THE RELATIONSHIP BETWEEN MATERNAL GLYCAEMIC CONTROL AND BIRTH OUTCOME AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Declaration

I, Paul Jasper Okoth Onyango, declare that this dissertation is my own work. It is being submitted to The University of the Witwatersrand, in partial fulfilment for the degree of Masters of Medicine in Obstetrics and Gynaecology. It has not been submitted for any degree or examination purposes at this institution, or any other university.

Paul Jasper Okoth Onyango

This 5th day of August 2016

Dedication

This research is dedicated to my beloved parents Hilda Atieno Onyango and the late Ibrahim Sitech Onyango Ogola.

Rest in Peace Dad.

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Abstract

Background:

The setting of this study was Chris Hani Baragwanath Academic Hospital (CHBAH) at the diabetic antenatal clinic (ANC). CHBAH is a tertiary hospital that serves 3 secondary level hospitals (Sebokeng, Klerksdorp-Tshepong and Natalspruit), 1 district hospital (Bheki Mlangeni), and 25 clinics in Soweto, Orange Farm and Lenasia.

The diabetic ANC offers a specialised multidisciplinary clinic for diabetic women and is run by an obstetrician, endocrinologist, dietician, diabetes nurse educator and midwives. The feto-maternal unit at CHBAH offers first and second trimester ultrasound services for all diabetic pregnant women. Foetal growth, liquor volume and foetal abnormalities were monitored using serial ultrasound scans. Foetal wellbeing was assessed by non-stress tests. Amniocentesis, only if indicated, was offered for women at high risk for Down's syndrome and in cases of preterm delivery to assess foetal lung maturity. First and second trimester screening blood tests are not routinely offered. Most pregnancies were allowed to go to 37 completed weeks, provided that optimal glycaemic control was achieved and that there were no obstetric indications for early delivery.

Women with GDM were recalled at 6 weeks postpartum and offered a 75gram OGTT (WHO diagnostic criteria for non-pregnant adults).

Objectives:

1. To investigate the relationship between maternal glycaemic control and neonatal outcome at CHBAH.

2. To determine overall glycaemic control in pregnant women with diabetes who have delivered at CHBAH.

3. To determine neonatal complications of babies born to diabetic mothers delivered at CHBAH.

Methods:

This was a retrospective cohort study of all women with diabetes who attended ANC at CHBAH and delivered between 1st January 2011 and 31st December 2011. The centre's database (bed letter, ANC booking cards and clinic record files) was searched for diabetic patients followed up at the clinic and delivered in that year. The patient records were reviewed for maternal demographics, ultrasound investigations, HbA_{1c} levels (done every four weeks as a measure of glycaemic control) and birth outcome (macrosomia, shoulder dystocia, neonatal hypoglycaemia, neonatal respiratory distress syndrome and congenital abnormalities).

Results:

During the period from 1st January 2011 to 31st December 2011, 120 patients with both Gestational Diabetes Mellitus (GDM) and Pre-gestational Diabetes Mellitus (PGDM) were followed up and delivered at CHBAH. Four patients were excluded from the study because of multiple pregnancy (1) and antiphospholipid syndrome (3) leaving a total number of 116.

The overall glycaemic control improved with each trimester. In the 1st trimester the mean HbA_{1c} was 9% and standard deviation was 2.0, and in the 2nd trimester the mean HbA_{1c} was 7.6% and standard deviation was 1.5 while in the 3rd trimester the mean HbA_{1c} was 7.1% and standard deviation was 1.3.

Thirty-six neonates that were delivered were macrosomic (birth weight above the 90th centile for gestational age). This was nearly one-third of the deliveries (31%). Twenty-five neonates had respiratory distress syndrome (21.5%). Seventeen neonates had neonatal hypoglycaemia (14.6%). There were five stillbirths (4.3%), two neonates with congenital abnormalities (1.7%) and two women had early neonatal deaths (1.7%).

Women with an HbA_{1c} of greater than 7% in the 3rd trimester were 2.83 times more likely to have a macrosomic neonate than women with an HbA_{1c} less than 7%. There was no statistically significant relationship found between HbA_{1c} levels and the other birth outcomes. There were no cases of shoulder dystocia, maternal deaths or life threatening maternal complications found in this study.

Conclusion:

Women with poor glycaemic control (HbA_{1c} greater than 7%) in the 3rd trimester were 2.83 times more likely to have a macrosomic neonate than women with good glycaemic control (HbA_{1c} less than 7%).

There was no statistically significant relationship found between HbA_{1c} levels and neonatal respiratory distress syndrome, neonatal hypoglycaemia, still birth, congenital defects, neonatal ICU admission and neonates that were ventilated.

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ABBREVIATIONS

ACHOIS: Australian Carbohydrate Intolerance Study in Pregnant Women

ADA: American Diabetes Association

ANC: Antenatal Clinic

ASD: Atrial Septal Defect

BMI: Body Mass Index

CHBAH: Chris Hani Baragwanath Academic Hospital

CPD: Cephalopelvic Disproportion

CS: Caesarean Section

DDCT: Diabetes Control and Complications Trial

DM: Diabetes Mellitus

END: Early Neonatal Death

EDD: Expected Date of Delivery

FSB: Fresh Still Born

GDM: Gestational Diabetes Mellitus

HAPO: Hyperglycaemia and Adverse Pregnancy Outcome study

HbA_{1c}: Glycated Haemoglobin

HIV: Human Immunodeficiency Virus.

IADPSG: International Association of Diabetes and Pregnancy study group.

ICU: Intensive Care Unit

IOL: Induction of Labour

LMP: Last Menstrual Period

MSB: Macerated Still Born

MAC: Micro Albumin to Creatinine Ratio.

MCV: Mean Corpuscular Volume

NDDG: National Diabetes Data Group

NICE: National Institute for Health and Clinical Excellence

NRTI: Nucleoside Reverse Transcriptase Inhibitors

NVD: Normal Vaginal Delivery

OGTT: Oral Glucose Tolerance Test

PCR: Protein to Creatinine Ratio

PGDM: Pre-Gestational Diabetes Mellitus

TOP: Termination of Pregnancy

VSD: Ventriculo-Septal Defect

WHO: World Health Organisation

1. INTRODUCTION

1.1. Background

"They gave birth astride a grave, with a grave awaiting both the mother and the foetus". This was the grim reality that awaited pregnant women with diabetes earlier in this century, as described by Drury. [1]

Diabetes mellitus (DM) in pregnancy is a concern to both the woman and foetus. Pre-existing diabetes increases the risk for miscarriage, preterm labour, pre-eclampsia, still birth, congenital anomalies, macrosomia, and birth injuries. Neonates that are born to women with DM have postnatal adaptation problems such as hypoglycaemia. [2]

Worldwide, the incidence of DM is growing rapidly. It was estimated that in 1985, approximately 30 million people had diabetes. This figure increased to 230 million in 2006, and 80% of these diabetics are found in the developing countries, India having the highest numbers. [3, 4]

1.2. Pre-gestational diabetes mellitus

Pre-gestational diabetes mellitus is defined as the onset of DM before pregnancy, and can either be Type 1 or Type 2 diabetes.

The rise in Type 2 diabetes mirrors the rising epidemic of obesity and its associated complications. These complications arise from hyperglycaemia and can be avoided if diabetes is diagnosed and managed early. In Africa, diabetes is only one of the numerous challenges affecting a continent with low resources, however, screening in pregnancy would offer a window of opportunity to manage this disease and improve both maternal and neonatal outcomes. [5]

In the United Kingdom, Type 1 DM affects approximately 1 in 200 to 300 pregnancies. [6, 7]

Type 1 DM is a state of absolute insulin deficiency. This type of diabetes usually manifests at

an early age and is associated with an autoimmune destruction of the pancreatic islet cells by autoantibodies. Type 2 DM is either caused by insulin resistance or defective insulin secretion, and usually manifest late in life. [8] In the general South African urban and peri-urban population, the prevalence rate of Type 2 DM is 3-10%. [9] However, the highest prevalence of Type 2 DM is found in elderly coloured community in Cape Town (28.7%) and in the Indian community of Durban (13%). [10, 11]

Regionally, Alemu et al. reported an incidence of 2.1% for Type 1 DM in rural Ethiopia while Beran et al. had a Type 1 DM prevalence of 3.5% in Mozambique. [12, 13]

