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COMPARISON OF GROWTH AND BODY COMPOSITION OF INFANTS BORN TO MOTHERS WITH, AND THOSE WITHOUT, GESTATIONAL DIABETES MELLITUS

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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in fulfilment of the requirements for the degree of

Master of Science in Medicine

Johannesburg, 2021

Declaration

I, **Martha Ngobeni**, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.



Signed on 23rd day of February 2021.

Dedication

I dedicate this dissertation to my parents, Samaria Ngayeni Manonga and the late Alfred Elias Manonga and who have withheld nothing good from me to give me the best start in life.

Acknowledgements

First, I would love to give my God, the creator of the Universe all the praise and glory for this finished work. If it had not been for the Lord on my side, nothing would have been possible. To my supervisors, Professor Shane Norris and Dr Shelley Macaulay I appreciate the academic guidance and support. The time sacrificed to make it possible for this master's work to be a success. Prof Norris for making MRC/WITS Developmental Pathways for Health Research Unit (DPHRU) a place of working and learning and creating an environment where one can evolve, all the knowledge I have thus far, about collecting quality data and running a project from start to finish. Due to the funding, locally from DPHRU and internationally from Emory University, the project was a success. Prof Norris, for paying my tuition fees from start to finish. I thank you all.

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To the postgraduate students (Clement, Glory, Lukhanyo, Gudhani, Adelaide, Stephanie, Larske, Tinashe, Refiloe) and research assistants (the late Nonhlanhla, Zintle), research nurses (Thokozile, Joy, Nthabiseng, Bonisiwe, Siphumelele), Peapod machine operators (Thabile and Lydia) and the DPHRU team, thank you for assisting me. Ansuyah, thanks a million for proofreading my work.

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Abstract

In low-middle-income countries like South Africa, the application of selective screening for gestational diabetes mellitus (GDM) is based on the presence of risk factors. Gestational diabetes mellitus is public health problem which results in short- and long-term consequences, like obesity, type 2 diabetes mellitus (T2DM) and cardiovascular disease for both the mother and child later in life.

Children exposed to GDM *in utero* are likely to be born macrosomic resulting from increased body fat composition. Early life exposures alter body composition by increasing adipose tissue while increasing the risk of non-communicable diseases (NCD). Furthermore, metabolic factors may influence rapid growth in infancy by increasing adipose tissue which increases the risk of NCD later in life.

Aim: This study aimed to assess the uptake of universal screening for GDM and to investigate the relationship between maternal factors and birth outcomes (growth and body composition) in infants born to mothers with and those without GDM.

Design: The study comprised of two sections: (i) the uptake of universal screening and effectiveness of selective screening for GDM (ii) a case-control longitudinal comparative study that followed infants born to mothers with (n = 22) and without (n = 110) GDM from birth until six months of age.

Data collection and analysis: Pregnant women who had been referred from district hospitals and local clinics in Soweto and surrounding areas (Orange Farm and Lenasia) to Chris Hani Baragwanath Academic Hospital (CHBAH) were invited to participate in the study. The following inclusion criteria were applied: women who were less than 20 weeks pregnant at recruitment, black South African (ethnicity verbally reported), 18 years of age or older and pregnant with singleton pregnancies that were naturally conceived. Furthermore, no foetal abnormalities could have been detected and the women could not have been diagnosed with pre-existing diabetes or epilepsy. These women were booked to have an oral glucose tolerance test (OGTT) performed between 24-28 weeks gestation. Body composition data on the infants were obtained from air-displacement plethysmography. Other collected data included socio-economic status (SES), obstetric history and anthropometric measurements of infants and mothers. Z-scores (weight, length, head circumference, body mass index (BMI)) and conditionals (weight and length) were treated as outcome variables. Data analysis included

descriptive, bivariates and multivariate analyses which were performed in STATA 14. The probability value of < 0.05 was considered statistically significant.

Results: The majority of the pregnant women were screened for GDM but 43% of them failed to take up the offer of an OGTT for various reasons, including lack interest in testing, difficulty in getting time off at work, relocating to another province, previously tested at CHBAH and kept rescheduling but failed to attend; these women were therefore excluded.

