of the Accra Metropolitan area. It has a 2000-bed capacity with a total OPD attendance of about 320 patients per day. It is the third-largest hospital in Africa. KBTH is Ghana's premier teaching hospital. It was established in 1923 by the then British Colonial Government under the leadership of Sir Frederick Gordon Guggisberg, the Governor of the then Gold Coast.

Korle Bu Teaching Hospital has a staff strength of about 3000. This consists of 400 doctors and about 1150 nurses. The rest are mainly auxiliary staff.

The hospital is a tertiary centre that serves the southern part of Ghana which is home to about a third of the whole country's population. It is the teaching hospital that serves as a training site for medical students at the University of Ghana Medical School as well as residents or postgraduate students from the Ghana College of Physicians and Surgeons, the West African College of Surgeons, the West African College of Physicians, etc.

The hospital has six clinical departments including the Surgery, Medicine and Therapeutics, Child Health, Obstetrics and Gynaecology, Polyclinic, and Accident and Emergency departments. The Department of Surgery comprises the General Surgical unit, Neurosurgery, Ophthalmology, ENT, Urology, and Orthopaedics units.

There are four other specialized clinical centres within its premises. These are the Cardiothoracic Unit, the Reconstructive, Plastics and Burns Centre, Radiotherapy and Nuclear Medicine Centre and the Audiology and Hearing Assessment Centre.

The Para-clinical departments include Pharmacy, Physiotherapy, and Diet Therapy.

The non-clinical departments include a Central Administration, Finance and Accounts, Kitchen, Laundry, Estates, Maintenance, and Engineering.

The Department of Obstetrics and Gynaecology, KBTH.

The Obstetrics and Gynaecology Department has a bed capacity of 415, of which 302 are found in Obstetrics and 113 are in Gynaecology. The department has 5 units named teams A, B, C, D, and E. Each unit has an assigned floor in the maternity block to which antenatal and postnatal cases are admitted. Also located in the maternity block is the sixth floor which is an amenity unit. The maternity block also has facilities on the ground floor for antenatal and postnatal clinics, fetal assessment centre, as well as emergency obstetric care.

The department is led by the Head of Department who has both administrative and academic oversight. Each unit is headed by a Senior Consultant with two or three other Consultants who supervise the work and training of Senior Residents, Junior Residents, and House Officers. The residents rotate through the 5 units during their period of training. Each Unit has specific days in the week for an antenatal clinic, gynaecology clinic, operating theatre sessions, and grand ward rounds. The on-call or duty days for the five working days are fixed for the units. The weekend duties rotate among the 5 teams. The on-call days for the week are also antenatal clinic days and the team-on-duty attends to all emergencies reporting to the department as well as on the wards. The labour ward is also managed by the team on duty.

Currently, there are five sub-specialty units in the department. These include Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, Gynaecologic Oncology, Urogynaecology, and Reproductive Health units. There are fellows in each of these units who are sub-specializing under the Ghana College of Physicians and Surgeons.

Patients attended to in the department are of various socioeconomic, cultural, and religious backgrounds. The average daily attendance at the antenatal clinic is 90. The maternity unit conducts approximately 9,500 deliveries annually. About 45 to 50% of deliveries are by caesarean section.

Sources of referrals

The department receives referrals from polyclinics, private clinics, maternity homes, and other hospitals (district and regional hospitals) both in the Greater Accra Region and other

regions in the southern part of Ghana. Some of these facilities function solely as clinics and attend to antenatal cases but do not have delivery suites. They, therefore, refer cases to be planned for delivery.

Labour ward

The department has two labour wards, one on the first floor of the maternity block and the other on the second floor. There are 18 first-stage beds. These are convertible for use in the dorsal lithotomy position during the second stage of labour. There is an ultrasound machine in the labour ward. A doctor's restroom is available in the labour ward to ensure 24-hour cover by obstetrics and anaesthesia residents.

There are three operating theatres but only two are currently functional. There are two recovery wards. The main one is located on the first-floor labour ward and has a 4-bed capacity. High-risk cases are sent there for recovery following surgery. It also doubles as our high-dependency unit where severely ill patients including pregnant women with DKA are managed. The second is the recovery annex which is located on the first-floor maternity ward. Low-risk cases are sent there for recovery after surgery. It has a 3-bed capacity.

Patients are admitted to the labour ward either from home through the obstetric emergency or antenatal wards as routine labour cases or referred with either a complication of labour or an obstetric emergency such as eclampsia or obstetric haemorrhage.

The Dr J. O. Armah Fetal Assessment Centre

This only used to be a basic obstetric ultrasound unit but has now evolved into a full-fledged fetal assessment centre since the inception of the Maternal-Fetal Medicine Program whose faculty and fellows run the place. The centre houses an ultrasound unit, a non-stress test unit, a high-risk clinic, and a simulation unit (Figure 11). All obstetric ultrasound scans including first-trimester scans for nuchal translucency and anatomy survey, fetal anomaly scans, growth scans, fetal doppler scans, etc are done here. The high-risk clinic provides multidisciplinary team care for high-risk cases including sickle cell disease, diabetes, renal, and autoimmune disease in pregnancy. The simulation centre has artificial intelligence-based ultrasound simulation as well as models and set-ups for obstetric emergency simulations. The fetal assessment centre serves as a training site for residents in the department, radiology, paediatrics, as well as residents from 37 Military Hospital. Other services provided in this centre include prenatal screening and invasive fetal testing like amniocentesis.

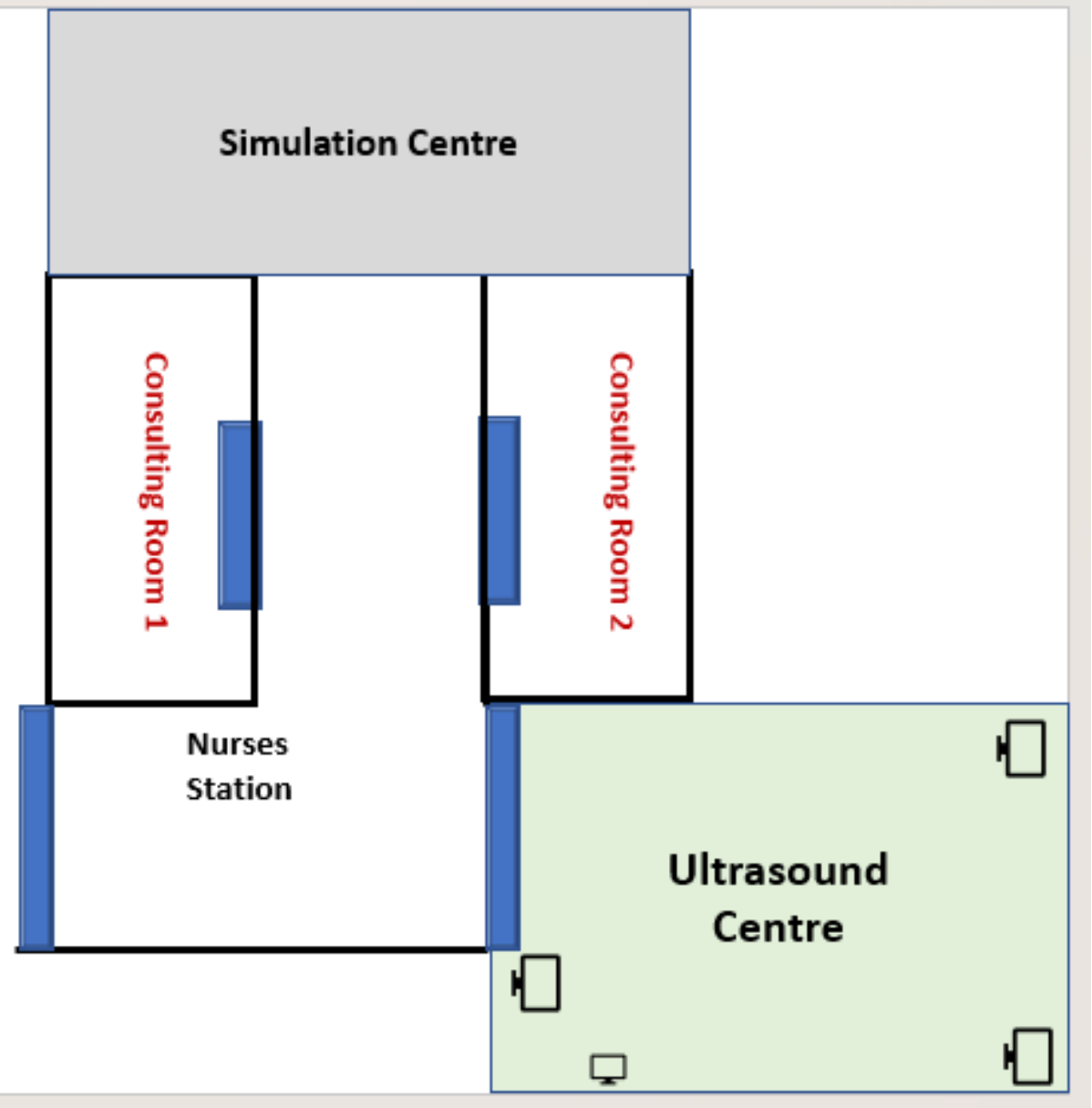


Figure 11: Layout of the Dr J. O. Armah Fetal Assessment Centre

Neonatal Intensive Care Unit (NICU)

An ultra-modern Neonatal Intensive Care Unit (NICU) is located on the 3rd floor of the maternity block and provides a 24-hour neonatal service. A Neonatologist is called to attend deliveries of extremely preterm babies and other high-risk pregnancies. All macrosomic babies, preterm babies, babies of diabetic mothers, and babies with congenital anomalies are transferred to the NICU.

Reproductive Health and Family Planning Unit

This unit is close to the maternity block. It was formerly called the family planning unit. The unit offers services on working days and offers a wide range of family planning methods. These include oral and injectable hormonal contraceptives, barrier methods, subdermal

implants, intrauterine contraceptive devices, and sterilizations. It is run by doctors and trained nurses. Currently, the unit is offering additional services in colposcopy and Pap smear.

Gynaecology Unit

The gynaecology unit is located a distance apart from the obstetrics unit of the department in the old Guggisberg blocks of the hospital. It comprises an outpatient clinic, wards, and a theatre complex that contains three separate functional theatres for both major and minor gynaecological procedures.

Outpatient clinic

The five units of the department take turns running the clinic from Monday to Friday. All varieties of gynaecological cases including early pregnancy complications are seen. Office procedures such as endometrial biopsies and Pap smears are performed at the clinic. Approximately 60 patients are attended to at the clinic each day.

Emergency room

Twenty-four-hour care is provided for all gynaecological emergencies coming to the hospital. The room is manned by the team on duty with a stationed House Officer and a Resident. Common emergencies seen here include miscarriages and their complications, ectopic pregnancies, and acute pelvic inflammatory disease.

Wards

There are three wards in the gynaecology unit. Ward E which has 33 beds caters to patients who are admitted for elective surgery. The two other wards Chenard Main and Chenard Annex together have 80 beds and cater for emergency cases as well as patients with malignancies.

Theatre

There are three operating rooms. Elective and emergency gynaecological surgeries are carried out here. One of the operating rooms houses a laparoscopy tower and that is where all diagnostic and interventional laparoscopies and hysteroscopies are carried out.

3.3 STUDY POPULATION

The study population was pregnant women with diabetes (known and newly diagnosed) presenting at the obstetrics ER or the labour ward, and those on admission at KBTH.

3.4 STUDY DURATION

The study spanned between 1st September 2021 and 28th February 2022.

3.5 ELIGIBILITY CRITERIA

The inclusion and exclusion criteria were as follows:

3.5.1 Inclusion criteria

- Pregestational Diabetes Mellitus
- Gestational Diabetes Mellitus
- Newly diagnosed diabetes in pregnancy

3.5.2 Exclusion criteria

- Renal disease in pregnancy

3.6 SAMPLING METHOD AND PROCEDURES

Consecutive sampling was done. Pregnant women with gestational DM, pregestational DM, or newly diagnosed DM who were seen at the obstetric ER or labour ward or admitted to the maternity ward for blood glucose control were all approached for recruitment. Written consent was sought from those who met the eligibility criteria.

For those who gave informed consent, a questionnaire was administered to obtain their demographic information and obstetric history. After filling out the questionnaire their urine was sampled and tested for ketones using the urine ketone dipstick. For those with urine ketones $\geq 2+$, a venous blood sample was taken and tested for pH and/or bicarbonate using the blood gas analyzer. Those with pH < 7.3 or bicarbonate < 15mmol/l were diagnosed as DKA. By this methodology, some women were screened more than once since screening was repeated at every admission even if they had previously been screened.

Women who developed DKA and recovered were still screened at subsequent admissions to pick up recurrent DKA.

DKA cases were managed according to the management protocol for DKA in pregnancy collaboratively developed by the departments of Obstetrics and Gynaecology and Internal Medicine of the Korle-Bu Teaching Hospital.

The screening was done over 6 months from 1st September 2021 to 28th February 2022.

The incidence of DKA in pregnancy was calculated as follows:

Incidence = (number of new cases of outcome) ÷ (number of people at risk of outcome) x 100%

= (number of DKA cases) ÷ (number of women screened) x 100%

All the women were followed up for maternal and fetal outcomes. The maternal outcomes included:

i. Admission to the intensive care unit (ICU)
ii. Mode of delivery
iii. Length of hospital stay
iv. Pre-eclampsia
v. Maternal mortality

The fetal outcomes included:

i. Polyhydramnios
ii. Macrosomia
iii. Congenital anomalies
iv. Abnormal fetal heart tracing
v. Fetal demise
vi. Preterm birth
vii. Apgar scores
viii. Neonatal hypoglycaemia
ix. Admission to the neonatal intensive care unit (NICU)
x. Early neonatal death

3.8 DATA MANAGEMENT AND ANALYSIS

Informed consent was obtained from participants. Confidentiality was ensured using alphanumeric codes rather than names. All files were locked in a cabinet only accessible to the researcher and research assistants. All computer files were password protected.

All data were checked for completeness and inconsistencies were resolved. Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 23. Demographic features, obstetric history, and clinical and biochemical profiles were analyzed using frequency, proportions, and mean ± standard deviation or median with interquartile range and presented in tables and charts. The Kolmogorov-Smirnov (K-S) and Shapiro-Wilk tests were used to assess the normality of the quantitative variables. The mean was determined for parametric variables and the median was determined for non-parametric variables.