In Sub Saharan Africa, Type 2 DM accounts for more than 90% of diabetic cases reported and like the rest of the world the prevalence is increasing. Population based prevalence in East Africa for Type 2 DM ranged from 1% in rural Uganda to 12% in urban Kenya. [14, 15]

New evidence from the HAPO study suggests a continuous linear relationship between maternal glucose levels below those diagnostic for DM and foetal growth, and that foetal growth can be modified by glucose lowering therapies. Evidence from ACHOIS trial indicate that treatment of GDM in the form of blood glucose monitoring, diet and lifestyle interventions and insulin therapy as required for glycaemic control reduces the rate of adverse perinatal outcome specifically (serious perinatal outcomes: death, shoulder dystocia, bone fracture and nerve palsy) were significantly reduced from 4% to 1% and that mothers receiving treatment had an improved health-related quality of life. Taken together, the current evidence indicates the importance of screening women at risk for GDM and treatment for maternal hyperglycaemia less severe than that used to define overt DM. [16, 17]

1.3. Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity that first occurs or is first detected in pregnancy. [18]

In women with GDM the pancreatic beta cell insulin production cannot keep up with the resistance to insulin produced by the placental hormones, that is, progesterone, cortisol, prolactin, human placental lactogen (hPL) and leptin. [19]

The incidence of GDM ranges between 3-14%. This range varies depending on the diagnostic criteria used and the ethnic population being studied. The mean incidence is 5%. [20]

Locally, Mamabolo et al. investigated the prevalence of GDM in women residing in the central region of the Limpopo Province, South Africa and reported a prevalence of 1.5% for GDM.[21] Ranchod et al. reported an incidence of 3.8% at Northdale Hospital in Pietermaritzburg, South Africa. [22]

Regionally, Seyoum et al. reported a prevalence of GDM of 3.7% in rural pregnant mothers in Northern Ethiopia. Swai et al. reported 0% prevalence in rural Tanzania after a 75gram OGTT was offered to 189 pregnant women and 2415 non pregnant women during a community screening programme in rural Tanzania. The 0% prevalence may in part be as a result of their leanness (mean BMI of 22.6 kg/m^2), physical activity since majority of women in rural Tanzania work on the land even when pregnant and their diet consisting of 75% carbohydrate with meat not eaten frequently [23, 24]

1.4. Glycated haemoglobin

Glycated haemoglobin (HbA_{1c}) is a marker of glycaemic control over the preceding 120 days, based on the life span of the adult red blood cell. [25, 26] It is formed by a non-enzymatic bond between the N-terminal valine of the haemoglobin beta-chain to glucose. [27] It is a haemoglobin variant and is accepted as a standardized measure of glycated haemoglobin. HbA_{1c} is reduced in pregnancy when compared to non gravid values. [28-30] This is as a result of foetal and placental utilization, and shorter red blood cell life span. [31, 32] HbA_{1c} value is increasingly used for the detection of diabetes. It decreases during pregnancy and varies with

gestational age and ethnicity. The baseline HbA_{1c} value may predict the risk of adverse pregnancy outcomes. [33]

The diabetic ANC at CHBAH defines good maternal glycaemic control as an HbA_{1c} of less than 7% or mean blood finger-prick glucose of 4-5 mmol/L. The mean was calculated every week by averaging the values in the weekly 6 point profile self recorded by each patient at home on the form shown in Appendix D. Poor glycaemic control was an HbA_{1c} greater than 7%. The relationship between HbA_{1c} and mean plasma glucose levels was defined using data collected from the diabetes control and complications trial (DCCT) as shown in table 1 below.[34]

Table 1: Relationship between HbA_{1c} and approximate mean plasma glucose levels [34]

HbA_{1c} (%)	Approximate mean plasma glucose (mmol/L)
4	3.5
5	5.5
6	7.5
7	9.5
8	11.5
9	13.5
10	15.5
11	17.5
12	19.5

1.5. HIV and diabetes

Diabetic patients, who were HIV infected, were found to have a higher initial weight when compared to non diabetics. Those with pre -HAART weights of more than 70 kg were found to have a significantly higher risk of developing diabetes compared to those patients with weights less than 50 kg. This is consistent with the fact that insulin resistance correlates with obesity. [35]

There was no association between diabetes and HIV specific factors. Neither $CD4^+$ count nor pre-HAART viral load influenced risk of developing diabetes. [36-38]

Glesby et al. found that there were lower HbA_{1c} values in HIV positive diabetic women compared to similar population of HIV negative diabetic women after adjusting for fasting glucose levels. This was as a result of higher MCV values in the HIV positive group. [39]

Similar results were published by Kim et al. where HbA_{1c} underestimated glycaemic levels in HIV positive patients. This was due to the use of NRTI (Abacavir), which increased the MCV. Glycated fructosamine may be a better option for the HIV positive patients. [40, 41]

1.6. Diagnostic criteria

Table 2: Diagnostic criteria for gestational diabetes [2, 42-45]

	WHO (75g test)	ADA (75g test)	ADA (100g test)	NDDG (100g test)	IADPSG (75g test)	NICE (75g test)	CDA (75g test)
Fasting	≥ 7.0	≥ 5.1	≥ 5.3	≥ 5.8	≥ 5.1	≥ 5.6	≥ 5.1
1hr	-	≥ 10	≥ 10	≥ 10.6	≥ 10.0	-	≥ 10
2hr	≥ 7.8	≥ 8.5	≥ 8.6	≥ 9.2	≥ 8.5	≥ 7.8	≥ 8.5
3hr	-	-	≥ 7.8	≥ 8.0	-	-	-
Notes	One abnormal value required	One abnormal value required	Two abnormal values required	Two abnormal values required	One abnormal value required	One abnormal value required	One abnormal value required

*Units in mmol/L

As shown above in Table 2, different associations use different criteria to diagnose GDM. The International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) published its recommendations on the diagnosis and classification of hyperglycaemia in pregnancy based on the HAPO study that used a one-step 75 gram test in order to standardize the glucose load internationally. The group further recommended a strategy for the detection and diagnosis of hyperglycaemic disorders in pregnancy. At the first

ANC visit, screen all or only high risk women for overt diabetes in pregnancy by either a fasting blood glucose ≥ 7.0 mmol/L or an HbA_{1c} level ≥ 6.5%, or a random blood glucose ≥ 11.1 mmol/L. Those diagnosed with overt diabetes in pregnancy were to receive treatment and follow up as pre-existing diabetics. Women who screened negative for overt diabetes in pregnancy at the first ANC visit were to be offered a 75 gram OGTT between 24-28 weeks gestation. [43]

The Canadian Diabetes Association (CDA) has a one-step approach as shown on Table 2 above and has a preferred two-step approach to screening and diagnosis of GDM. Screening is initially done using the 50 gram glucose challenge test administered in the non fasting state. Blood glucose concentration is measured 1 hour later.

- If the blood glucose concentration is < 7.8 mmol/L then that is a negative screen.
- If the blood glucose concentration is between 7.8-11.0 mmol/L then that is a positive screen and a confirmatory 75 gram OGTT is performed using the following criteria where by ≥ 1 of the values is needed for the diagnosis:
  - Fasting blood glucose concentration ≥ 5.3 mmol/L
  - 1 hour blood glucose concentration ≥ 10.6 mmol/L
  - 2 hours blood glucose concentration ≥ 9.0 mmol/L
- If the blood glucose concentration is ≥ 11.1 mmol/L that is diagnostic for GDM and does not require a 75 gram OGTT [45]

In a South African setting more so in public hospitals such as CHBAH where resources are limited, the number of patients attending ANC is overwhelming and patient follow up in poor, then a two-step approach would not be as successful as a one-step approach. It would take more time and money to screen women twice and some women would get lost to follow up.

At the time this study was conducted CHBAH antenatal diabetic clinic was using the NDDG 100 gram oral glucose tolerance test diagnostic criteria. There is however a change now to use the NICE diagnostic criteria at our teaching hospitals so as to identify more patients with GDM as follows:

- Random blood glucose of > 11 mmol/L
- Either fasting blood glucose ≥ 5.6 mmol/L or blood glucose of ≥ 7.8 mmol/L two hours after a 75 gram oral glucose tolerance test (OGTT) performed after overnight fasting, from 24 weeks gestation onwards. [2]

1.7. Problem Statement

Local studies conducted in South Africa have shown a relationship between maternal glycaemia control and birth outcomes. At CHBAH a study done by Huddle auditing the outcome of pregnancy in diabetic women in Soweto, between 1992 and 2002 did not look directly at HbA_{1c} as a marker of glycaemic control versus birth outcome. [46]

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) published in June 2005 and Hyperglycaemia and Adverse Pregnancy outcome (HAPO) published in May 2008 are Western based multi-centre studies that have been published most recently. [16, 17]

Our study population differs from those of the Western world in terms of population race, weight, HIV status and anti-retroviral treatment. We would therefore like to explore whether glycaemic control as measured by HbA_{1c} target levels at CHBAH has an effect on birth outcome in our study population.

2. LITERATURE REVIEW

2.1. Introduction

Diabetes mellitus in pregnancy has been associated with various adverse birth outcomes, increased maternal morbidity and mortality.

Locally at CHBAH, Huddle K audited the outcome of 733 diabetic pregnancies over 11 years. He found a Caesarean section rate greater than 60%, perinatal mortality rate was 3.7%, major congenital malformations were seen in 11 (1.5%) of pregnancies and that there were 2 (0.3%) maternal deaths. [46]

2.2. Risk factors

Risk factors for gestational diabetes include: [42]

- Obesity (Body mass index >30kg/m^2)
- Previous history of GDM
- Family history of diabetes
- Racial origin (Asian, Hispanic, African-Caribbean are associated with increased risk)
- Increasing maternal age
- Previous macrosomic infant
- Polycystic ovary syndrome
- Multiple gestations.

2.3. Adverse outcomes

The adverse birth outcomes this study will explore include the following:

2.3.1. Macrosomia

Foetal macrosomia has been defined in several ways. This includes birth weight > 4000g or > 90th centile of the new-born, adjusted for race, gestational age and sex. The 90th centile has also been used to define large for gestational age (LGA).

Pedersen in 1954 suggested that maternal hyperglycaemia caused an increased exposure of the foetus to hyperglycaemia which then led to hyperinsulinaemia further stimulating protein, glycogen and lipid synthesis which resulted in excessive foetal growth. [47] This theory was recently confirmed (2008) by the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study that showed a continuous linear relationship between maternal glycaemia and both foetal insulin and growth in women with Type 1 DM. In Type 1 DM, maternal HbA_{1c} levels correlated with birth weight. [16]

A second explanation for foetal macrosomia is "lipid overflow". Circulating maternal lipids in well controlled GDM women directly correlate to foetal lipids and foetal growth. [48]

Causes of macrosomia in pre-gestational Type 1 and Type 2 diabetics differ. In the woman with pre-gestational Type 1 diabetes it appears that the antepartum HbA_{1c} is the most significant variable therefore glycaemic control determines macrosomia while in the woman with pre-gestational Type 2 diabetes with good glycaemic control it is the pre-gestational BMI that determines occurrence of macrosomia. [49]

Associated maternal morbidity resulting from foetal macrosomia includes prolonged labour, shoulder dystocia, brachial plexus injury, operative delivery, postpartum haemorrhage, infections and perineal tears. [50] Neonatal morbidity includes hypoglycaemia, hypertrophic cardiomyopathy, hyperbilirubinaemia and respiratory disorders. [51]

In a non-diabetic population, the overall rate of macrosomia is 7-9%. [52]

The incidence of macrosomia in GDM is dependent on maternal glycaemic control. If good glycaemic control is not achieved, the incidence of macrosomia can be as high as 20-40%. [53] Knowledge of identifiable antenatal risk factors for macrosomia can allow timely intervention and prevention of complications. These risk factors include;

- Maternal pre-pregnancy weight. Women who have a high body mass index are more likely to have larger infants. [54-58]
- Excessive maternal weight gain during pregnancy is a risk factor for macrosomia. [54]
- Prolonged pregnancies and advance gestational age is a risk factor for macrosomia. 3-10 % of post dates deliveries are macrosomic. [59]
- Multiparity and grand multiparity increase the risk. Increased parity has been associated with 100 to 150 grams increase in foetal weight gain. [60, 61]
- Foetal sex, male infants generally weigh more the female infants. This association has been confirmed by recent studies. [62]
- Polyhydramnios greater than 60th centile for gestational age has been associated with macrosomia. [63]

2.3.2. Shoulder Dystocia

The definition and incidence of shoulder dystocia varies worldwide. The Royal College of Obstetricians and Gynaecologists defines shoulder dystocia as "a delivery that requires additional obstetric manoeuvres to release the shoulders after gentle traction has failed". [64]

The American College of Obstetricians and Gynaecologists defines it as ''delivery that requires additional obstetric manoeuvres following failure of gentle downward traction on the foetal head to effect delivery of the shoulders''. Shoulder dystocia is a complication seen in 0.6-1.4% of all births. [65]

The incidence rises to 5-9% in infants with birth weight of 4000-4500 grams. [66]

It is known that the risk of shoulder dystocia, even in premature infants, is significantly higher in diabetic pregnant women than in non-diabetic women due to altered neonatal body composition. In macrosomic infants, the risk is further increased. The absolute risk of infant brachial plexus injury ranges from 12-35% in macrosomic infants. [67-69]

Shoulder dystocia can cause complications to both mother and infant. The new born may suffer contusions, fractures, hypoxia resulting in cerebral palsy and brachial plexus damage.[70]

The mother has an increased risk of having tears to her perineum, cervix, episiotomy extension, third/fourth degree tears and post partum infections. There is also an increased risk of post partum haemorrhage requiring transfusion. Other morbidity may include bladder atony, femoral nerve palsy, injury to pubic symphysis and possible uterine rupture. [71]

Risk factors for shoulder dystocia include: [66, 72, 73]

- Macrosomia ($\geq$ 4500 grams)
- Diabetes.
- Induction of labour.
- Assisted (instrumental) vaginal delivery.
- Previous shoulder dystocia.
- Maternal obesity (BMI > 30kg/m^2) and increased weight gain during pregnancy.
- Ethnicity: android type pelvis in African Americans.
- Foetal presentation.
- Foetal sex; Male infants are bigger than female infants.
- Post-dates pregnancy increases risk of macrosomia thus increasing risk of shoulder dystocia.
- Prolonged second stage of labour.

2.3.3. Neonatal hypoglycaemia

Neonatal hypoglycaemia is internationally defined as a blood glucose level ≤ 2.6 mmol/L in neonates. It is not the maternal glycaemic control during pregnancy that determines the incidence of neonatal hypoglycaemia, rather, maternal glycaemic control during labour. The recommended blood glucose levels during labour are between 4-7 mmol/L. [74]

The prevalence of early neonatal hypoglycaemia is about 25% depending on maternal glycaemic control during delivery. [75]

At CHBAH, our protocol is to use Alberti's regime during labour and delivery of all our diabetic women in a high care area to control maternal glucose levels. It is our standard of care to run 1 litre 5% dextrose-saline with 20 mmol of potassium chloride at 125 ml per hour with insulin (Humulin R) according to hourly finger prick blood glucose level as follows;

- If the blood glucose concentration is less than 4 mmol/L, no insulin is administered
- If the blood glucose concentration is between 4-8 mmol/L, then 8 units of Humulin R insulin is added into 1 litre 5% dextrose-saline and run at 125 ml per hour
- If the blood glucose concentration is more than 8 mmol/L, then 16 units of Humulin R insulin is added into 1 litre 5% dextrose-saline and run at 125ml per hour. [76]

Neonatal hypoglycaemia is secondary to foetal hyperinsulinaemia and the cessation post delivery of maternally driven hyperglycaemia. As a result, the foetal hyperinsulinaemia leads to a hypoglycaemic state due to reduced glucose intake. High levels of insulin supress a compensatory increase in free fatty acids and hepatic gluconeogenesis. [77] In severe acute hypoglycaemia, the foetal brain is the most affected organ, especially the white matter with haemorrhage, middle cerebral artery infarction and basal ganglia / thalamic abnormalities noted. [78]

2.3.4. Neonatal respiratory distress

Concerns over an increased stillbirth rate and increased incidence of foetal macrosomia have driven obstetricians to consider delivery at earlier gestations usually between 34–38 weeks. This may reduce the stillbirth rate, but it increases iatrogenic prematurity causing neonatal complications particularly respiratory distress syndrome. [75]

Respiratory distress syndrome is an acute restrictive pulmonary disease where there is generalized atelectasis that occurs shortly after birth in premature infants due to surfactant deficiency, leading to progressive ventilation failure. [79] Maternal diabetes is known to affect normal foetal lung maturity. Therefore, infants born from diabetic women have a higher risk of respiratory distress syndrome. This is due to deficient surfactant production. [80] It is thought that foetal hyperinsulinaemia suppresses surfactant synthesis by inhibiting lecithin synthesis, thus reducing Type 2 pneumocytes uptake of choline. [81, 82]

The risk of respiratory distress syndrome can be potentially reduced by the administration of corticosteroids to all diabetic mothers to induce maturation of the foetal lung. Corticosteroids however, may disrupt glycaemic control and this can be minimised by increasing insulin doses. The use of corticosteroids is now standard protocol for non-diabetic pregnant women with planned delivery before 37 weeks. [83]

Corticosteroids also benefit preterm infants further by reducing the risk of neonatal death, cerebroventricular haemorrhage, necrotising enterocolitis, and systemic infections. [84]

At CHBAH, if preterm induction of labour was anticipated due to obstetric indications such as poor obstetric history, foetal macrosomia or maternal indications such as worsening retinopathy, nephropathy and neuropathy, then betamethasone 12mg intra muscular injection was given in 2 doses 12 hours apart.