The entire group was analyzed for maternal and fetal outcomes. Maternal outcomes analyzed included ICU admission, mode of delivery, length of hospital stay, and maternal mortality. Fetal outcomes analyzed included fetal heart tracing, fetal demise, gestational age at fetal demise, gestational age at delivery, prematurity, gender, condition of baby, Apgar score at 5 minutes, birth weight, multiple gestation, polyhydramnios, congenital anomalies, neonatal hypoglycaemia, NICU admission, duration of NICU admission, and early neonatal death.

The association between DKA and maternal characteristics, maternal outcomes as well as fetal outcomes was determined by logistic regression using a confidence interval (CI) of 95%. Odds ratios were obtained and measurements with p-value <0.05 were deemed statistically significant. Multivariate analysis was done to control for confounders and adjusted odds ratios were determined.

3.9 ETHICAL AND LEGAL CONSIDERATIONS

The Ghana College of Physicians and Surgeons approved the study to be conducted after reviewing the proposal. The research proposal was submitted to the Korle Bu Teaching Hospital Scientific and Technical Committee/ Institutional Review Board, and they gave ethical clearance. Permission was also sought from the Department of Obstetrics and Gynaecology of the Korle Bu Teaching Hospital to conduct the study in the department, and it was granted. The purpose of the study and its benefits were thoroughly explained to the study participants and informed consent was obtained. There was no form of coercion, and the

women were assured of no fear of penalty should they decline to participate. All participants were assured of confidentiality. There was no conflict of interest.

CHAPTER 4: RESULTS

4.1 OVERVIEW

All pregnant women with diabetes who came for admission to Korle Bu Teaching Hospital and met the eligibility criteria were recruited after obtaining consent. Over the recruitment period from 01 September 2021 to 28 February 22, a total of 258 pregnant women with diabetes were admitted and there were 3,369 deliveries in all. The prevalence of diabetes among these women was 7.7%. Out of these 258 women with diabetes, 234 (90.7%) were recruited. These women were all followed up till delivery, except for one who was lost to follow-up. The loss to follow-up was excluded from the analysis. Forty-four of the women had urine ketones ≥2+. Out of these six had DKA (Figure 15).

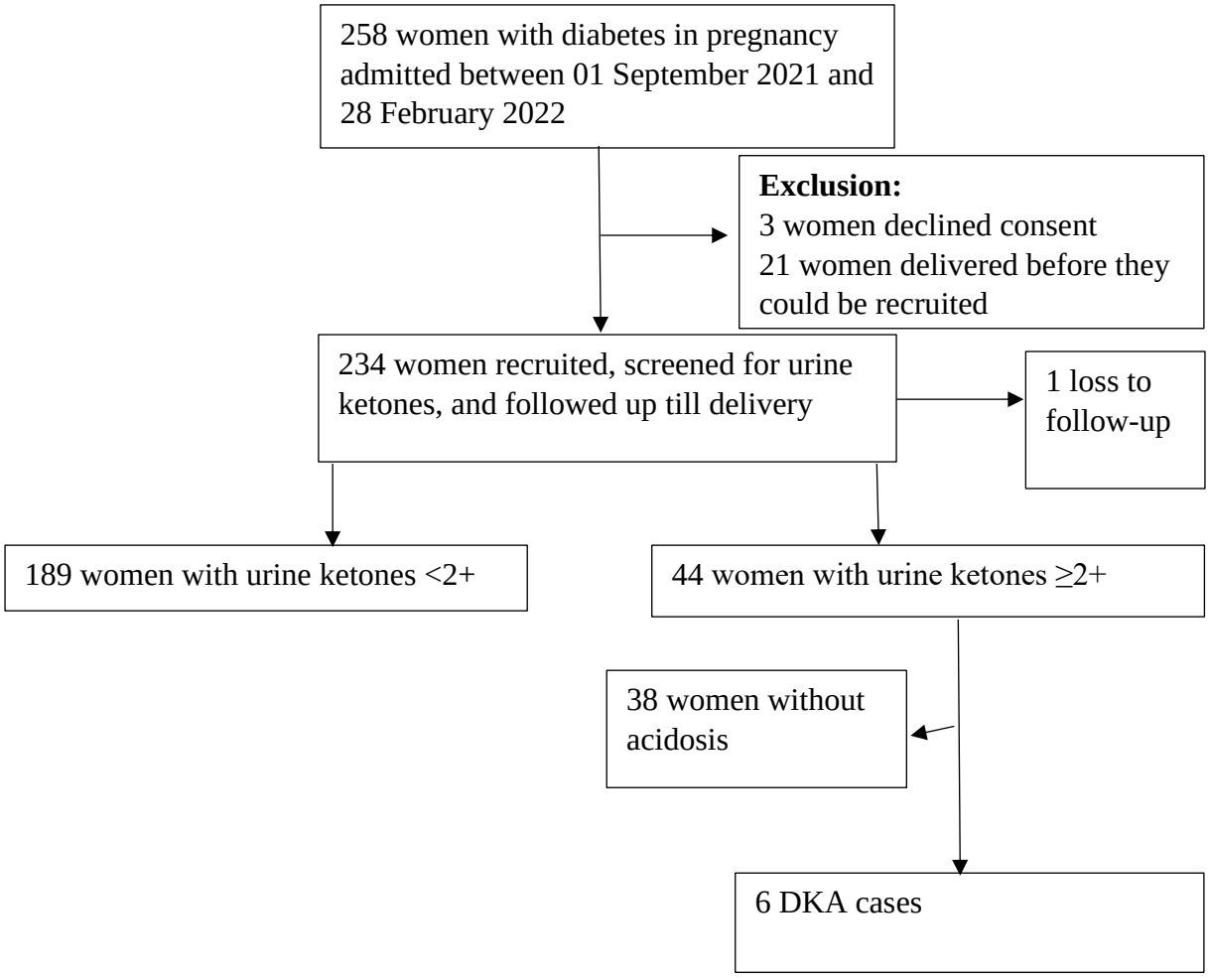


Figure 12: Overview of study process

4.2 DEMOGRAPHIC DETAILS

Table 3 summarizes the demographic details of the study participants. The mean age was 33.8 (SD = 4.6). The age distribution is demonstrated in figure 13. Most of them were married (87.1%), had tertiary education (45.5%), and were Christian (91.4%). Family history of diabetes was positive for nearly half of them. Only a minority (13.7%) had pre-gestational diabetes, out of which there was only one type 1 DM. All the rest had gestational diabetes (diabetes diagnosed for the first time during the index pregnancy).

Table 3: Maternal demographic characteristics of pregnant women with diabetes

Characteristics (N=233)		**Values**
Age		33.8±4.6
Marital status	Single	16 (6.9)
	Married	203 (87.1)
	Co-habiting	13 (5.6)
	widowed	1 (0.4)
Level of education	None	10 (4.3)
	Basic School	60 (25.8)
	Senior High School	57 (24.4)
	Tertiary	106 (45.5)
Religion	Christianity	213 (91.4)
	Islam	20 (8.6)
Positive family history of diabetes mellitus		107 (45.9)
Type 1 diabetes		1 (0.4)
Type 2 diabetes		31 (13.3)
Gestational diabetes		201 (86.3)

Values are given as mean ± SD or number (percentage).

4.3 OBSTETRIC HISTORY

The median gravidity was 3 (3-5) and parity 1 (1-2). A quarter of the women had a previous history of macrosomia and over a fifth had a previous history of diabetes in pregnancy. Most women booked in the first trimester at a mean gestational age of 12 (SD = 4.1) weeks. Multiple gestations made up 4.3% and polyhydramnios complicated 4.7% of the pregnancies. The median gestational age at enrolment was 35 (30-38) weeks. This is summarized in table 4.

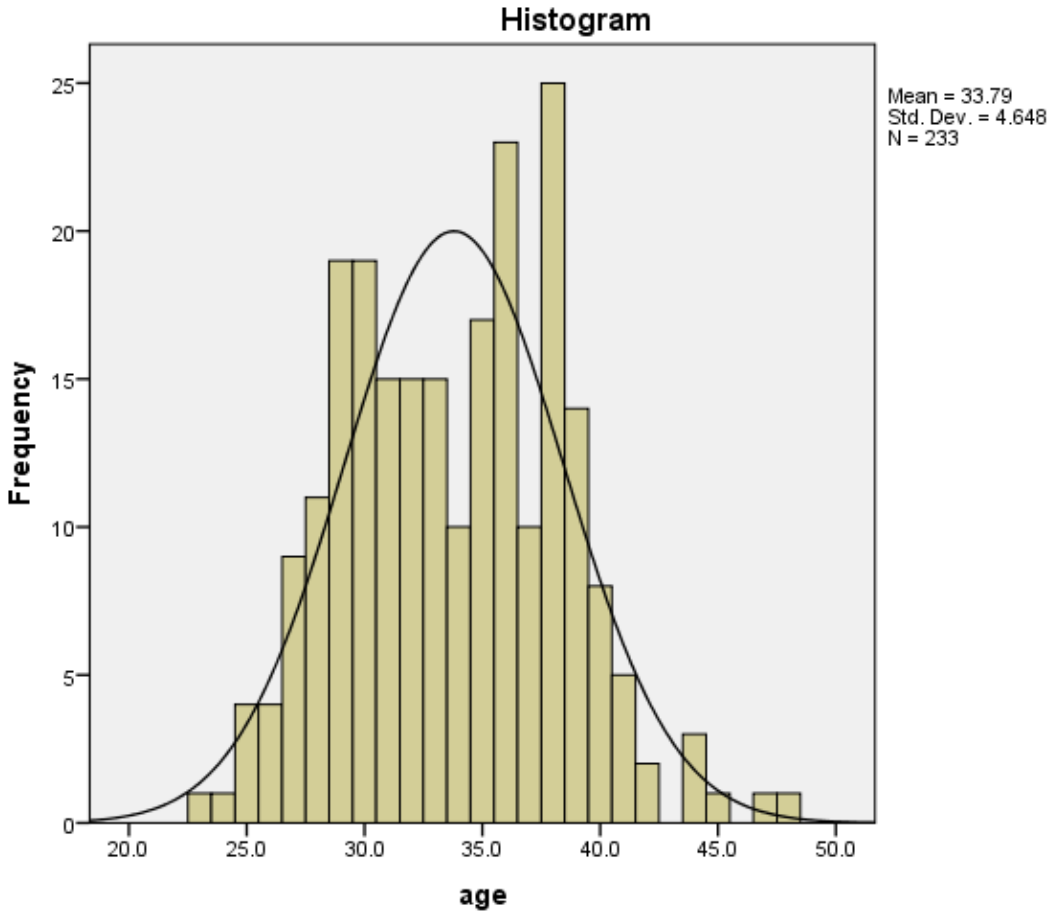


Figure 13: Age distribution

Table 4: Obstetric history of pregnant women with diabetes

Characteristics (N=233)	Values
Gravidity	3 (2-5)
Parity	1 (1-2)
Number of pregnancy losses	0 (0-1)
Number of previous stillbirths or neonatal deaths	0
History of previous macrosomia	59 (25.3)
Previous history of diabetes mellitus in pregnancy	51 (21.9)
Gestational age at booking/ dating ultrasound (weeks)	12.1±4.1
Multiple gestation in the current pregnancy	10 (4.3)
Polyhydramnios in the current pregnancy	11 (4.7)
Gestational age at enrolment (weeks)	35 (30-38)

Values are given as median (interquartile range), mean±SD, or number (percentage).

4.4 CLINICAL AND BIOCHEMICAL PROFILE AT RECRUITMENT

At recruitment, the mean random blood glucose was 7.8 (SD = 3.5) mmol/l. Nearly a fifth had significant ketonuria (urine ketones ≥2+) (Figure 14) and from that group, the mean serum bicarbonate was 18.7 (SD = 4.7) mmol/l. Over half of the women had no comorbidities. The commonest comorbidities were hypertension (23.6%) and pre-eclampsia (15.0%). Eight percent of them had multiple comorbidities. This is summarized in table 5.

Table 5: Clinical and biochemical profile at recruitment

Characteristics (N=233)		Values
Random blood glucose (mmol/l)		7.8±3.5
Urine ketones	<2+	188 (81.1)
	≥2+	44 (18.9)
pH (n=17)		7.4±0.1
Serum bicarbonate (n=43)		18.7±4.7

Comorbidities	Hypertension	55 (23.6)
	Pre-eclampsia	35 (15.0)
	IUGR	4 (1.7)
	Hyperthyroidism	2 (0.8)
	Placenta praevia	5 (2.1)
	None	133 (57.1)

Values are given as mean ± SD or number (percentage).

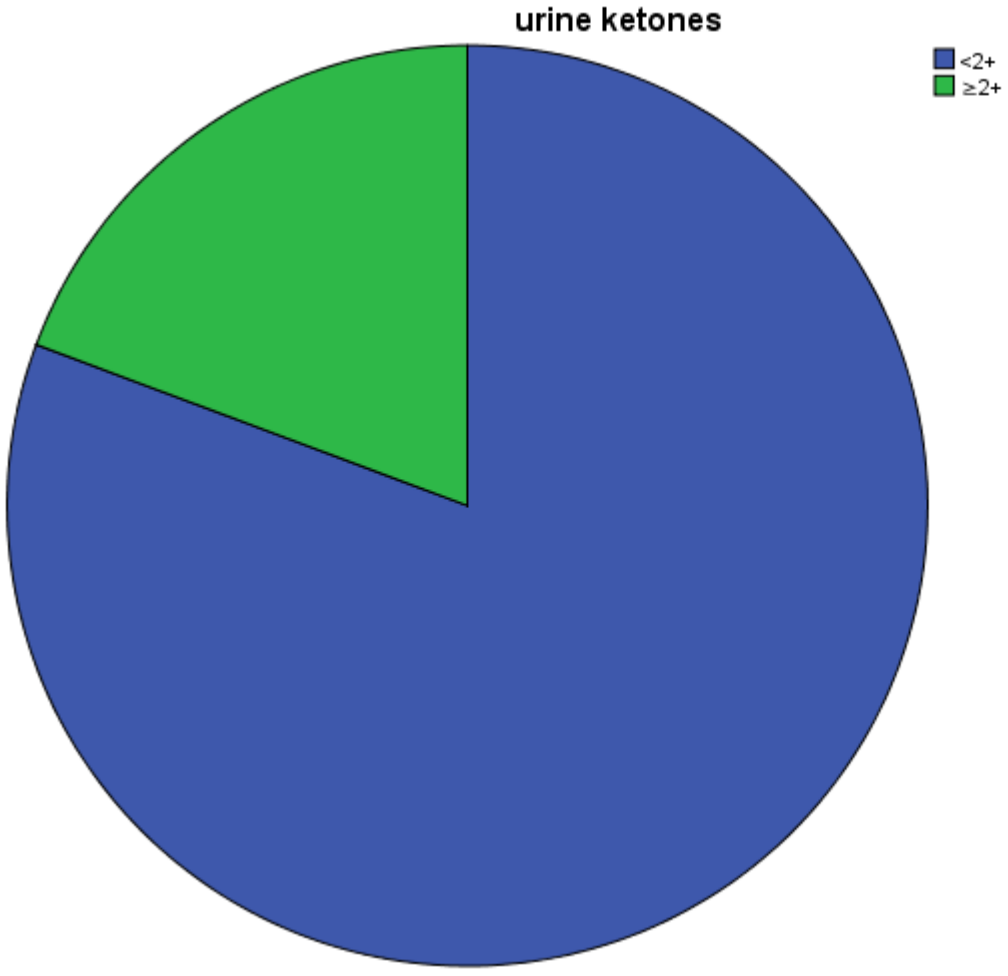


Figure 14: Proportion of significant ketonuria

4.5 MATERNAL OUTCOMES

Six women had DKA over the study period. By this the incidence of DKA was calculated as follows:

Incidence of DKA = (number of DKA cases) ÷ (number of women screened) x 100%

= 6 ÷ 233 x 100%

= 2.6% (Figure 15)

A third of them developed DKA in the first trimester and the rest (66.7%) developed it in the second and third trimesters. Half of the DKA cases occurred in women with pregestational DM and the other half in gestational DM. The incidence of DKA was 9.4% among women with pregestational diabetes and 1.5% among women with gestational diabetes. There were two cases of euglycaemic DKA (33.3%). One case was precipitated by protracted vomiting (16.7%) and one by infection (16.7%). Two cases were newly diagnosed diabetics (33.3%) and two had poor glucose control (33.3%). Each of the DKA cases was managed using the protocol outlined in appendix III. All of them recovered from DKA. One was delivered on the same day DKA was diagnosed, another was delivered 3 days after diagnosis. All the rest were delivered remotely from the time DKA was diagnosed, with a median interval between DKA diagnosis and delivery of 21 weeks. None of them had a recurrence of DKA.

Three women (1.3%) out of the entire study population were admitted to the ICU. The median length of hospital stay was 5 (4-11) days (Figure 16). Unfortunately, there were 3 maternal mortalities, giving a case fatality rate of 1.3% and a maternal mortality ratio of 1,339 per 100,000 live births. Nearly two-thirds of the women had caesarean delivery. Previous caesarean delivery was the most common indication (48.0%). Majority of those who delivered vaginally had induction of labour (60.0%). This is summarized in table 6.

Table 6: Maternal outcomes among pregnant women with diabetes

Characteristics (N=234)		Values
DKA		6 (2.6)
ICU admission		3 (1.3)
Mode of delivery		
Vaginal, n = 80 (34.3)	Spontaneous	32 (40.0)
	Induced	48 (60.0)
Caesarean, n = 153 (65.7)	Elective	81 (52.9)
	Emergency	72 (47.1)
Length of hospital stay (days)		5 (4-11)
Maternal mortality		3 (1.3)

Values are given as median (interquartile range) or number (percentage).

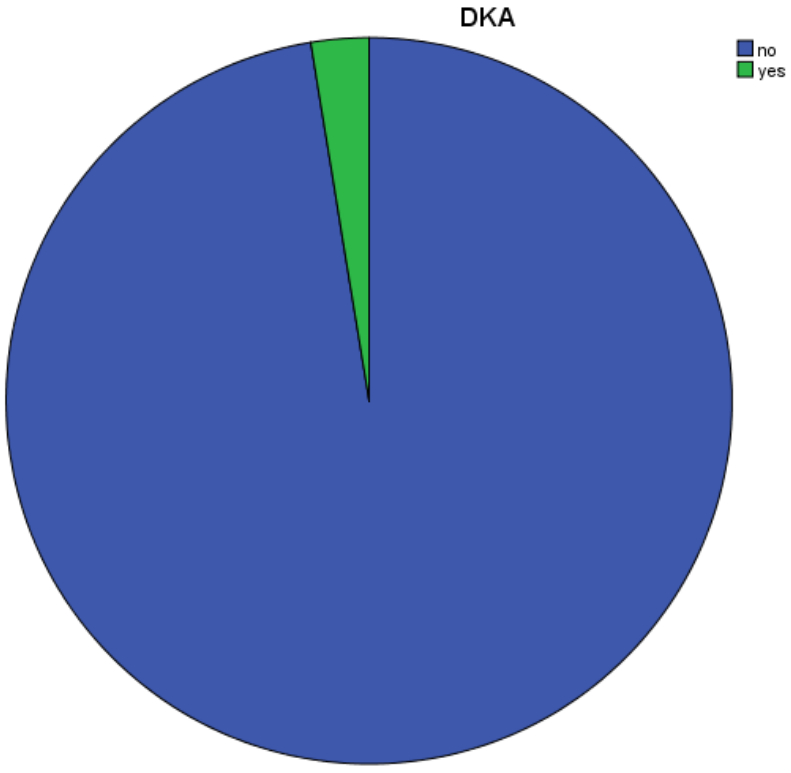


Figure 15: Incidence of DKA

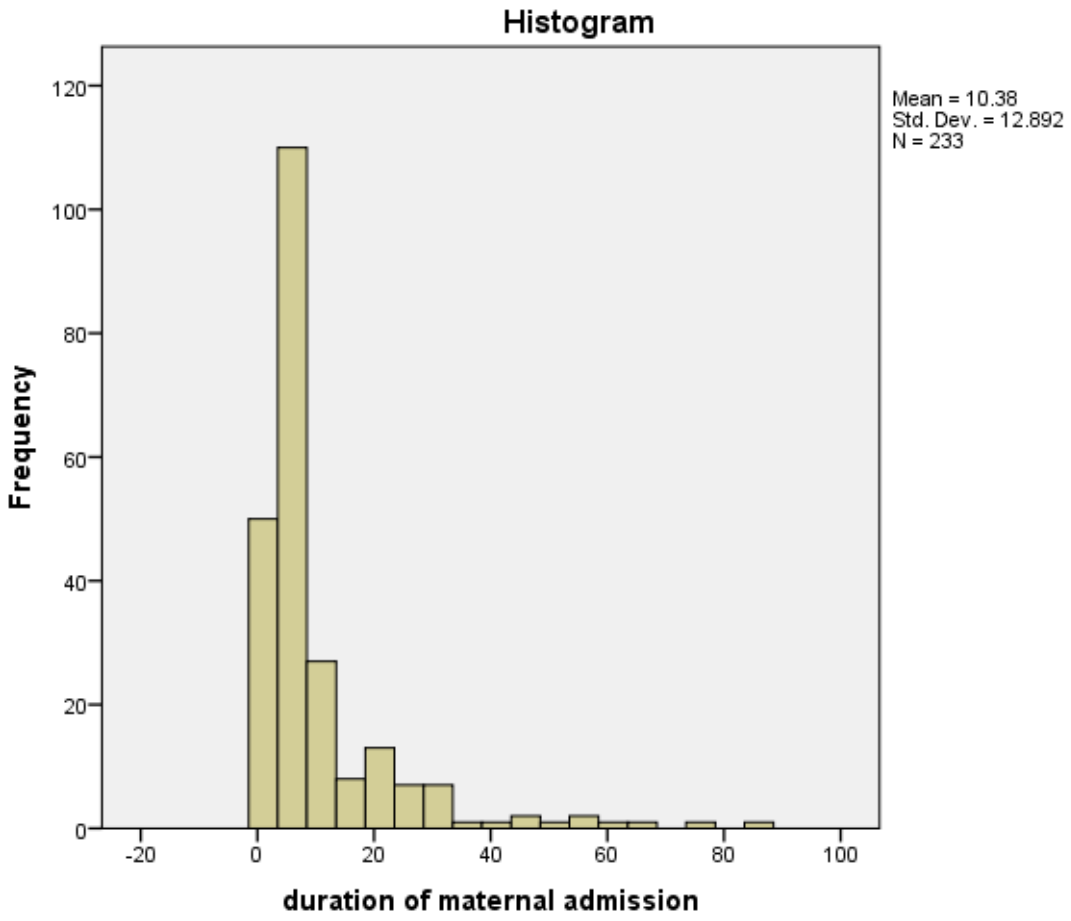


Figure 16: Maternal length of hospital stay

4.6 FETAL OUTCOMES

As table 7 shows, 241 babies were delivered. Fetal heart tracing was done for just over a third of them, most of which were normal.

The median gestational age at delivery for the entire cohort was 38 (37-38) weeks. Preterm delivery occurred in a fifth. Males formed the majority (54.5%) of the babies in the study and there was one baby with ambiguous genitalia. Most babies were live born but 2.1% were fresh stillbirths, and 5.0% were macerated stillbirths. In all there were 17 stillbirths and 11 early neonatal deaths, giving a perinatal mortality rate of 116 per 1,000 births. Seven percent of the babies had an Apgar score <7 at 5 minutes. One baby was born at home without a skilled attendant and thus had no Apgar scores recorded. The mean birth weight was 3.2kg (SD±0.9). Macrosomia (birth weight ≥4.0kg) made up 14.2% (Figure 17). Polyhydramnios and neonatal hypoglycaemia complicated 4.7% and 8.7% of cases respectively. There were ten sets of twins (4.3%).

There were thirteen fetuses (5.4%) with congenital anomalies. In total 22 congenital anomalies were identified (Figures 18 and 19). Some of the fetuses had multiple anomalies. The commonest anomaly in the group was cardiac and it occurred in 2.9% of the fetuses, followed by central nervous system anomalies including anencephaly (Figure 20). Some rare anomalies were also identified in the group including levocardia with abdominal situs inversus (Figure 21) and parasitic twin (Figure 22). The child with situs inversus had no other anomaly. She was delivered at term and is doing well. The parasitic twin was successfully separated by the paediatric surgeons.

Close to a third of the babies were admitted to NICU for a median duration of 4 (1-7) days. The commonest indications for NICU admission included prematurity (26.7%), hypoglycaemia (14.0%), macrosomia (11.3%), congenital anomalies (9.9%), and respiratory distress (7.0%).

Table 7: Fetal outcomes among pregnant women with diabetes

Characteristics (N=241)		**Values**
Fetal heart tracing	Normal	70 (29.0)
	Abnormal	16 (6.7)
	Not done	155 (64.3)
Gestational age at delivery (weeks)		38 (37-38)
	Prematurity (<37 weeks)	52 (21.5)
	Late preterm (34 to <37 weeks)	30 (12.4)
	Moderate preterm (32 to <34 weeks)	8 (3.3)
	Very preterm (<32 weeks)	14 (5.8)
Gender	Male	131 (54.5)
	Female	109 (45.2)
	Ambiguous genitalia	1 (0.4)
Condition of baby	Live birth	224 (92.9)
	Fresh stillbirth	5 (2.1)
	Macerated stillbirth	12 (5.0)

Apgar score at 5 minutes (n=223)[1]	≥7	208 (93.3)
	<7	15 (6.7)
Birth weight (kg)		3.2±0.9
	Macrosomia (BW ≥ 4.0kg)	34 (14.2)
Twins		10 (4.3)
Polyhydramnios		11 (4.7)
Congenital anomalies		13 (5.4)
	Cardiac anomalies	7 (2.9)
	CNS anomalies	3 (1.2)
	Genitourinary anomalies	3 (1.2)
	GIT anomalies	3 (1.2)
Neonatal hypoglycaemia		21 (8.7)
NICU admission		71 (29.5)
Indication for NICU admission (n=71)		
	Prematurity	19 (26.7)
	Hypoglycaemia	10 (14.0)
	Macrosomia	8 (11.3)
	Congenital anomaly	7 (9.9)
	Respiratory distress	5 (7.0)
Duration of NICU admission (days)		4 (1-7)
Early neonatal death		11 (4.6)

Values are given as median (interquartile range), mean ± SD, or number (percentage).

[1] One baby was delivered at home without a skilled attendant and thus had no Apgar scores recorded.