The incidence of respiratory distress syndrome was much higher in infants delivered by caesarean section than vaginal delivery. [85]

Caesarean sections at CHBAH were done only for obstetric indications and elective caesarean sections were done as early as possible during the day.

2.3.5. Congenital abnormalities

The leading cause of infant death in the United States is birth defects, and affects approximately 1 in 33 neonates. [86, 87] The risk of major congenital anomalies and spontaneous abortion increases as the HbA_{1c} value increases. Hyperglycaemia during embryogenesis is a known risk factor for cardiovascular system, central nervous system, musculoskeletal system defects and once the HbA_{1c} levels are less than 5 standard deviations above the normal mean, the risk of congenital anomalies is not increased. [88, 89]

A possible theory for increased incidence of neural tube defects in diabetes is that maternal hyperglycaemia results in an increase in glucose levels in the embryo, leading to biochemical abnormalities that in turn increase oxidative stress. This inhibits the Pax3 gene required for neural crest development, which further leads to the derepression of the p53-dependant cell death, resulting in impaired neural tube closure. [90, 91]

Peri-conceptional HbA_{1c} values that are less than 7.0% to 7.5% reduce the risk of congenital malformations. An HbA_{1c} of less than 9.3% has a spontaneous abortion rate of 12.4% and congenital anomaly rate of 3%. With an increased value of HbA_{1c} of 14.4% or more, the rate of spontaneous abortion increases to 40%. [92]

However, in diabetic pregnant women with good glycaemic control, the risk is similar to that of a non-diabetic pregnant woman. [93]

Gestational diabetes mellitus has been associated with birth defects. [94, 95] This association between congenital birth defects and GDM may be to a large extent an association with Type 2 DM. This is because some women diagnosed with GDM may very well be undiagnosed Type 2 diabetics. [94, 96]

Pre-pregnancy obesity is a risk factor for Type 2 DM has been associated with birth defects, raising the question whether the association of GDM with congenital birth defects is more likely to occur among infants of women with pre-pregnancy obesity. [97-99]

Correa et al. examined the associations between diabetes mellitus and 39 birth defects. The study found that there was a significant association between PGDM and seven non-cardiac defects namely anencephaly, anotia/microtia, cleft lip with or without cleft palate, anorectal atresia, bilateral renal agenesis/hypoplasia, longitudinal limb deficiencies; and 11 cardiac defects including tetralogy of Fallot, dextro-transposition of great vessels, atrial ventricular septal defect, total anomalous pulmonary venous return, aortic stenosis, perimembranous ventricular septal defect, atrial septal defect secundum and ventricular outflow tract obstruction. They also found an association between three non-cardiac defects; cleft palate, cleft lip and anorectal atresia and three cardiac defects; tetralogy of Fallot, pulmonary valve stenosis and atrial septal defect secundum with GDM. [100]

Table 3: Examples of congenital birth defects [100]

Cardiac birth defects	Non cardiac birth defects
• ASD: secundum • VSD: perimembranous • Tetralogy of Fallot • Dextro-transposition of great vessels • Total anomalous pulmonary venous drainage	• Cleft lip with or without cleft palate • Spina bifida • Hydrocephaly • Bilateral renal agenesis/ hypoplasia • Anorectal atresia • Sacral agenesis/caudal dysplasia

Sacral agenesis is a rare congenital abnormality but specific to children of diabetic mothers. In the general population the incidence is 0.005-0.01%. Higher frequencies ranging 0.1-0.2% are seen in children born to diabetic mothers. Approximately 16 to 20% of children with sacral agenesis have mothers with diabetes mellitus. [101]

Murphy et al. found that glycaemic control was of utmost importance as a risk factor for congenital birth defects in pregnancies complicated by Type 1 and Type 2 diabetes. HbA_{1c} at booking was the only independent risk factor for congenital birth defects in Type 2 diabetics and that Type 2 diabetics had better outcomes than Type 1 diabetics.[102]

3. STUDY METHODOLOGY

3.1. Objectives

1. To investigate the relationship between maternal glycaemic control and neonatal outcome at CHBAH.
2. To determine overall glycaemic control in pregnant women with diabetes who have delivered at CHBAH.
3. To determine neonatal complications of babies born to diabetic mothers delivered at CHBAH.

3.2. Methods

3.2.1. Setting

The setting of this study was Chris Hani Baragwanath Academic Hospital (CHBAH) at the diabetic antenatal clinic (ANC). CHBAH is a tertiary hospital that serves 3 secondary level hospitals (Sebokeng, Klerksdorp-Tshepong and Natalspruit), 1 district hospital (Bheki Mlangeni), and 25 clinics (Enerdale, Eldorado Park, Lawley, Lenasia, Lenasia South, Protea South, Stretford, Zola, Lilian Ngoyi, Orange Farm, Barney Molokwane, Finetown, Kliptown, Diepkloof, Meadowlands, Moroka, Noordgesig, Orlando, Mandela-Sisulu, Michael Maponya, Tladi, Mofolo, Itineleng, Chiamelo and Thembehle) in Soweto, Orange Farm and Lenasia. The clinic offers maternity services to a large number of low and high risk pregnancies. The population served by CHBAH is almost entirely of African ethnicity both local South Africans and foreign African immigrants who are more often from poor socio-economic backgrounds. The socio-economic situation has been worsened by the HIV/AIDS pandemic, which has had a negative impact on social, economic, maternal, infant and child health.

CHBAH has a combined diabetic and obstetric ANC managed by a multidisciplinary team comprised of an experienced obstetrician with special interest in the management of diabetes in pregnancy, internal medicine specialist (endocrinologist), a diabetes nurse educator and midwives. CHBAH has a feto-maternal medicine unit that conducts ultrasound scans for this high risk clinic. New patients were initially hospitalised for clinical and biochemical assessment. While in the ward, they were taught self blood glucose monitoring and documentation in the blood glucose profile chart (Appendix D). The women were also educated on diabetic diet which has 1800-2000 kcal complex carbohydrate diet divided into 3 main meals and a late night snack. They were also taught how to self-administer insulin and upon discharge from the hospital, patients returned two weekly for follow up until 32 weeks gestation and then weekly until 37 completed weeks when they were readmitted for delivery. Patients were screened and referred to the combined diabetic and obstetric specialist ANC from local clinics if: [76]

- They were known Type 1 or Type 2 DM;
- They had a previous history of GDM;
- They had a family history of diabetes;
- They had a weight > 100kg or BMI > 40kg/m^2;
- They had a previous unexplained stillbirth;
- They had a previous macrosomic baby (> 4000g);
- They were aged > 40 years;
- They had polycystic ovarian syndrome;
- They had polyhydramnios in the current pregnancy;
- They had persistent glycosuria on urine dipstick of 1+ on two occasions or 2+ on one occasion;
- They had a random blood sugar more than 10 mmol/L;

- They had an abnormal OGTT.

The study population were all the patients who attended the diabetic antenatal clinic from 2010-2011 whose pregnancies ended (delivered or miscarried) between 1st January 2011 to 31st December 2011. Patients were identified through clinic records.

Women with either pre-gestational diabetes mellitus (PGDM) or gestational diabetes mellitus (GDM) were included. At the first visit all patients had a physical examination, blood pressure measurement, weight and height for body mass index (BMI).

The BMI for patients was measured as the weight in kilograms divided by the square of the height in metres (Weight/Height^2). For example, if weight is 70 kilograms and the height is 1.75 meters then the BMI= 70/1.75^2 then the BMI is 22.9 kg/m^2.

Initial investigations included:

- HbA_{1c} (less than 7% = good control and more than 7% = poor control).
- Urine dipstick for patients with PGDM, if proteinuria was absent, a micro albumin to creatinine ratio (MAC) was done. If proteinuria was present, then a urine protein to creatinine was done (PCR).
- Fundoscopy to assess end organ damage and all women with proliferative retinopathy were referred to an ophthalmologist.
- Baseline ultrasound scans done by the maternal and feto-maternal medicine unit.

3.2.2. Study Design

This was a retrospective cohort study.

3.2.3. Study Population

The study population included all women with diabetes on follow up at the CHBAH diabetes ANC from 2010-2011 whose pregnancies ended (delivered or miscarried) between 1st January 2011 and the 31st December 2011.

There were a total of 120 diabetic patients who attended clinic and whose pregnancies ended within that year. These patients were identified through the ANC clinic records.

3.2.4. Exclusion Criteria

Women with diabetes and any of the following conditions will be excluded as they may adversely affect neonatal outcome directly:

1. Multiple pregnancies.
2. Known teratogenic exposure.
3. Congenital infections excluding HIV.
4. Antiphospholipid syndrome.

3.2.5. Data Analysis

Data was analysed using STATA software with the aid of a statistician. Statistical significance was determined by a p-value of < 0.05. Frequency tables were generated for most of the variables and summary statistics were presented. Means (with standard deviations) and medians (with inter-quartile ranges) were described for continuous (numerical) variables. Students T-test for parametric data and the Mann-Whitney test for non-parametric data were used to determine frequency distribution. Standard deviations and median with ranges was used for descriptive statistics. Frequency was expressed as a percentage with 95% confidence intervals. Univariate analysis was used to determine how variables were associated with adverse birth outcomes.

3.2.6. Ethical Considerations

The study was approved by the Human Research Ethics Committee of The University of Witwatersrand (Ethics Clearance Certificate: M121176).

Permission to perform the study at The Chris Hani Baragwanath Academic Hospital was obtained from the CEO of the institution.

Each patient was allocated a study number, which appeared on the data sheet. Names were not used to safeguard confidentiality.

4. RESULTS

4.1. Maternal Outcome

A total of 120 patients with diabetes were seen at the combined diabetic and obstetric specialist ANC at CHBAH and delivered from 1st January 2011 to 31st December 2011. Of the 120 patients, 4 were excluded from the study (1 with multiple pregnancy and 3 had antiphospholipid syndrome) as per the protocol leaving a total number of 116 patients who were enrolled in this retrospective study.

Table 4: Demographic characteristics, mean HbA_{1c} and ultrasound findings of patients attending diabetic antenatal clinic at Chris Hani Baragwanath Academic Hospital

Characteristics	Frequency
Age	**n=116 (%)**
15 – 20	5 (4.3)
21 – 25	11 (9.5)
26 – 30	21 (18.1)
31 – 35	32 (27.6)
36 – 40	35 (30.2)
>41	12 (10.3)
Parity	**n=116 (%)**
0	22 (19)
1	19 (16.4)
2	50 (43)
3	16 (13.8)
4	7 (6)
5	1 (0.9)
6	1 (0.9)
Gravidity	**n=116 (%)**
1	14 (12.1)
2	17 (14.7)
3	49 (42.2)
4	21 (18.1)
5	9 (7.8)
6	4 (3.4)
7	2 (1.7)

Characteristics	Frequency
Previous miscarriage	**n=116 (%)**
0	94 (81)
1	19 (16.4)
2	1 (0.9)
3	1 (0.9)
6	1 (0.9)
Number of ANC visits	**n=110 (%)**
1- 5	25 (21.6)
6 – 10	56 (48.3)
11 - 15	30 (25.8)
>16	5 (4.3)
HIV status	**n=116 (%)**
Negative	94 (81)
Positive	21 (18.1)
Unknown status	1 (0.9)
HbA_{1c}	**Mean (standard deviation)**
1st trimester	9.0% (2.0)
2nd trimester	7.6% (1.5)
3rd trimester	7.1% (1.3)
Ultrasound pathology	**n=110 (%)**
Normal Ultrasounds	102 (92.7)
Oligohydramnios	6 (5.5)
Cardiac abnormality	1 (0.9)
Increased Nuchal Translucency	1 (0.9)

Table 4 above shows the demographic characteristics, mean HbA_{1c} and ultrasound findings of patients attending diabetic antenatal clinic at CHBAH. The majority of women (57.8%) were between 31–40 years. 48.3% managed to attend the combined diabetic and obstetric specialist ANC 6–10 times during their pregnancy. The majority of women (92.7%) had normal ultrasound scans.

The mean booking gestational age was 19 weeks. The range was from 4 weeks to 35 weeks gestation. The median gestational age at delivery was 37 completed weeks with an interquartile range of 28–38 weeks. The mean booking weight was 82.4 kg with a range from 52.5 kg to 135 kg. The mean booking haemoglobin was 12.2 g/dL with a range from 7.7 g/dL to 16.5 g/dL. 115 patients were RH positive and only 1 patient was RH negative. 114 patients were RPR negative and two patients were RPR positive. 94(81%) patients were HIV negative, 21 patients, (18.1%) patients were HIV positive and one patient (0.9%) had an unknown HIV status. The mean CD4 count was 283 cells/mm^3, ranging from 22 cells/mm^3 to 914 cells/mm^3.

There were 86 (74.1%) caesarean section deliveries and 30 (25.9%) normal vaginal deliveries. There were no assisted vaginal deliveries. The main indications for caesarean section deliveries were foetal distress (33.7%), elective caesarean section (23.2%) and failed induction of labour (17.4%) as shown in Table 5 below.

Table 5: Indications for Caesarean Section for patients who attended the combined diabetic and obstetric ANC at Chris Hani Baragwanath hospital who delivered from 1st January 2011 to 31st December 2011.

Indications for caesarean section	n = 86 (%)
Foetal distress	29 (33.7)
Elective caesarean section	20 (23.2)
Failed induction of labour	15 (17.4)
Poor obstetric history	4 (4.6)
Hypertension	4 (4.6)
Breech	4 (4.6)
Oligohydramnios	3 (3.5)
Antepartum haemorrhage	2 (2.4)
Cephalopelvic disproportion	2 (2.4)
Cord presentation	1 (1.2)
Foetal anomaly	1 (1.2)
Chorioamnionitis	1 (1.2)

4.2. Pre-Gestational and Gestational Diabetes Mellitus

Of the 116 patients in this study, 73 (63%) had pre-gestational diabetes mellitus (PGDM), and 43 (37%) had Gestational diabetes mellitus (GDM) as illustrated in Figure 1 below.

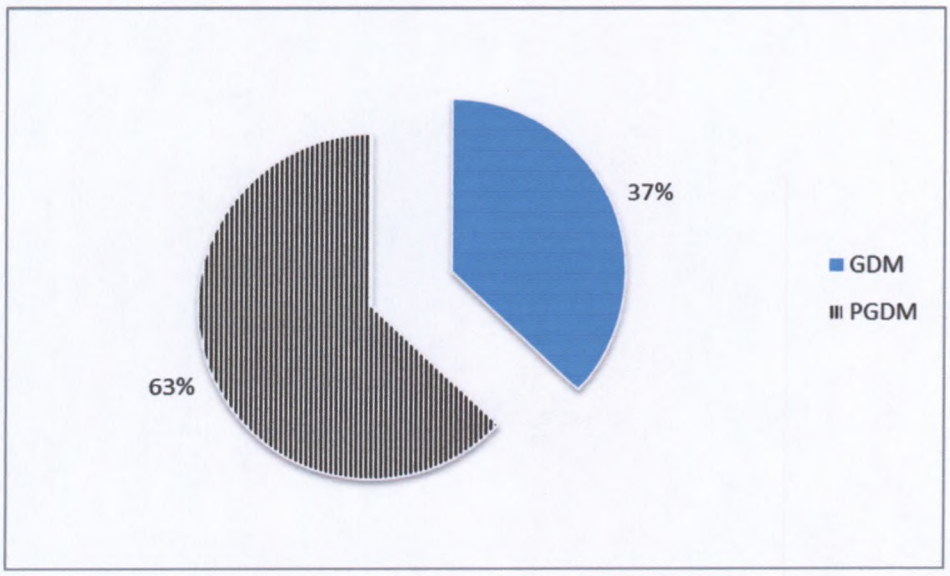

Figure 1: Percentage of GDM and PGDM in study (n=116).