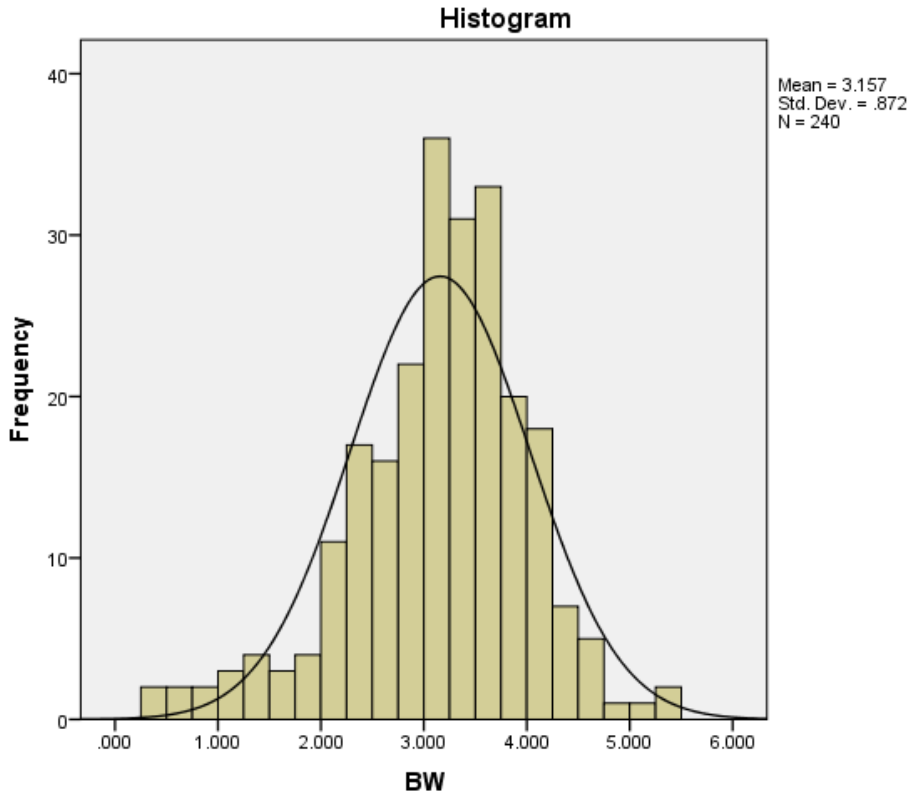


Figure 17: Distribution of birth weight

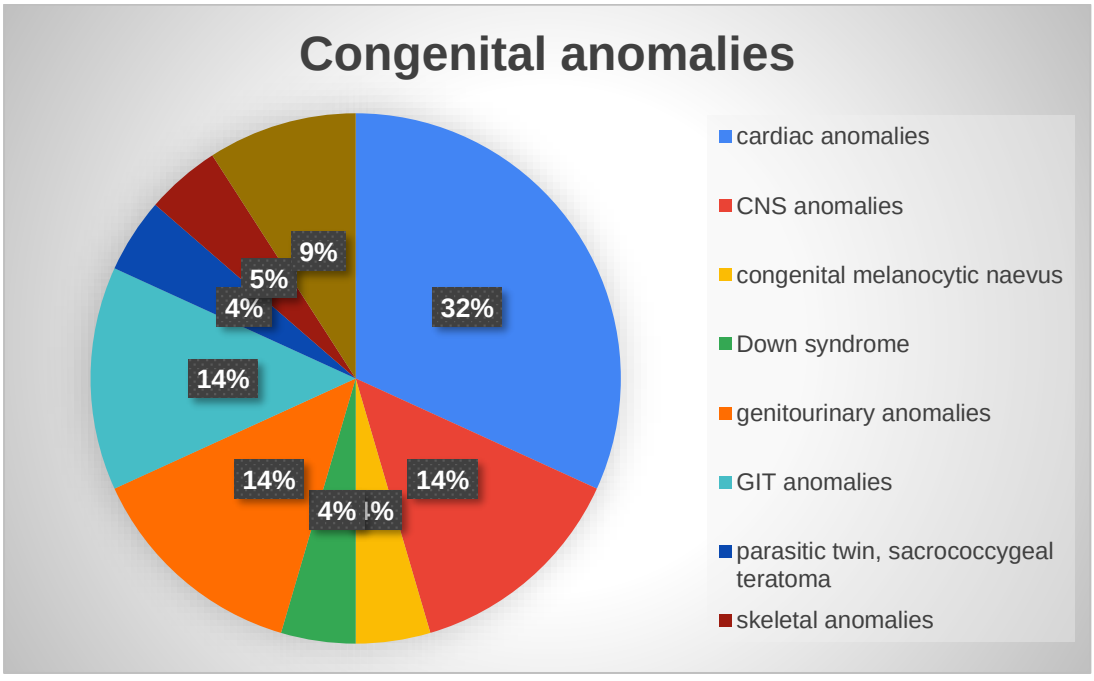


Figure 18: Congenital anomalies

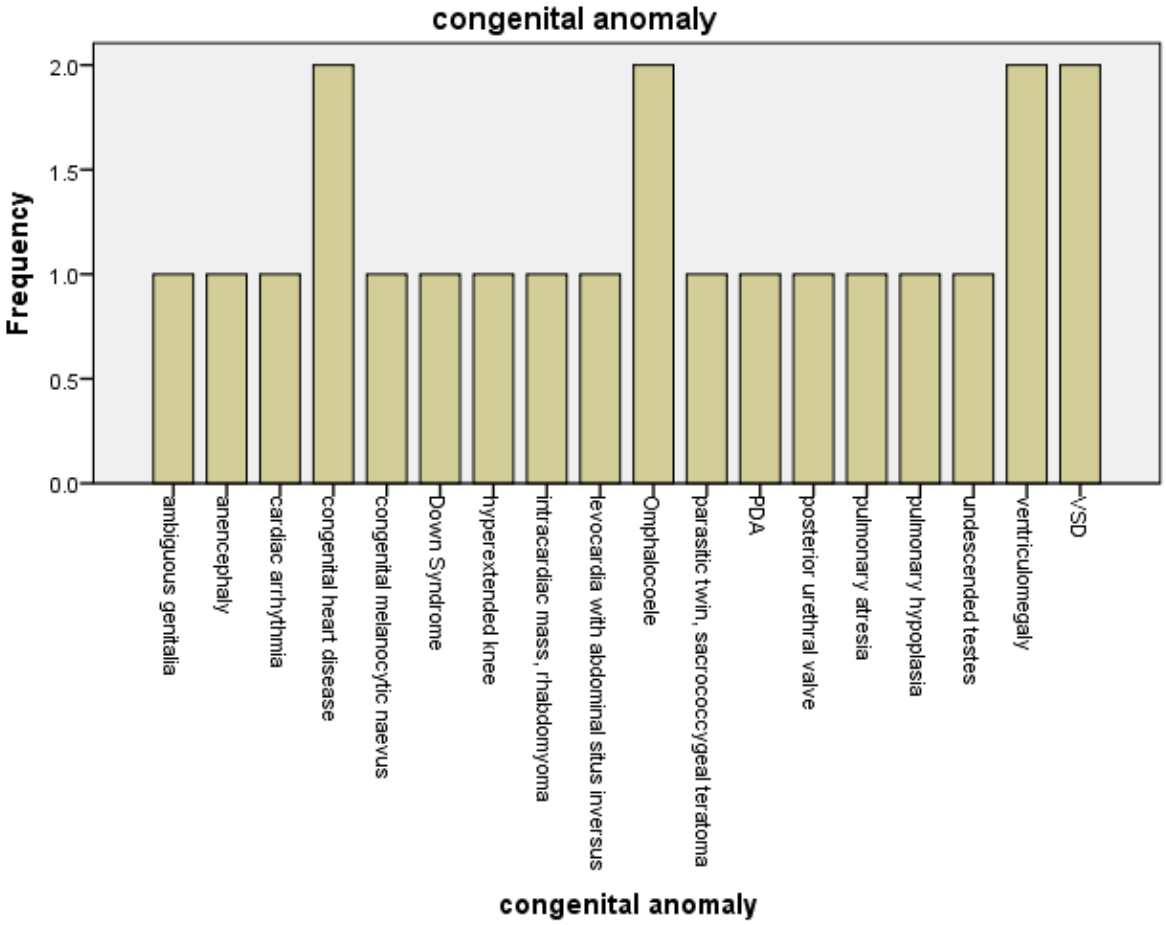
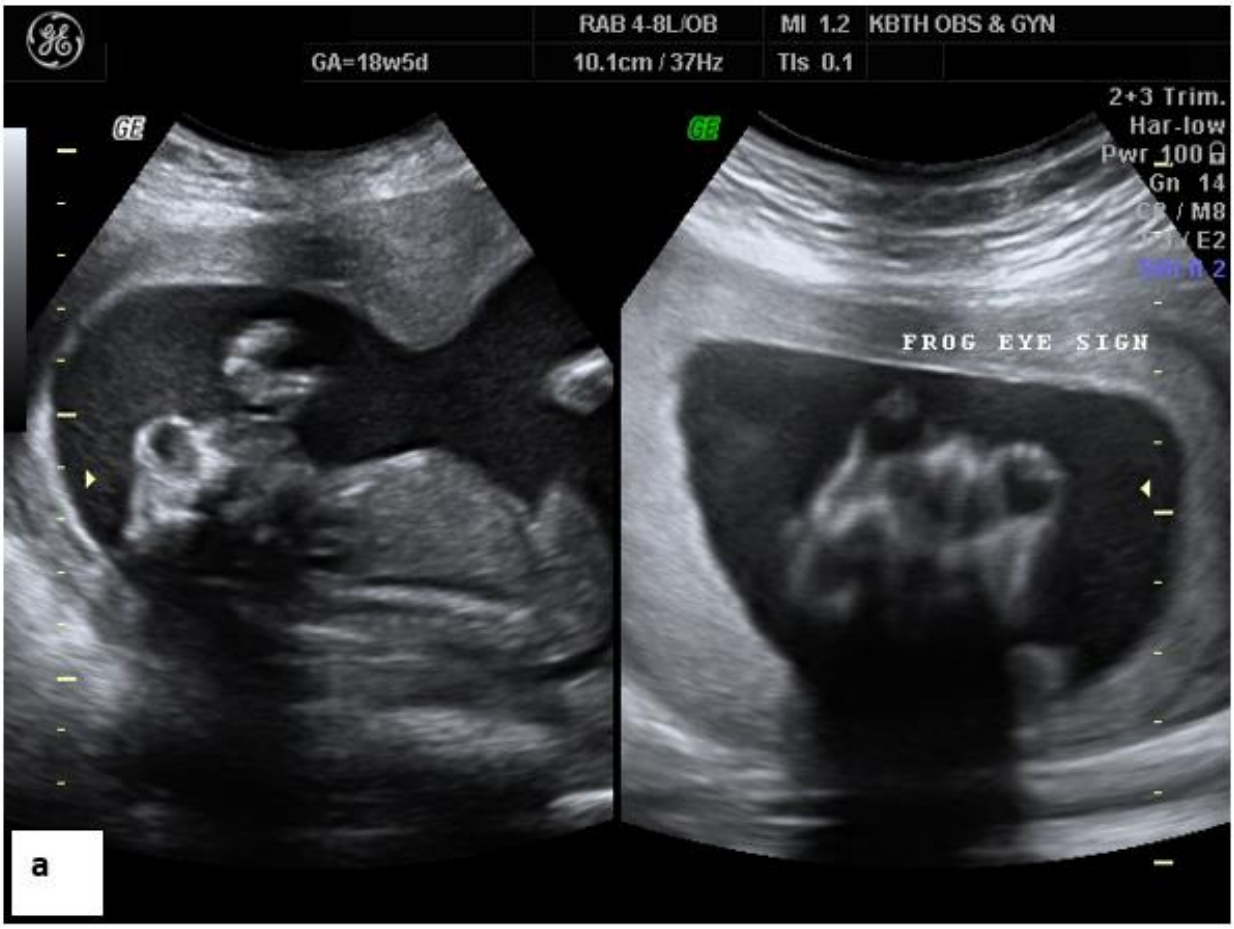


Figure 19: Breakdown of congenital anomalies


RAB 4-8L/OB
MI 1.2
KBTH OBS & GYN
GA=18w5d
10.1cm / 37Hz
TIs 0.1
2+3 Trim.
Har-low
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Gn 14
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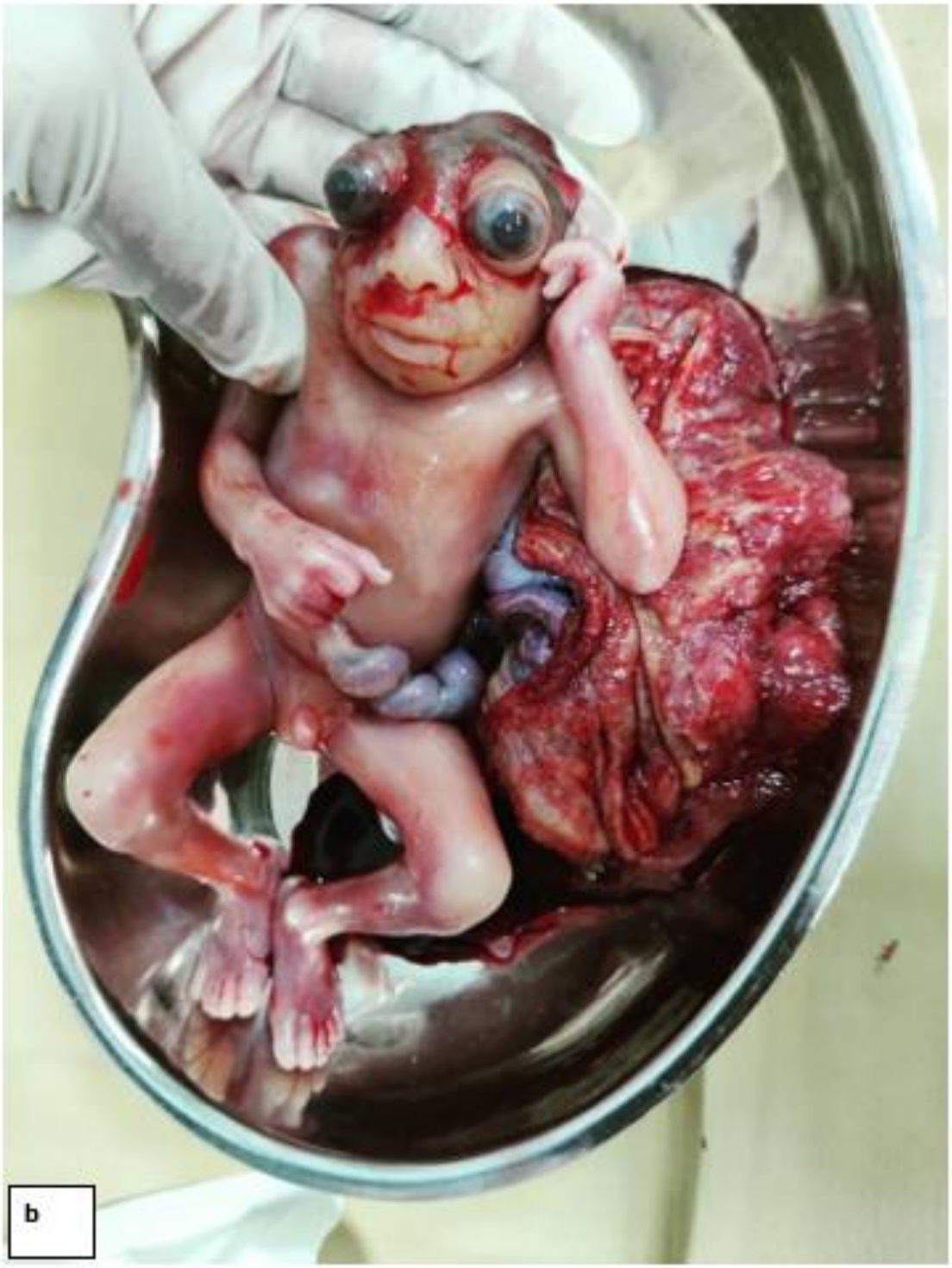
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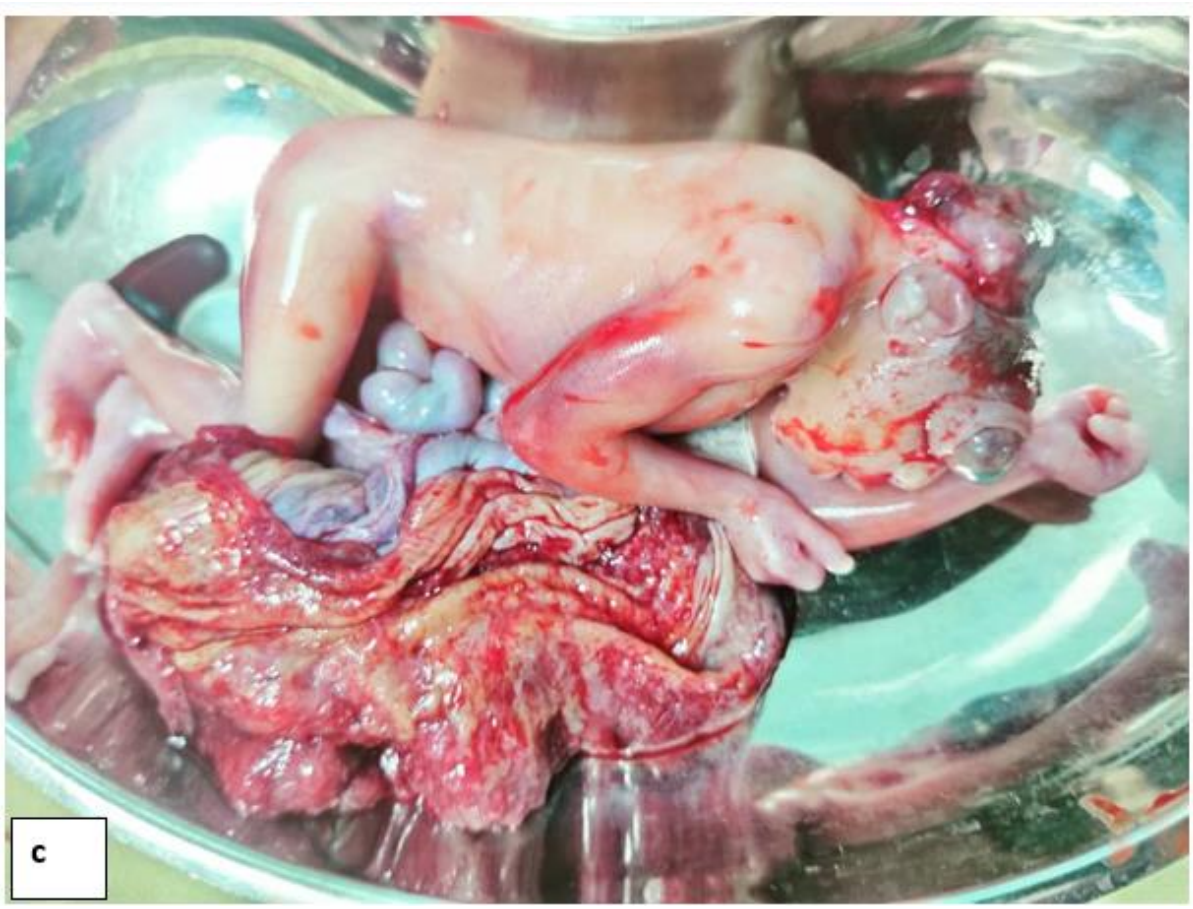
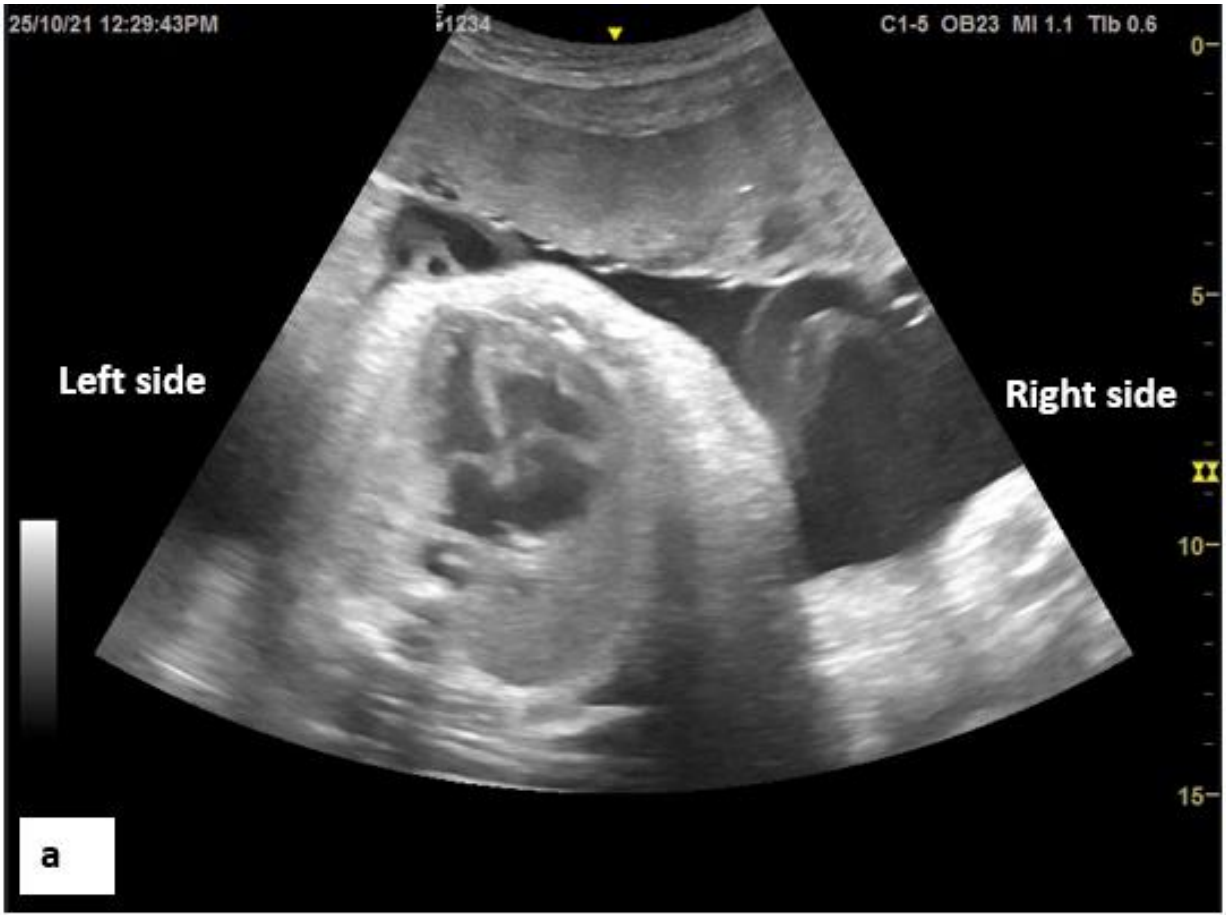


Figure 20: Anencephaly a) ultrasound images b) frontal view demonstrating frog eye sign c) acrania (with permission from the patient)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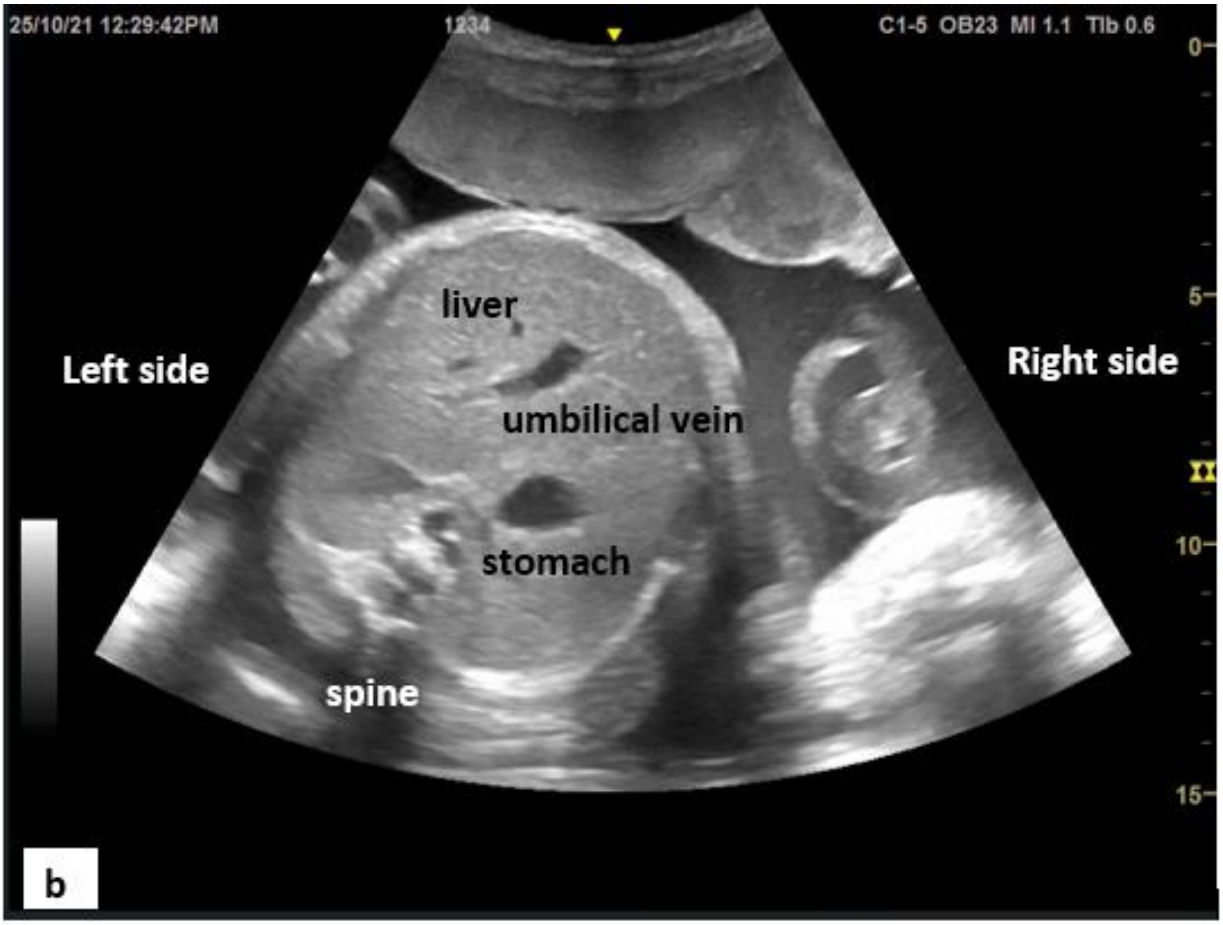
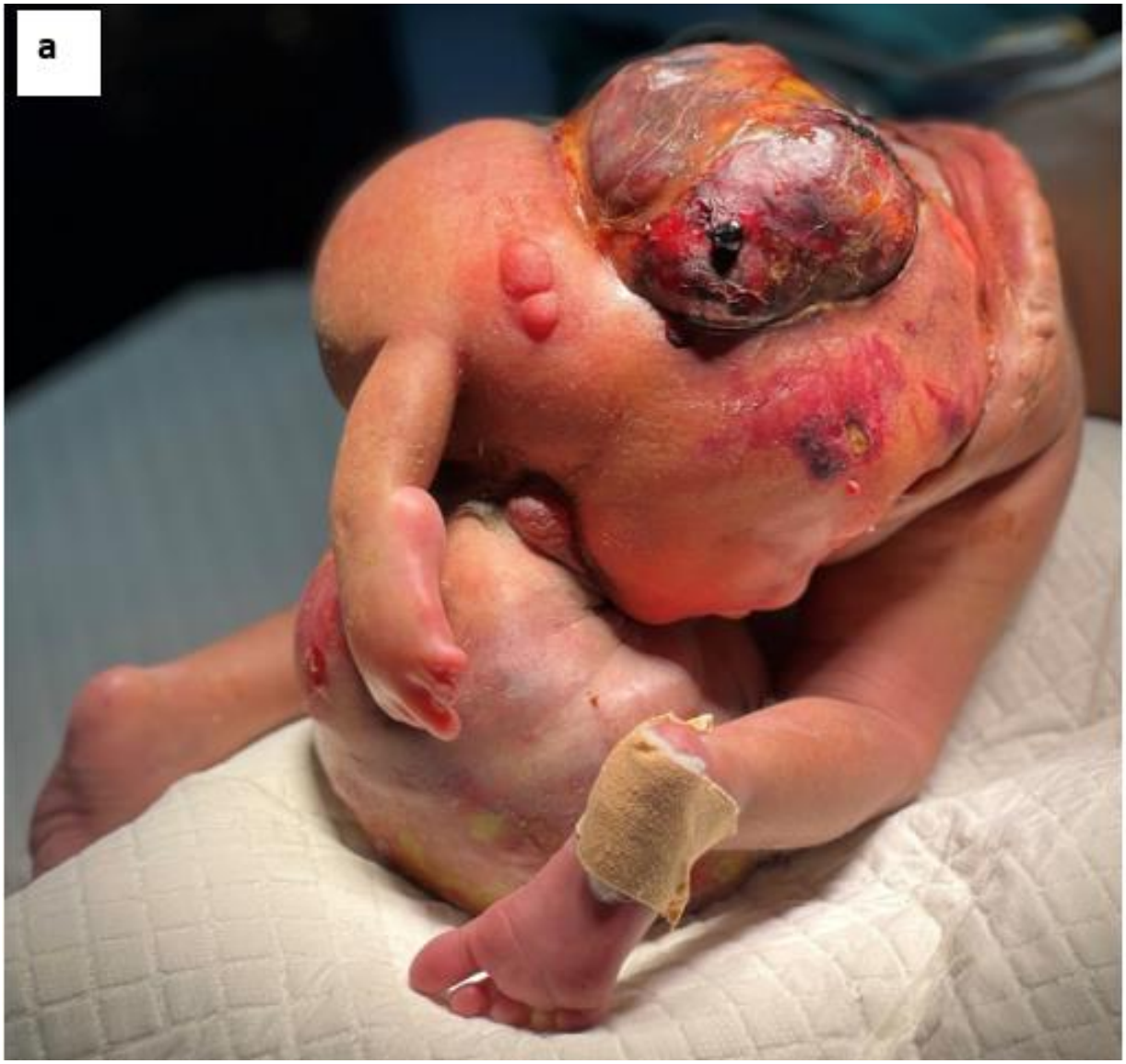