Table 6 below shows the method of glycaemic control in both GDM and PGDM groups. The majority of the women namely 74 (63.8%), were on insulin therapy while 29 patients (23.3%) were on metformin only and 13 patients (11.2%) were on both metformin and insulin therapy and only 2 women (1.7%) had a diet based glycaemic control.

Table 6: Method of glycaemic control in GDM and PGDM groups of patients attending diabetic antenatal clinic at Chris Hani Baragwanath Academic Hospital

	Diet Only n (%)	Insulin n (%)	Metformin n (%)	Metformin and Insulin n (%)	Total
GDM	1 (2.3)	31 (72.1)	9 (20.9)	2 (4.7)	43
PGDM	1 (1.4)	43 (58.9)	18 (24.7)	11 (17.1)	73
TOTAL	2 (1.7)	74 (63.8)	29 (23.3)	13 (11.2)	116

4.3. Neonatal outcome

The total number of NICU admissions was 42 (36%). 25 neonates had RDS (21.5%). 12 (10.3%) neonates with RDS required ventilation. 11 (9.5%) neonates had hypoglycaemia.

Most of the neonates delivered had birth weights between 2500–3499 grams as shown in Figure 2 below. The mean neonatal weight was 2821 grams. 36 neonates (31%), weighed above the 90th centile (macrosomia) and 2 neonates (1.7%), weighed below the 10th centile (small for gestational age). There were no cases of shoulder dystocia or birth injury.

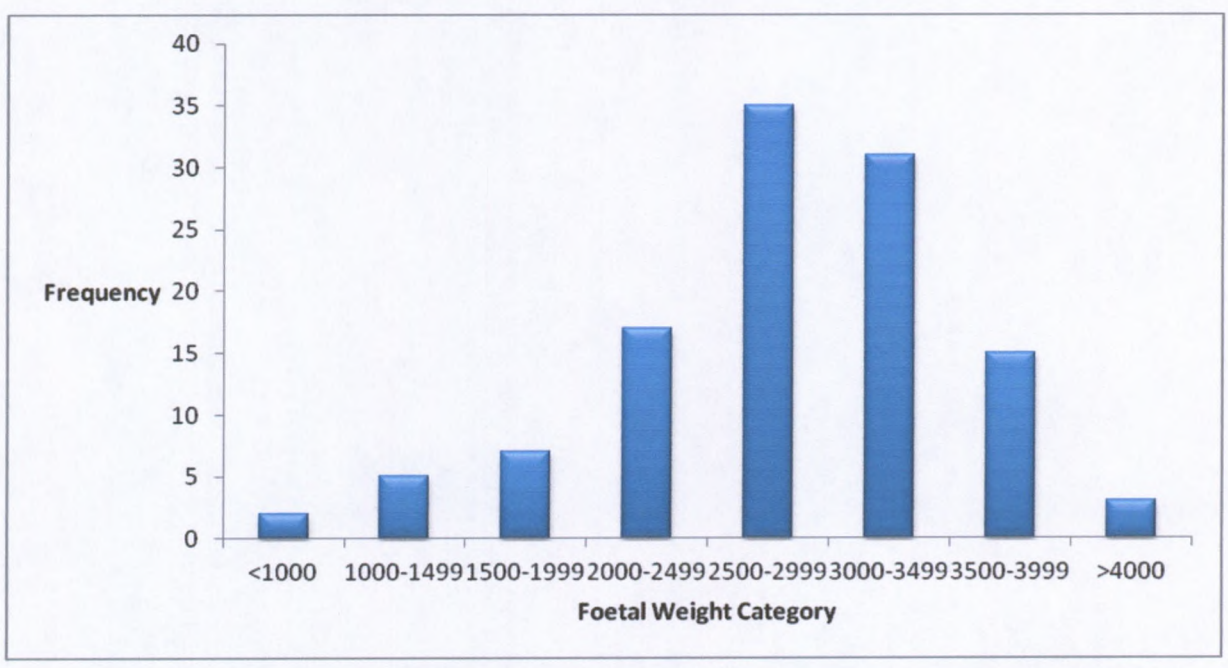

Figure 2: Graph showing foetal weight distribution of babies born to diabetic women attending the diabetic antenatal clinic at CHBAH

The mean number of ANC visits was 8.5 ranging from 1 to 17 clinic visits.

17 neonates, (14.6%) had hypoglycaemia (blood glucose less than 2.6 mmol/L). 25 neonates, (21.5%) had respiratory distress syndrome and 12 (10.3%) required ventilation. The total number of women who received steroids was 18 (16%). Out of the 25 neonates who had respiratory distress syndrome only seven received steroids.

In this study, there were 3 (2.6%) macerated still births (MSB), 2 (1.7%) fresh still birth (FSB) and 2 (1.7%) patients, had early neonatal deaths (END).

The 1st MSB, 580 grams at 25 weeks gestation was from a 17 year old primigravida who had PGDM for 13 years. Her glycaemic control was poor with 1st trimester mean HbA_{1c} of 13.2% and 2nd trimester mean of 9.4%. The 2nd MSB, 1480 grams at 28 weeks had poor glycaemic control with mean 1st trimester HbA_{1c} of 9.2%. The 3rd MSB, 1110 grams at 31 weeks gestation booked late at 24 weeks and had poor glycaemic control with mean 2nd trimester HbA_{1c} of 10.7% and 3rd trimester mean HbA_{1c} of 10.6%.

The 1st FSB, 2130 grams at 35 weeks gestation was delivered by caesarean section for foetal distress. She had booked late at 33 weeks and did not have any HbA_{1c} results at the time of delivery. She was hypertensive on Methyldopa (Aldomet), anaemic with an Hb 8.3g/dL, was on HAART with a CD4 count of 331 cells/ml and had renal impairment. The 2nd FSB, 2840 grams at 38 weeks gestation was delivered by caesarean section for failed induction of labour. She was a 36 year old Para 4 Gravida 5 with GDM and a history of one previous FSB at term. Her glycaemic control was good throughout her pregnancy with mean 1st, 2nd and 3rd trimester HbA_{1c} of 6.8%, 6.7% and 6.8 % respectively.

The 1st END, 3310 grams was delivered by caesarean section for foetal distress. Maternal glycaemic control was poor with 1st, 2nd, and 3rd mean $HbaA_{1c}$ of 9.5%, 7.1% and 9.4% respectively and the records show that the neonate suffered apnoea. The 2nd END was 2870

grams at 36 weeks gestation, was delivered by caesarean section due to foetal distress and had a poor 5 minute Apgar score of 2. Maternal glycaemic control was poor with 2nd trimester mean HbA_{1c} of 11.3%.

A regression analysis of variables versus the following outcomes; macrosomia, still birth, neonatal hypoglycaemia, congenital defects, neonates ventilated, NICU admission and caesarean section. Women with poor glycaemic control ($HbA_{1c} > 7\%$) in the 3rd trimester were 2.83 more likely to have a macrosomic neonate than women with good glycaemic control ($HbA_{1c} < 7\%$). There was no statistically significant relationship found between the variables maternal age, HIV status, booking gestation, booking weight with the outcome macrosomia.

There was also no statistically significant relationship between all the variables and the other outcomes; still birth, neonatal hypoglycaemia, congenital defect, neonates ventilated, NICU admission and caesarean section (Table 7).