Figure 21: Levocardia with abdominal situs inversus. Ultrasound of fetus in cephalic presentation with spine positioned posteriorly. a) 4-chamber view of the heart with the apex pointing towards the left. b) axial view of the abdomen with the stomach on the right and liver with the umbilical vein on the left (with permission from the patient)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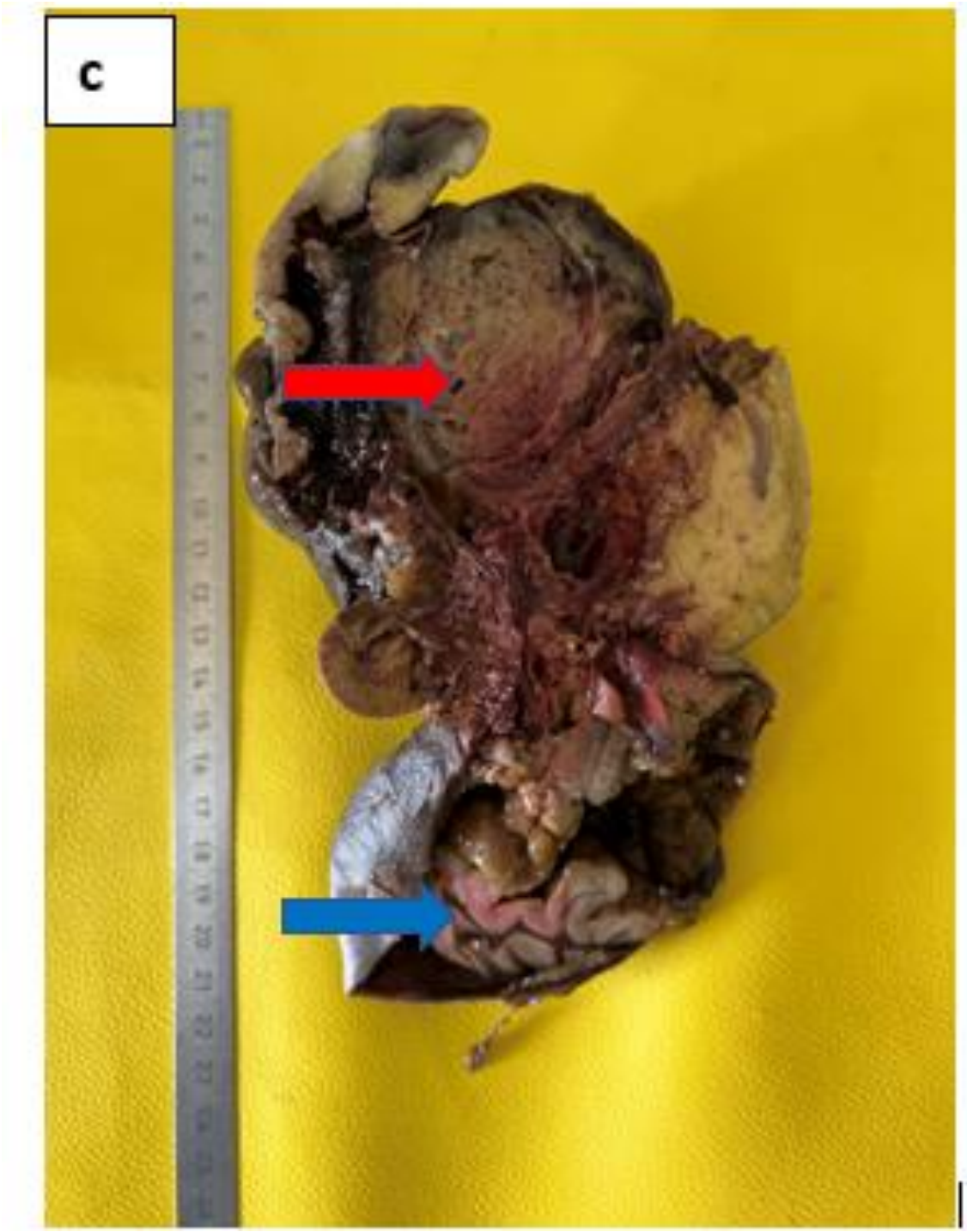

Figure 22: Parasitic twin. a) Sacrococcygeal mass with a lower limb and large cyst with a thick wall. b) Bagged sacrococcygeal mass excised. c) Parasitic twin measuring 170 x 130 x 110mm with cut surface demonstrating brain matter (blue arrow) in the cystic extension as well as lung tissue (red arrow) (with permission from the patient)

4.7 ASSOCIATION BETWEEN MATERNAL CHARACTERISTICS AND DKA

As demonstrated in Table 8, there was a statistically significant association between type of diabetes and DKA. Women with pregestational DM were at a higher risk of developing DKA compared to those with gestational DM (OR 7.107, p = .020). After adjusting for age as a potential confounding factor, pregestational DM (OR 6.751, CI 1.289-35.374) was significantly and positively associated with DKA. None of the other maternal characteristics had a statistically significant association with DKA. Parity was adjusted for age, previous history of macrosomia was adjusted for previous diabetes in pregnancy, and comorbidities adjusted for age and pregestational DM. These adjustments for potential confounders, however, made no significant difference.

Increasing RBS is associated with an increased risk of DKA (OR 1.560, p = .014). For every mmol/l increase in RBS, the odds of developing DKA are 1.56 times higher.

4.8 ASSOCIATION BETWEEN DKA AND MATERNAL OUTCOMES

There was no statistically significant association between DKA and maternal outcomes including duration of admission and mode of delivery as shown in Table 8. After adjusting for comorbidities, and for age, parity, and previous history of macrosomia respectively, there was still no significant association between DKA, and these two outcomes stated above. There was no ICU admission or maternal mortality in the DKA group so the odds ratio could not be determined for these outcomes.

4.9 ASSOCIATION BETWEEN DKA AND FETAL OUTCOMES

As shown in Table 9, there was no statistically significant association between DKA and fetal outcomes for both crude odds ratios and adjusted odds ratios after adjusting for potential confounders. Fetal demise and gestational age at delivery were both adjusted for anomalies. The condition of the baby at birth was adjusted for prematurity and anomalies. Birth weight was adjusted for gestational age at delivery and gender. Anomalies were adjusted for maternal age and pregestational DM. NICU admission was adjusted for gestational age at delivery, birth weight, Apgar score, hypoglycaemia, and anomalies. In the DKA group, there was no Apgar score <7, no neonatal hypoglycaemia, and no early neonatal death. Therefore, odds ratios could not be determined for these fetal outcomes.

Table 8: Association between DKA and maternal characteristics and outcomes

Maternal characteristics/ outcomes		DKA	Non-DKA	OR (95% CI)	p-value	AOR (95% CI)	p-value
Maternal characteristics							
Age	<35 years	2	121	.44 (.08-2.44)	.291		
	≥35 years	4	106				
Family history of DM	Positive	3	104	1.18 (.23-5.99)	.578		
	Negative	3	123				
Type of DM	Pregestational	3	29	7.11 (1.37-36.95)	.020	6.75 (1.29-35.37)	.024
	Gestational	3	198				
Parity	≥1 prior birth	5	176	.69 (.08-6.04)	.598	.82 (.09-7.42)	.859
	Nullipara	1	51				
Previous history of macrosomia	Yes	2	57	1.49 (.27-8.36)	.475	1.65 (.28-9.68)	.581
	No	4	170				
Comorbidities	Yes	3	97	1.34 (.27-6.78)	.517	1.26 (.24-6.67)	.785
	No	3	130				
Maternal outcomes							
Admission duration	≤5 days	1	120	.18 (.02-1.55)	.118	.18 (.02-1.59)	.123
	>5 days	5	107				
Mode of delivery	Caesarean	3	150	1.95 (.38-9.88)	.338	2.02 (.44-12.19)	.327
	Vaginal	3	77				
ICU admission	Yes	0	3	**	.924		
	No	6	224				
Maternal mortality	Yes	0	3	**	.924		
	No	6	224				

****** The measured outcome did not occur in the DKA group so odds ratio could not be determined.

CI: confidence interval, OR: odds ratio, AOR: adjusted odds ratio, DKA: diabetic ketoacidosis, ICU: intensive care unit

Table 9: Association between DKA and fetal outcomes

Fetal outcomes		DKA	Non-DKA	OR (95% CI)	p-value	AOR (95% CI)	p-value
Fetal demise	Yes	1	14	3.16	.323	3.10	.320
	No	5	221	(.35-28.89)		(.33-28.84)	
Congenital anomalies	Yes	1	12	3.72	.286	2.55	.442
	No	5	223	(.40-34.37)		(.23-27.81)	
Gestational age at birth	Preterm	2	49	.53	.373	.63	.620
	Term	4	186	(.09-2.96)		(.10-3.86)	
Condition of baby	Live birth	5	219	2.74	.358	2.21	.537
	Stillbirth	1	16	(.30-28.86)		(.18-27.3)	
Apgar score at 5 minutes[a,b]	≥7	5	203	**	.704		
	<7	0	15				
Birth weight	<4.0kg	5	202	.82	.603	.60	.657
	≥4.0kg	1	33	(.09-7.21)		(.06-5.81)	
Gender[c]	Male	128	3	.84	.573		
	Female	106	3	(.17-4.23)			
Neonatal hypoglycaemia[a,b,d]	Yes	0	21	**	.604		
	No	5	195				
NICU admission[a,d]	Yes	1	71	.51	.477	.23	.279
	No	4	146	(.06-4.68)		(.02-3.30)	
Neonatal death[a]	Yes	0	11	**	.812		
	No	5	208				

[a] Only live births were analysed (224)

[b] One baby was delivered at home and had no Apgar score, nor blood glucose recorded

[c] One baby had ambiguous genitalia

[d] Two babies died within minutes of delivery

****** The measured outcome did not occur in the DKA group so odds ratio could not be determined.

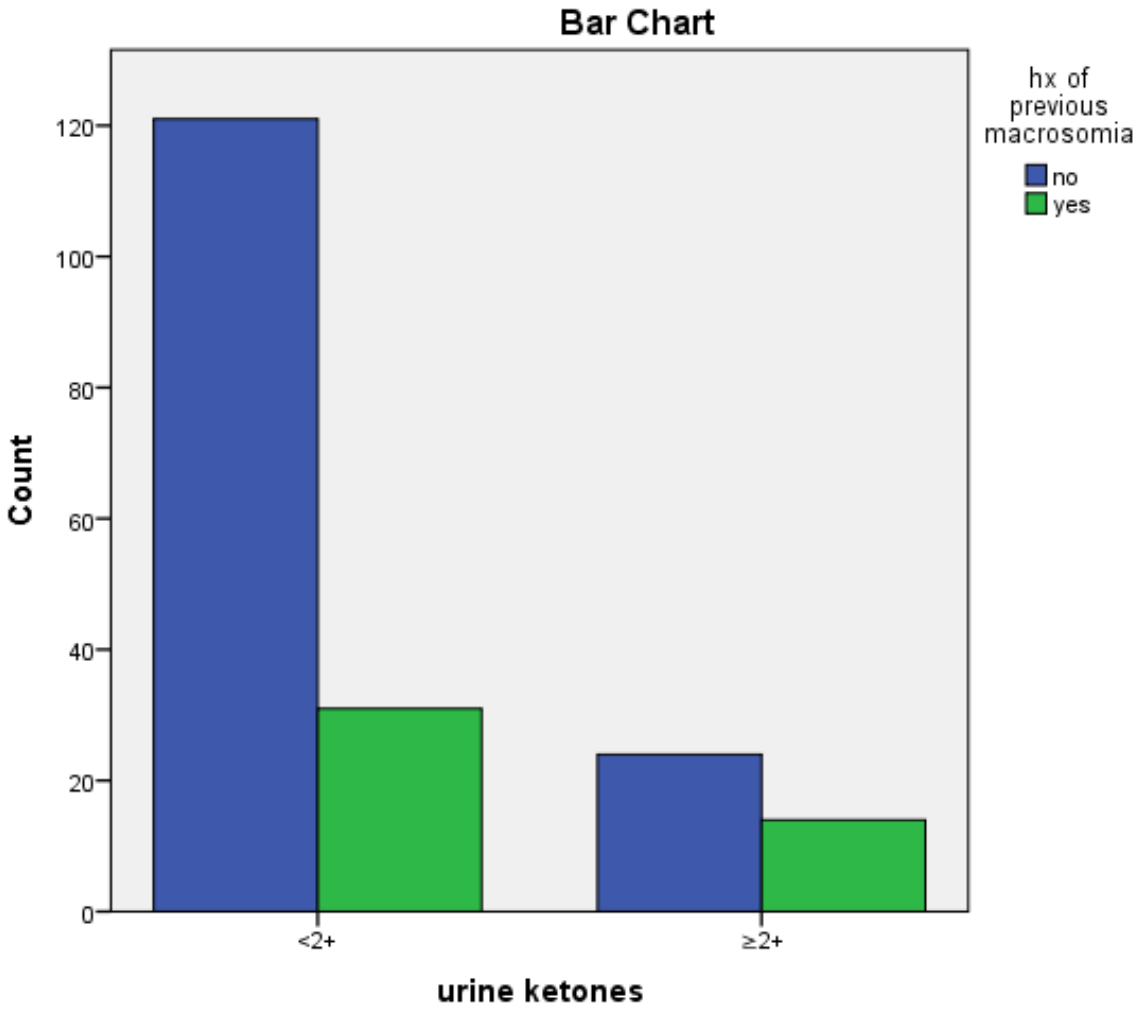

Figure 23: Relationship between previous macrosomia and significant ketonuria

There was a positive correlation between significant ketonuria and a previous history of macrosomia (Figure 23). Women with a previous history of macrosomia have an increased risk of significant ketonuria in their index pregnancy (OR2.277, p = .036).

CHAPTER 5: DISCUSSION

5.1 STUDY POPULATION

In this study, 90.7% of the pregnant women with diabetes who were admitted to Korle Bu Teaching Hospital over the study period were recruited and were all followed up till delivery. This is a good representation of the population of women with diabetes in pregnancy in KBTH. The prevalence of diabetes observed over the study period was lower than what pertained in 2019 in the same institution according to data from the biostatistics unit (8% vs 10%). Some women were never screened for diabetes throughout their pregnancies, contrary to the recommendation by Oppong *et al* in 2015 [7]. The number of deliveries too was lower during the study period (3,369) compared previous years (4,750 in 2019). The reduced attendance and deliveries may have been partly due to the covid-19 pandemic, which made people visit the hospital less frequently or stick to facilities within their vicinity.

The prevalence of diabetes in pregnancy was closer to what Oppong *et al* found in 2015 in Accra, Ghana (10%) than the low prevalence of 1.7% Oputa *et al* recorded in Nigeria [7][8]. It must be noted, however, that Oppong *et al* sampled their study participants from the outpatient clinic while we sampled ours from patients on admission. The prevalence was similar to that quoted by Rougerie *et al* (5-10%) [6]. The proportion with gestational diabetes too was much higher than what was found in Nigeria (86% vs 61%) [8]. These women had diabetes diagnosed for the first time during the index pregnancy. It is quite likely that among this population would be some women with pregestational diabetes who had never been diagnosed before the pregnancy. Postpartum follow-up and oral glucose tolerance test at the end of puerperium would distinguish such women from true gestational diabetics.

Risk factors for diabetes in pregnancy identified among the women in the study include a family history of diabetes (45.9%), previous macrosomia (25.3%), and previous history of diabetes in pregnancy (21.9%). These are considered high-risk [8].

5.2 DKA

The incidence of DKA in pregnant women with diabetes over the study period was 2.6%. This agrees with the incidence of 1-3% reported by Coutada *et al* [12]. The incidence of DKA among pregnant women with pre-gestational diabetes was found to be 9.4% which is within the range of 5 to 10% reported by Caughey *et al* [24]. The incidence was much lower

in gestational diabetes (1.5%), which is consistent with the literature. Of the women who had DKA, 66.7% of them developed it in the second and third trimesters. This higher incidence observed in the second and third trimesters is similar to the findings by Guo *et al* [26] and Baagar *et al* [2]. DKA occurs most commonly in type 1 diabetes, followed by type 2 diabetes, then gestational diabetes [2][34]. In this study, however, there was only one woman with type 1 diabetes, and she did not develop DKA. DKA occurred in type 2 diabetes and gestational diabetes in equal proportions.

In pregnancy, DKA occurs at lower mean blood glucose [14] and our study findings were consistent with this (mean blood glucose of 18.2mmol/l in the DKA group). Euglycaemic DKA, albeit rare, occurs more commonly in pregnancy. Up to 30% of DKA occurring in pregnancy are euglycaemic [30], and we had a similar finding of 33.3% in this study. One of the cases with euglycaemic DKA had gestational diabetes and the other had type 2 diabetes. The precipitating factors of DKA in our cases were like what Montoro *et al* demonstrated. The majority were due to poor glycaemic control and newly diagnosed DM. The proportions attributable to infection and vomiting were also similar to what is stated in the literature [10].

All the cases of DKA were managed per the protocol outlined in appendix III. Four of them were managed in a high-dependency unit with perfusors and the other two were managed on the ward with the modified Alberti regimen. Those two were managed on the ward because the high-dependency unit was full at the time of their diagnoses. All the cases recovered from DKA. The management protocol was strictly adhered to. This was easy to achieve because some of the resources needed, including blood glucose strips, blood ketone strips, and blood gas analyses were made available to the patients at no cost. These came out of the resources allocated to the study. Adherence to the protocol most likely improved the outcomes of DKA in this study. Two-thirds of the DKA cases were delivered remotely from the gestational age at which DKA was diagnosed, and none of them had a recurrence. This is likely to have impacted the fetal outcomes because more attention was paid to them following their DKA incidents, including tighter glycaemic control to prevent a recurrence. This may have likely reduced the risk to the fetus by the time of delivery.

5.3 ASSOCIATION BETWEEN MATERNAL CHRACTERISTICS AND DKA

In keeping with other studies, ours showed no difference in demographics between women with DKA and those without. We found it interesting that of the women who had significant ketonuria, only 13.6% had DKA. This underscores the importance of using the diagnostic criteria for DKA as outlined by the Joint British Diabetes Societies guidelines [14] appropriately in order not to misdiagnose diabetic pregnant women with significant ketonuria as DKA. Euglycaemic DKA was relatively common as reported by Dargel *et al* [38]. Awareness of this entity is critical in preventing devastating outcomes in pregnant women with diabetes as the index of suspicion would be high even if blood glucose is normal.

5.4 MATERNAL OUTCOMES

The caesarean section rate for the study population was very high (65.7%), with previous caesarean delivery being the biggest contributor (48.0%). In a diabetic population, although one would expect fetal macrosomia to be a major contributor to caesarean section rate, it only accounted for 11% in this study. DKA did not influence the mode of delivery as caesarean section rate in the cases was similar to the controls. No woman had caesarean delivery for fetal indications during an episode of DKA. This conforms with the recommendations of the Royal College of Obstetricians and Gynaecologists [10]. In our study, 66.7% of the DKA cases were managed successfully and delivered at a much later gestational age, similar to Baagar *et al* who did the same for 70% of their DKA cases [2].

There were three ICU admissions from the study population, all of which ended in maternal mortality. The first had a pulmonary embolism, the second had a pulmonary embolism and acute kidney injury secondary to sepsis, and the third had septicaemia secondary to peri-auricular abscess with intracranial extension. None of them had DKA. There was no mortality among the DKA cases, just like Baagar *et al* [2] reported. This must be because maternal mortality from DKA has improved to <1% in recent years [11] due to advances in management.

5.5 FETAL OUTCOMES

Five percent of the fetuses had congenital anomalies. This finding reinforces the fact that the risk of congenital anomaly in diabetes is 1.5 to 2 times higher than that in the general population which is 1-3% [39]. Half of these fetuses had multiple anomalies. The most prevalent congenital anomalies were congenital heart disease and central nervous system anomalies, which are consistent with the literature [39]. Only one of the DKA cases had a congenital anomaly and it was levocardia with abdominal situs inversus. Contrary to what is expected, none of the two cases of DKA in the first trimester resulted in congenital anomalies.

Seven percent of the fetuses had abnormal fetal heart tracing. Interestingly, all the fetal heart tracings from the DKA group were normal.

The rate of fetal demise in the DKA group was 16.7%. This rate falls within the range of 9 to 36% reported by Caughey *et al* [24]. Baagar *et al* and Morrison *et al* reported a similar rate of 16% [2] and 15.7% [43] respectively. Diguisto *et al* did a comparative study and reported a 16% stillbirth rate in women with DKA compared to 2% in matched controls [51]. Contrary to their findings, we found that the stillbirth rate was similar between the DKA group and their controls.

In this study, we found a preterm delivery rate of 33.3% in the DKA group. This is at variance with the study by Bryant *et al* which found preterm delivery in 55% of cases [27]. Morrison *et al* also found a higher preterm delivery rate (43.6%) in their study [43] with risk factors being maternal smoking and higher pre-DKA HbA1C. Although we did not measure these risk factors in our study, smoking is rare in our population and 50% of our DKA cases had gestational diabetes and may have had lower HbA1C. These factors could explain why we recorded a much lower preterm delivery rate.

Baagar *et al* found an interesting association between male fetus and the risk of DKA in pregnancy. In their study, they observed that most infants born to mothers with DKA were male (12 males vs 3 females) [2]. In our study, however, we found equally distributed genders.

There was no significant difference in Apgar scores in our study. Diguisto *et al* reported a 5-minute Agar score <7 in 11% of the DKA group and 7% of the control group [51].

We found no association between DKA and neonatal hypoglycaemia, unlike Diguisto *et al* who reported hypoglycaemia in 37% of DKA and 19% of controls [51].

5.6 STUDY LIMITATIONS

Our study had some limitations, and these are outlined below:

1. For the women with pre-gestational diabetes, it was quite difficult to distinguish type 1 from type 2 with certainty. The one case of type 1 diabetes had already been diagnosed a few years ago and she was well-informed about her diagnosis. A few women knew they had type 2 diabetes, but the rest were presumed to have type 2 diabetes based on their age at diagnosis and the fact that they were on metformin even if they were taking insulin as well.
2. Due to resource constraints, screening for DKA was done with urine ketones instead of blood ketones. This may have impacted the diagnostic yield and consequently the incidence of DKA. However, monitoring of DKA cases was done using blood ketones.
3. Due to time and resource constraints, follow-up could not continue to the end of puerperium when some undiagnosed pre-gestational diabetics could have been distinguished from the true gestational diabetics after doing an oral glucose tolerance test at 6 weeks postpartum.
4. The number of DKA cases obtained was small. Barring time constraints it would have been good to extend the study period to get more numbers to enhance the power of the inferences made from it. The small sample size may have impacted the relationship observed between DKA and maternal and fetal outcomes as the numbers may have been too small to show a clear trend.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

Diabetic ketoacidosis is a complication of diabetes that can have devastating effects. There is a clear correlation between high blood glucose and DKA. In pregnancy, however, DKA can occur at relatively lower blood glucose and even when blood glucose is normal (euglycaemic DKA). Because of this, in pregnancy, a high index of suspicion is needed to diagnose promptly and manage effectively. Prompt diagnosis and treatment tend to improve maternal and fetal outcomes.

In our study, every pregnant woman with diabetes who was admitted was screened for ketosis. By so doing we were able to diagnose DKA even in women who did not have the classic presentation. This early diagnosis helped avoid poor outcomes in these women.

The incidence of DKA in pregnant women with diabetes was found to be 2.6%, two-thirds of which occurred in the second and third trimesters. Half of the cases were women with gestational diabetes. High blood glucose positively correlated with the odds of having DKA. For every mmol/l increase in RBS, the odds of developing DKA were 1.56 times higher. However, a third of the cases were euglycaemic DKA. This highlights the importance of routine screening of pregnant women with diabetes for ketosis. All the cases recovered from DKA. There was no maternal mortality among the DKA cases. The availability of resources from the study made it possible to adhere to the management protocol and this improved the maternal and fetal outcomes. Our study did not find any significant difference in maternal and fetal outcomes between pregnant women with DKA and those without.

6.2 RECOMMENDATIONS

The following recommendations are made based on the experience from this study and the findings.

1. All pregnant women with diabetes must be screened for ketosis (urine ketones or blood ketones) at every antenatal visit and whenever they report for emergency care.
2. Pregnant women with diabetes should be managed by a multidisciplinary team including an obstetrician (maternal-fetal medicine specialist where available), endocrinologist, diabetes nurse, midwife, and dietitian. A special high-risk clinic should be dedicated to these women where they can be attended to by all the members of the multidisciplinary team.

3. All pregnant women with diabetes must be taught and encouraged to do self-monitoring of blood glucose. This immensely helps in achieving good glycaemic control. Access to affordable glucose monitoring devices is key.
4. The DKA in pregnancy protocol must be adhered to ensure good outcomes. Availability of resources must be ensured to guarantee adherence.
5. Appropriate training should be offered to clinical staff involved in the management of DKA in pregnancy, especially the high dependency unit staff. This training should include adherence to management protocol.
6. A multi-centre study on DKA in pregnancy and maternal and fetal outcomes should be considered to give a broader scope of the disease burden. This study should also measure protocol adherence and its effect on outcomes.

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APPENDIX

APPENDIX I: PARTICIPANTS INFORMATION SHEET AND INFORMED CONSENT FORM

Research Title: Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle Bu Teaching Hospital

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BACKGROUND AND PURPOSE OF STUDY

Diabetic ketoacidosis (DKA) in pregnancy is an obstetric complication that poses significant risks to both mother and baby. Diabetes affects 10% of pregnancies in Accra. One to three percent of diabetes in pregnancy is complicated by DKA. DKA is characterized by high blood sugar, blood or urine ketones, and acidosis (lowered blood pH). In pregnancy, DKA occurs at lower blood sugar levels and is more common in the second and third trimesters. Rarely, DKA can occur at normal blood sugar levels and this is termed euglycaemic DKA. It occurs more commonly in pregnancy. Precipitating factors include excessive vomiting, insulin noncompliance, infection, and drugs that tend to raise blood sugar. Symptoms include vomiting, abdominal pain, fast breathing, palpitations, and lethargy. Treatment involves iv fluid replacement, insulin therapy, correction of electrolyte imbalance, treatment of precipitating factors, and monitoring of maternal and fetal response to therapy.

The purpose of this study is to determine the burden of DKA in pregnancy in Korle Bu Teaching Hospital, and the effects of DKA on mother and baby. This would provide

information that would serve as the justification for mobilizing more resources for the effective management of this condition to get the best outcomes.

STUDY PROCEDURE AND PARTICIPANT INVOLVEMENT

The study participants would include all pregnant women with known diabetes mellitus or newly diagnosed with diabetes mellitus. After explaining the study and its purpose, you would be made to sign or thumbprint an informed consent form if you volunteer to join the study. A questionnaire would be administered to obtain demographic information and obstetric history. Your urine sample would be taken and tested for ketones. If you have urine ketones ≥2+, your blood sample (2ml) would be taken and tested for pH or bicarbonate. If you are found to have DKA, standard management would be commenced for you right away.

You will not be paid for participating in the study. You will not incur any cost for participation either.

You are not obliged to participate in this study. After agreeing to participate in this study, you are free to change your mind and withdraw at any time. There will be no consequence, or loss of benefit or care if you decline to participate, or withdraw your participation.

CONFIDENTIALITY

To ensure confidentiality, a unique alphanumeric code would be generated for you and that is what would be used to label all your samples and your file, instead of your name. All information provided would be strictly kept confidential, and only accessible to the researcher and research assistants.