Table 7: Regression analysis – Variables versus outcomes

	Macrosomia	Still birth	Neonatal hypoglycaemia	Congenital defect	Neonates ventilated	NICU admission	Caesarean section
Characteristic	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**	**Univariate analysis OR (95% CI) p-value**
Age	1.02 (0.96 – 1.08) 0.55	0.97 (0.85 – 1.11) 0.67	0.98 (0.91 – 1.06) 0.63	1.10 (0.85 – 1.41) 0.48	1.08 (0.97 – 1.20) 0.15	1.03 (0.97 – 1.10) 0.38	1.03 (0.96 – 1.09) 0.45
HIV Negative **HIV Positive**	0.29 (0.79 – 1.04) 0.06	1.14 (0.12 – 10.73) 0.91	1.14 (0.12 – 10.73) 0.91	No result	0.38 (0.05 – 3.13) 0.37	0.49 (0.17 – 1.45) 0.20	1.08 (0.36 – 3.27) 0.89
HbA_{1c} (1st trimester) • Less than 7% • More than 7%	No result	0.22 (0.13 – 3.69) 0.29	No result	No result	0.22 (0.14 – 3.69) 0.29	0.17 (0.12 – 2.26) 0.18	No result
HbA_{1c} (2nd trimester) • Less than 7% • More than 7%	1.02 (0.36 – 2.92) 0.96	0.52 (0.06 – 7.54) 0.53	2.42 (0.47 – 12.40) 0.29	No result	0.89 (0.20 – 4.10) 0.89	1.24 (0.44 – 3.50) 0.68	1.00 (0.32 – 3.14) 0.99
HbA_{1c} (3rd trimester) • Less than 7% • More than 7%	2.83 (1.24 – 6.46) 0.01	0.66 (0.06 – 7.54) 0.74	1.63 (0.58 – 4.60) 0.40	No result	1.70 (0.49 – 5.94) 0.41	1.59 (0.73 – 3.50) 0.25	0.91 (0.38 – 2.19) 0.84
Gestational age at booking	0.97 (0.93 – 1.02) 0.23	0.94 (0.85 – 1.04) 0.25	0.98 (0.93 – 1.04) 0.50	0.99 (0.85 – 1.15) 0.88	1.03 (0.96 – 1.11) 0.37	1.03 (0.99 – 1.08) 0.16	0.98 (0.93 – 1.02) 0.33
Booking weight	0.99 (0.98 – 1.02) 0.77	1.00 (0.97 – 1.04) 0.85	1.00 (0.98 – 1.02) 0.70	1.05 (0.98 – 1.11) 0.17	1.01 (0.98 – 1.04) 0.41	1.01 (0.99 – 1.02) 0.30	1.00 (0.99 – 1.02) 0.86

5. DISCUSSION

In this study, glycated haemoglobin (HbA_{1c}) was the main variable of interest being used as a reflection of long term maternal glycaemic control. This control was then compared to birth outcome. Bad outcome was defined as the presence of the following: macrosomia, neonatal respiratory distress syndrome, neonatal hypoglycaemia, stillborn, congenital defects, neonatal ICU admission and neonates ventilated.

Women with poor glycaemic control (HbA_{1c} more than 7%) in the 3rd trimester were 2.83 times more likely to have a macrosomic neonate than women with good glycaemic control (HbA_{1c} less than 7%) as shown in table 7

There was no statistically significant relationship found between HbA_{1c} levels and neonatal respiratory distress syndrome, neonatal hypoglycaemia, stillborn, congenital defects, neonatal ICU admission and neonates that were ventilated.

Thirty-six neonates (31% of deliveries) were macrosomic and this represented almost one-third of all the deliveries in keeping with a study done by Daponte et al. and unlike their study that identified 3 cases of shoulder dystocia, this study did not have any incidents of shoulder dystocia. [103] Of the 36 macrosomic neonates, 21 (58%) had poor glycaemic control in the 3rd trimester.

Other studies have shown that there is significantly better maternal and perinatal outcome in women treated for diabetes in pregnancy. Crowther et al. in 2005, published the results of a 10 year multi-centre randomized clinical trial (ACHOIS) which showed a reduction in adverse perinatal outcome (defined by one or more of the following: shoulder dystocia, bone fracture, nerve palsy and death) in the intervention group (1% vs. 4%) and that treatment of GDM improved the woman's health related quality of life. Neonates born to women who

received dietary advice, glucose monitoring and insulin therapy had lower birth weights than those who received routine care. [17]

Katon et al. showed that women whose HbA_{1c} increased from the time of diagnosis to time of delivery, had a higher prevalence of macrosomia compared to those whose HbA_{1c} levels decreased or remained unchanged. [104]

With regards to the second objective of this study, looking into overall glycaemia control in pregnant women with diabetes who have delivered at CHBAH I found that the mean HbA_{1c} of the group improved as gestation progressed. Median HbA_{1c} in 1st trimester was 9.2%, in the second trimester 7.2% and in the 3rd trimester were 7.2%. Good glycaemic control at the CHBAH diabetic ANC clinic was an HbA_{1c} of less than 7%. This was only achieved by 3 patients in the 1st trimester, 25 patients in the 2nd trimester and 63 patients in the 3rd trimester. This could possibly be due to late gestational age at booking.

Regarding the third objective, this study set out to look for some of the well documented birth defects seen in women with diabetes mellitus. Correa et al. examined the association between diabetes mellitus and 39 birth defects. The results showed that PGDM was significantly associated with a wide range of non-cardiac defects while GDM was associated with fewer non cardiac defects. [100] This study only had two congenital defects, one neonate had Down's syndrome with club feet and the other had a skin tag on the left ear. The woman who delivered an infant with Down's syndrome and club feet was a 39 year old para 1 gravida 6 with GDM and hypothyroidism on Levothyroxine (Eltroxin). She had two previous miscarriages and two previous still births. She had booked early at 6 weeks gestation, had a haemoglobin level of 13.7 g/dL, and was Rhesus positive, RPR negative and HIV negative. She had good glycaemic control with 1st trimester mean HbA_{1c} of 5.5%, 2nd trimester mean HbA_{1c} of 6.3% and 3rd trimester HbA_{1c} of 6.5% on metformin and glibenclamide. She was delivered at 34 weeks gestations by caesarean section for foetal anomaly seen on

ultrasonography. The neonate weighed 1980 grams with a 5 minute Apgar score of 8. However, more information about the foetal anomaly scan done between 18 to 23 weeks gestation was not available.

Down's syndrome is the most common chromosomal defect and the risk increases with advancing maternal age. [105] Narchi et al. examined the association between infants of diabetic mothers and Down's syndrome and found that the incidence was 2.75 times higher in infants of diabetic mothers than in non-diabetic mothers. [106] Other studies have concluded that 75% of women with neonates who suffered Down's syndrome had an altered carbohydrate metabolism. [107] There were no maternal deaths or life threatening maternal complications found in this study.

The number of caesarean sections performed 86 (74.1%) were high, and this can be attributed to our reluctance to allow pregnancies to go beyond 38 weeks gestation. The majority of the caesarean sections were due to foetal distress 29 (33.7%), elective caesarean sections in women who had one or more previous caesarean sections 20 (23.2%) and failed induction of labour 15 (17.4%).

The mean booking gestation was 19 weeks, ranging from 4 weeks to as late as 35 weeks showing that women with PGDM continue to present late to the ANC. This could be due to socio-economic reasons, women not being aware of preconception management and the heavy burden caused by high demand for antenatal services in Soweto against limited resources.

There is need to educate general practitioners and midwives in the primary health and family planning clinics in preconceptional counselling and early referral to the diabetic ANC. [103]

Ideally, women with PGDM should be seen at the ANC before conception and her pregnancy should be planned. She should receive information on risks and outcomes for both mother and baby. This information should include: [2]

- The role of diet and exercise for women with a BMI greater than 27kg/m^2
- The increased risk of a baby with macrosomia, which would increase the risk of birth injury and caesarean section
- The need for assessment of retinopathy and nephropathy before conception
- The possibility of transient neonatal complications that may require neonatal ICU admission
- Maintaining their HbA_{1c} level to less than 6.5%, if achievable without causing hypoglycaemic episodes and aim for excellent glycaemic control during pregnancy as this would likely reduce the risk of congenital anomalies, foetal morbidity and mortality
- Recommendation that women with HbA_{1c} greater than 10% delay conception by using effective contraception until glycaemic control is achieved.
- Discontinuing statins and angiotensin-converting enzyme inhibitors before conception or as soon as pregnancy is confirmed.

6. LIMITATIONS

The major limitation of this study was its retrospective nature. There was lost or partially completed data especially related to neonatal outcome. This could have influenced the end results.

All maternal records were available however, 33 neonatal files were missing. As the diabetic ANC kept its own records of the birth and the neonatal condition, information was easily retrieved from back up of records on all 120 patients who delivered during the study period.

The maternal demographic data, monthly HbA_{1c} and significant neonatal outcome (Apgar score, birth weight, congenital abnormalities, neonatal hypoglycaemia, and neonatal respiratory distress syndrome) were recorded at the clinic as the mothers were followed for 6 weeks post-delivery at the clinic.