PARTICIPANT INFORMED CONSENT FORM

Research Title: Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle Bu Teaching Hospital

PARTICIPANT'S STATEMENT

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and satisfactorily explained to me in a language I understand (English [ ] / Twi [ ] / Ga [ ]). I fully understand the contents and any potential implications as well as my right to change my mind and withdraw even after signing this form. I voluntarily agree to be part of this research.

Name or initials of participant…… ID Code ……..

Participant's signature/ Thumbprint Date

…….. ……

INVESTIGATOR STATEMENT AND SIGNATURE

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed.

Researcher's name …….

Signature ……. Date …….

APPENDIX II: DATA COLLECTION SHEET

Research Title: Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle Bu Teaching Hospital

SOCIO-DEMOGRAPHIC INFORMATION

1. Participant's ID: ……
2. Age (years): ……
3. Place of abode: ……
4. Marital status: a. Single [ ] b. Married [ ] c. Co-habiting [ ]
   d. Divorced/Separated [ ] e. Widowed [ ]
5. Level of Education: a. None [ ] b. Basic School [ ]
   c. Senior High School [ ] d. Tertiary [ ]
6. Occupation: ……
7. Religion: a. Christianity [ ] b. Islam [ ]
   c. Traditional [ ] d. Other (specify) …….
8. Family history of Diabetes Mellitus: a. Yes [ ] b. No [ ]
9. History of type 1 Diabetes Mellitus: a. Yes [ ] b. No [ ]
10. History of type 2 Diabetes Mellitus: a. Yes [ ] b. No [ ]

OBSTETRIC HISTORY

11. Number of pregnancies (including current pregnancy): …….
12. Number of previous births (excluding current pregnancy): ……
13. Number of pregnancy losses: ……..
14. Number of previous stillbirths or neonatal deaths: …….
15. History of previous macrosomia: a. Yes [ ] b. No [ ]
16. Previous history of diabetes mellitus in pregnancy: a. Yes [ ] b. No [ ]
17. Estimated due date: …….
18. Gestational age at booking/ dating ultrasound (weeks): …….
19. Multiple gestation in current pregnancy: a. Yes [ ] b. No [ ]
20. Polyhydramnios in current pregnancy: a. Yes [ ] b. No [ ]

CLINICAL PROFILE AT RECRUITMENT

21. Gestational age (weeks): …….....
22. Random blood sugar (RBS) (mmol/l): ……
23. Urine ketones: a. ≤ 2+ [ ] b. > 2+ [ ]
24. Venous blood pH: ……..
25. Serum bicarbonate: …….....
26. Associated co-morbidities: a. Hypertension [ ] b. Pre-eclampsia [ ]
    c. SCD [ ] d. IUGR [ ]
    e. Other (specify) ……..

OUTCOME DATA

27. Maternal ICU admission: a. Yes [ ] b. No [ ]
28. Fetal heart tracing: a. Normal [ ] b. Abnormal (specify)……..
    c. Not done [ ]
29. Fetal demise: a. Yes [ ] b. No [ ]
30. Gestational age at fetal demise: …….
31. Gestational age at delivery: ……
32. Mode of delivery: a. Vaginal [ ] b. Caesarean [ ]
33. Onset of labour if vaginal: a. Spontaneous [ ] b. Induced [ ]
34. If Caesarean section
    a. Type: a. Elective [ ] b. Emergency [ ]
    b. Indication: ……..
35. Sex of baby: a. Male [ ] b. Female [ ]
36. Condition of baby: a. Live birth [ ] b. Fresh SB [ ] c. Macerated SB[ ]
37. Apgar score at 1 minute: …….
38. Apgar score at 5 minutes: ……
39. NICU admission: a. Yes [ ] b. No [ ]
40. Indication for NICU admission: ……..
41. Duration of hospital stay (days):: a. Ward……b. NICU admission……c. Total length of stay……
42. Death at NICU: a. Yes [ ] b. No [ ]
43. Early Neonatal Death: a. Yes [ ] b. No [ ]

44. Neonatal hypoglycaemia: a. Yes [ ] b. No [ ]

45. Duration of maternal admission (days): …….

46. Maternal mortality: a. Yes [ ] b. No [ ]

APPENDIX III: PROTOCOL FOR MANAGEMENT OF DKA IN PREGNANCY

- Advise pregnant women with diabetes to seek urgent medical care if they become hyperglycaemic or unwell.
- Test urgently for ketonuria if a pregnant woman with any form of diabetes presents with hyperglycaemia or is unwell.
- Immediately admit or refer women with suspected diabetic ketoacidosis to a health facility with critical care (HDU) services, where they can receive multidisciplinary medical, anaesthetic, and obstetric care.
- **Beware of Precipitating factors:** protracted vomiting, hyperemesis gravidarum, infections, insulin non-compliance, medications precipitating diabetic ketoacidosis in pregnancy including beta sympathomimetic agents and corticosteroids, insulin pump failure, and conditions such as gastroparesis.
- **Symptoms:** polyuria, polydipsia, nausea, vomiting, abdominal pain, weakness, weight loss
- **Signs:** hyperventilation, ketotic breath, tachycardia, hypotension, dry mucous membranes, disorientation, shock, coma, abnormal fetal heart tracing
- **Diagnostic criteria: a triad of hyperglycaemia, ketonaemia/ketonuria and acidosis**
    - Blood ketone level ≥ 3.0 mmol/l or urine ketone level ≥ 2+
    - Blood glucose level > 11.0 mmol/l or known diabetes mellitus regardless of blood glucose level (euglycaemic DKA)
    - Bicarbonate < 15.0 mmol/l and/or venous pH < 7.3
- **Management:**

Using a perfusor

- 0.9% normal saline at 1l/hour x 1 hour, 500ml/hour x 4 hours, 250ml/hour x 8 hours, then 150ml/hour. Add 10% dextrose at 125ml/hr or 5% dextrose/dextrose saline at 250 ml/hr when blood glucose <13-15mmol/l.

- Insulin infusion at a fixed rate of 0.1iu/kg/hr by a perfusor is the treatment of choice. Increase by 1iu/hr if the treatment target is not achieved. Women with pregestational diabetes who are on basal insulin should not discontinue it.

Without a perfusor

- In the absence of a perfusor, resort to the use of modified Alberti regimen where 5-10 iu of soluble insulin is given intramuscularly (IM) every hour with hourly monitoring of blood glucose.
- 0.9% normal saline at 1l/hour x 1 hour, 500ml/hour x 4 hours, 250ml/hour x 8 hours, then 150ml/hour intravenously.
- When blood glucose <13-15mmol/l, switch to sliding scale. Add 10% dextrose at 125ml/hr or 5% dextrose/dextrose saline at 250 ml/hr while giving the soluble insulin subcutaneously every 4 hours.

Other interventions

- Give 40mmol of KCl per litre of ongoing iv fluids if $K^+ \leq 5.5$mmol/l. Ensure adequate urine output. If $K^+ < 3.3$mmol/l, correct hypokalaemia before starting insulin infusion.
- Identify and treat the cause.
- Monitor capillary glucose and blood ketones (or urine ketones if blood ketone testing is not available) hourly for the first 6hrs
- Monitor venous pH, bicarbonate, and serum potassium 2hrly for the first 6hrs

- **Treatment targets:**
  - Decrease in blood ketone levels by 0.5 mmol/l/h
  - Increase in venous bicarbonate levels by 3 mmol/l/h
  - Decrease in capillary glucose levels by 3 mmol/l/h

Switching to biphasic insulin

- Insulin and insulin infusion should not be stopped until patients can eat and drink normally.

- Twice daily SC insulin should be started at least 1h before discontinuation of insulin infusion (with rapid-acting insulin analogues you may stop sliding scale at the same time as starting SC)

- **Recovery** is defined as:
  - Blood ketone level < 0.6mmol/l (or urine ketones ≤1+ if blood ketone testing not available)
  - pH > 7.3
  - Serum bicarbonate > 15mmol/l
- For gestation ≥28 weeks, offer a cardiotocograph to monitor fetal heart rate. Normalization of fetal heart tracing may occur 4 to 8hrs after correcting DKA.
- The decision to deliver should be individualized and based on maternal status, gestational age, fetal status, response to therapy, co-morbidities, and past obstetric history.
- Delivery for fetal indications should be reserved for fetal impairment that persists after maternal resuscitation.
- Emergency Caesarean section before maternal stabilization should be avoided as it could further aggravate the maternal condition.

APPENDIX IV: LETTER OF APPROVAL

The Rector
Ghana College of Physician and Surgeons
Accra

Dear Rector,

VETTING OF DR. JEFF OSEI AGYPONG PROPOSAL

Thanks for the ecopy of the corrected dissertation proposal.

COMMENT: The candidate has answered all the queries raised after my assessment. With regard to the first query on the 10% prevalence rate at the ANC which he has corrected to 10% for diabetic patients among the deliveries, he needs to provide the period of the data collection, and also add a reference if possible. He may be asked to proceed with the main work.

Thank you very much.

APPENDIX V: IRB APPROVAL

MEDICAL DIRECTORATE
KORLE BU TEACHING HOSPITAL

9th July, 2021

THE HEAD
DEPT OF OBSTETRICS AND GYNAECOLOGY
KORLE BU

LETTER OF INTRODUCTION – DR. JEFF OSEI AGYAPONG
"DIABETIC KETOACIDOSIS IN PREGNANCY AND MATERNAL AND FETAL OUTCOMES IN KORLE BU TEACHING HOSPITAL"

I have the pleasure to introduce to you the above named Investigator from Department of Obst & Gynae, Korle Bu. Dr. Jeff Osei Agyapong sought and has been granted approval to conduct a study entitled: "Diabetic Ketoacidosis in Pregnancy and maternal and fetal outcomes in Korle Bu Teaching Hospital".

He is to contact you to discuss the commencement date of the study.

Please verify his identity with a Government issued National ID card and accord him the needed assistance.

Attached is the Scientific and Technical Committee and Institutional Review Board approval, which specifies the terms.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/MD/63/21

Your Ref. No......

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-6
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

9th August, 2021

DR. JEFF OSEI AGYAPONG
DEPT OF OBSTETRICS AND GYNAECOLOGY
KORLE BU

INSTITUTIONAL APPROVAL: KORLE BU TEACHING HOSPITAL-SCIENTIFIC AND TECHNICAL COMMITTEE/INSTITUTIONAL REVIEW BOARD (KBTH-STC/IRB/00074/2021

Following approval of your study entitled "Diabetic ketoacidosis in pregnancy and maternal and fetal outcomes in Korle Bu Teaching Hospital" by the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board.

I am pleased to inform you that institutional approval has been granted for the conduct of your study in Korle Bu Teaching Hospital.

Please contact the Heads of Departments to discuss the commencement date of the study.

Please note that, this institutional approval is rendered invalid if the terms of the Institutional Reviewed Board/Scientific and Technical Committee approval are violated.

Sincere regards,

Dr. Ali Samba
Director of Medical Affairs
For: Chief Executive

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/IRB/00074/21

Your Ref. No......

KORLE BU TEACHING HOSPITAL
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3rd August, 2021

DR JEFF OSEI AGYAPONG
DEPT OF OBSTETRICS AND GYNAECOLOGY
KORLE BU TEACHING HOSPITAL
P. O. BOX 77, KORLE BU, ACCRA, GHANA

"DIABETIC KETOACIDOSIS IN PREGNANCY AND MATERNAL AND FETAL OUTCOMES IN KORLE-BU TEACHING HOSPITAL"

KBTH-IRB /00074/2021

INVESTIGATOR: Dr Jeff Osei Agyapong

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled: "**Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle-Bu Teaching Hospital**"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th June, 2022. You are to submit annual report for continuing review.

Sincere regards,

DR. DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB

Cc: The Chief Executive Officer, KBTH
The Director of Medical Affairs, KBTH

And the date of this
Letter should be quoted
My Ref. No. KBTH/IRB/93R1
Your Ref. No......

KORLE BU, ACCRA.

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7th July, 2021

DR JEFF OSEI AGYAPONG
DEPT OF OBSTETRICS AND GYNAECOLOGY
P. O. BOX 77, KORLE BU, ACCRA, GHANA

SCIENTIFIC AND TECHNICAL COMMITTEE APPROVAL
PROTOCOL IDENTIFICATION NUMBER: KBTH-STC 00074/2021

The Korle Bu Teaching Hospital Scientific and Technical Committee (KBTH-STC), on 7th July, 2021 approved your submitted study protocol.

TITLE OF PROTOCOL: "Diabetic Ketoacidosis in Pregnancy and Maternal and Fetal Outcomes in Korle-Bu Teaching Hospital"

PRINCIPAL INVESTIGATOR: Dr Jeff Osei Agyapong

This approval requires that you **forward your approved document to Korle Bu Teaching Hospital –Institutional Review Board (KBTH-IRB) for the ethical aspect of the proposal to be assessed before the project can be initiated.**

This STC approval is valid till 30th December, 2021

You may, however, request extension of the approval period, or renewal as the case may be, should the study extend beyond the stated period.

Upon completion, you are required to submit a final report on the study to the STC. This is to enable the STC ensure among others that, the project has been implemented as per the approved protocol. You are also required to inform the KBTH-STC and Research Directorate of any publications that may emanate from the research findings.

Kindly note that, should the need arise, the KBTH-STC or IRB may institute appropriate measures to satisfy itself that study is being conducted according to the highest scientific and ethical standards.

Please note that any modification to the study protocol without Scientific Technical Committee (STC) approval renders this approval invalid.

Sincere regards,

Prof. G. Obeng Adjei
Chairman, KBTH-STC

Cc: The Chairman, KBTH-IRB

APPENDIX VI: WORK SCHEDULE

Year	2021									2022		
Month	Mar	Apr	May	Jun	Jul	Aug	Sep - Feb			Mar - Oct		Nov
Writing and review of the proposal												
Submission for review and ethical clearance												
Training of research assistants and pretesting												
Pilot project												
Data collection												
Data entry and cleaning												
Analysis and preparation of manuscript												
dissemination												

APPENDIX VII: BUDGET AND RESOURCES

ITEM	COST (GHS)
Stationery	100
Printing	300
Internet	250
Binding	50
Blood glucose meter	200
Blood glucose strips	400
Blood ketone meter	240
Blood ketone strips	240
Urine ketone dipsticks	100
Heparin tubes	100
Blood gas analysis	2560
Stipend for research assistants	1800
Miscellaneous	200
Total	**6540**

Cost in USD: $1112