There is need for improving record keeping at CHBAH, perhaps in the form of electronic data capturing. This has been shown to improve patient follow and postnatal care. [108]

The second limitation was the sample size of 116, which was probably insufficient to find other adverse birth outcomes.

7. CONCLUSION

Women with poor glycaemic control (HbA_{1c} more than 7%) in the 3rd trimester were 2.83 times more likely to have a macrosomic neonate than women with good glycaemic control (HbA_{1c} less than 7%).

There was no statistically significant relationship found between HbA_{1c} levels and neonatal respiratory distress syndrome, neonatal hypoglycaemia, still born status, congenital defects, neonatal ICU admissions and ventilated neonates.

8. RECOMMENDATIONS FOR FUTURE SIMILAR STUDIES

There is a need to address pre-conceptual glycaemic control and its relationship to perinatal outcomes. This could be done as a multi-centre study over a longer time period with the aim of having a larger sample size.

A strategy for the detection and diagnosis of hyperglycaemic disorders in women not known to have diabetes prior to pregnancy would be early testing in a high risk population and if results are not diagnostic, a 75 gram OGTT between 24-28 weeks should be performed. [43]

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10.APPENDICES

10.1. Appendix A: Data Sheet

DATA SHEET

Study number: _____

RELATIONSHIP BETWEEN MATERNAL GLYCAEMIIC CONTROL AND BIRTH OUTCOME AT CHRIS HANI BARAGWANATH HOSPITAL

Maternal and foetal demographics		Unknown
Age		
Parity		
Gravidity		
Miscarriage	Yes:	
	No:	
Gest age at miscarriage:		
Stillborn (IUFD)	Yes:	
	No:	
Gest age of IUFD:		
PGDM	Yes:	
	No:	
Age of onset:		
Gestational Age		
at booking:		
at diagnosis of GDM:		
at delivery:		

Previous surgery		
Hb		
Rh		
RPR		
HIV		
*CD4		
*PMTCT		
*HAART		
*Neither		
Booking Weight		
Family History of Diabetes Mellitus (Y = 1 n= 0)		
Gestation at First Formal Sonar		
Sonar Pathology Identified		
- Heart action		
- Foetal movements		
- Presentation		
- Placental site		
- Placental grade		
- Placental structure		
- Amniotic fluid volume		
- Cord		
- Head		
- Brain		
- Face		

- Spine		
- Neck/skin		
- Thorax		
- Heart		
- Abdomen		
- GIT		
- Kidneys		
- Genitalia		
- Extremities		
- Skeletal		
Maternal Smoking		
Initiation of Folic Acid Supplement		
Estimated Date of Delivery		
EDD by:		
LMP		
1st SONAR		
BOOKING PALPATION		
Number of Antenatal Admissions		
Reason for admission • HGT control		
• Induction of labour		
• BP control		
• Steroids		
• Treatment of infections		

- UTI - Respiratory tract infection - Others		
• TOP for congenital anomaly		
• Pre term labour		
• Others		
Use of Steroids for foetal lung maturation		
Gestational Age at time of Steroid Use		
Type of Control Dietary Insulin Oral hypoglycaemic drugs		
HbA_{1c} levels	Gestational week	

Antenatal Complications

Preterm Labour	
Polyhydramnios	
Oligohyraminos	
Preterm prelabour rupture of membranes	
Prelabour rupture of membranes	
Gestational Hypertension	
Chronic Hypertension	
Preeclampsia	
Unclassified non proteinuric hypertension	
Unclassified proteinuric hypertension	
Antepartum haemorrhage	
Other	

Foetal Outcomes

Foetal Weight:	Range	Exact weight
>5000g		
4500 - 4999g		
4000 - 4499g		
3500 - 3999g		
3000 - 3499g		
2500 -2599g		
2000 - 2499g		
1500 - 1599g		
1000 - 1499g		
<1000g		
Gestational Age at Birth by clinical estimation		
Spontaneous labour	Y:	N:
Duration of labour		
Induction of labour		
yes:		
no:		
successful induction:	Y:	N:
Induction agent: oral misoprostol:		
Prandin Gel:		
Prepidil (dinoprostone) Gel:		
balloon catheter induction:		
oxytocin:		

Mode of Delivery NVD C/S Indication for CS: repeat C/S: foetal distress: failed induction of labour: poor progress and failed AOL: delayed second stage: failed assisted delivery: Other:	
Assisted vaginal delivery	
5 Minute APGAR	
Birth Injury bone fracture nerve palsy	
Shoulder Dystocia	
Genital tract injuries (3rd and 4th degree tears	
PPH requiring blood transfusion	
Hysterectomy	
Other significant outcomes transitional unit admission: neonatal ICU :	
Other significant outcomes: maternal death	
Neonatal Hypoglycaemia (<2.6mmol/L)	

Neonatal respiratory distress requiring Neonatal ICU	
Hypoxic ischaemic encephalopathy	
Congenital birth defects: • Cardiovascular	
• Musculoskeletal	
• CNS	
• Renal anomalies	
• GIT	
• Others	
Neonatal hyperbilirubinemia	
Neonatal ABG's pH: BE: Lactate: Glucose:	
Congenital anomalies	
Macrosomia	
Stillbirths	
Other neonatal outcome	

10.2. Appendix B: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Paul J Onyango

CLEARANCE CERTIFICATE	**M121176**
PROJECT	The Relationship between Maternal Glycaemic Control and Perinatal Outcome at Chris Hani Baragwanath Hospital
INVESTIGATORS	Dr Paul J Onyango.
DEPARTMENT	Department of Obstetrics & Gynaecology
DATE CONSIDERED	30/11/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/11/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Robert Nyakoe

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

10.3. Appendix C: Permission from Chris Hani Baragwanath Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 08 November 2012

TITLE OF PROJECT: The relationship between maternal glycaemic control and perinatal outcome at CHBAH

UNIVERSITY: Witwatersrand

Principal Investigator: Dr P J Onyango

Department: Obstetrics and Gynaecology

Supervisor (If relevant): Dr R Nyakoe

Permission Head Department (where research conducted): Yes

Date of start of proposed study: December 2012
Date of completion of data collection: June 2013

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 08 November 2012

.....
Approved/Not Approved
Hospital Management
Date: 12/11/12.

10.4. Appendix D: Blood Glucose Profile Chart

DIABETES IN PREGNANCY CLINIC

BLOOD GLUCOSE PROFILES

NAME: ....

DATE	BB	AB	BL	AL	BS	AS	Hypo	Time	Comments	Insulin Dose (Actrapid/Protaphane)					
										Before Breakfast		Before Lunch	Before Dinner		Late Night
										P	A	A	P	A	P

fjj 2005/10/31

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THE RELATIONSHIP BETWEEN MATERNAL GLYCAEMIC CONTROL AND BIRTH OUTCOME AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL DR. PAUL JASPER ONYANGO Dedication This research is dedicated to my beloved parents Hilda Atieno Onyango and the late Ibrahim Sitech Onyango Ogola. Rest in Peace Dad. II III Abstract Background: The setting of this study was Chris Hani Baragwanath Academic Hospital (CHBAH) at the diabetic antenatal clinic (ANC). CHBAH is a tertiary hospital that serves 3 secondary level hospitals (Sebokeng, Klerksdorp-Tshepong and Natalspruit), 1 district hospital (Bheki Mlangeni), and 25 clinics in Soweto, Orange Farm and Lenasia. The diabetic ANC offers a specialised multidisciplinary clinic for diabetic women and is run by an obstetrician, endocrinologist, dietician, diabetes nurse educator and midwives. The feto-maternal unit at CHBAH offers first and second trimester ultrasound services for all diabetic pregnant women. Foetal growth, liquor volume and foetal abnormalities were monitored using serial ultrasound scans. Foetal wellbeing was assessed by non-stress tests. Amniocentesis, only if indicated, was offered for women at high risk for Down's syndrome and in cases of preterm delivery to assess foetal lung maturity. Most pregnancies were allowed to go to 37 completed weeks, provided that optimal glycaemic control was achieved and that there were no obstetric indications for early delivery. Women with GDM were recalled at 6 weeks postpartum and offered a 75gram OGTT (WHO diagnostic criteria for non-pregnant adults). IV Objectives: 1. To investigate the relationship between maternal glycaemic control and neonatal outcome at CHBAH. 2. To determine overall glycaemic control in pregnant women with diabetes who have delivered at CHBAH. 3. To determine neonatal complications of babies born to diabetic mothers who have delivered at CHBAH.

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