At birth, the mean ± standard deviation weight of infants born to mothers with GDM was 3396g ± 502 while the mean weight for infants born to mothers without GDM was 3472 g ± 610 (p = 0.587). At six months, the mean weight was 7401 g ± 853 of infants born to mothers with GDM compared to 7389 g ± 1240 of infants born to mothers without GDM (p = 0.948). Despite there being no statistically significant difference in length (p = 0.721) at birth, the length of infants exposed to GDM was 49.64 cm ± 3.17 slightly longer than unexposed to GDM was 49.37 cm ± 3.32. At six months of growth, the mean lengths were 64.04 cm ± 1.88 versus 64.49 cm ± 2.98 in infants exposed and unexposed to GDM respectively (p = 0.511). There was no statistical difference at birth in the median head circumference of infants born to women with, 35.48 cm (34.63-36.40) and without, 35.15 cm (34.90-35.60) GDM (p = 0.351). Despite the statistical non-significance at six months, the head circumference of infants born to women with GDM were slightly bigger than infants born to women without GDM (p = 0.963).

According to the BMI-for-age, infants in both groups were not overweight or obese in the first six months of life. The weight gain of infants exposed to GDM was significant at one (p = 0.005), three (p < 0.001), four (p = 0.026) and six months (p < 0.001) of age compared to the infants unexposed to GDM. In addition the conditional length growth of the infants born to mothers with GDM showed significant growth at birth (p = 0.004), two (p = 0.001) and five months (p = 0.049) compared to infants born to mothers without GDM in the first six months of life.

Gestational age was the main predictor of majority of the birth outcomes, including birth weight (β = 159.82, 75.36; 244.27, p < 0.001), length (β = 1.08, 0.62; 1.55, p < 0.001) and head circumference (β = 0.20, 0.00; 0.40, p = 0.048). The greatest effect on infants' weight (β = 358.57, 48.41; 668.53, p = 0.024), length (β = 371.51, 65.09; 677.93, p = 0.018), head circumference (β = 0.75, 0.01; 1.49, p = 0.047), conditional weight (β = -0.27, -0.50; -0.03, p = 0.027) and conditional length (β = -0.29, 0.06; 0.51, p = 0.012) was maternal obesity. Maternal tertiary educational level was a determinant of fat mass index (β = 3.20, 0.68; 5.72, p = 0.013)

and fat free mass index (β = 4.45, 0.36; 8.55, p = 0.033). In addition secondary schooling was significantly associated with infants' weight (β = 617.60, 99.24; 1135.97, p = 0.020), length (β = 633.94, 119.07; 1148.82, p = 0.016) and fat mass index (β = 2.40, 0.02; 4.77, p = 0.048). Furthermore, neonatal sex was a negative predictor of conditional weight index (β = -0.27, -0.43; -0.12, p = 0.001) and conditional length index (β = -0.46, -0.61;-0.32, p < 0.001). Infant growth (conditional weight and length) during the first month of life was significantly associated with maternal GDM status.

Conclusion: It is of concern that 43% of mothers declined to be tested for GDM, even though the service was offered at no cost. In the first six months of life there were no significant differences in the growth and body composition of infants born to women with and without GDM. Maternal obesity, gestational age and maternal education were major determinants of the infant anthropometry and body fat. The findings of this study add to the understanding of growth and body composition of infants born to women with and without GDM in South African.

Table of Contents

Declaration....i

Dedication....ii

Acknowledgement....iii

Abstract....iv

CHAPTER ONE: Introduction....1

1.1 Background....2

1.2 Problem statement....2

1.3 Research questions....5

1.4 Aim of the study....5

1.5 Study objectives....6

CHAPTER TWO: Literature review....7

2.1 The health burden of diabetes mellitus....8

2.2 Early infant growth and adiposity....17

2.3 Infant body composition....18

2.4 Risk of obesity and gestational diabetes mellitus in the South African context....20

2.5 Study Motivation....21

CHAPTER THREE: Methodology....22

3.1 Study population and setting....23

3.2 The pregnancy study inclusion criteria....25

3.3 Follow up of infant-mother pairs....28

3.4 Infant body composition....30

3.5 Reliability and validity of results....31

3.6 Data cleaning and preparation....32

3.7 Statistical analysis....32

3.8 Ethics Clearance....33

CHAPTER FOUR: Results - Uptake of universal screening and the effectiveness of selective screening for gestational diabetes mellitus....34

4.1 Characteristics of women screened for gestational diabetes mellitus 35
4.2 Effectiveness of selectively screening women for GDM at Chris Hani Baragwanath Academic Hospital 37
4.3 Barriers to the uptake of universal screening for GDM 38
CHAPTER FIVE: Results - Longitudinal follow-up of infants 39
5.1 Maternal and infant characteristics 40
5.2 Bivariate associations 46
5.3 Multiple linear regressions 50
5.4 Conditional weight and length associations with maternal GDM status 61
CHAPTER SIX: Discussion and Conclusion 62
6. 1 Summary of findings 63
6.2 The uptake of universal screening and the effectiveness of selective screening for GDM 66
6.3 Infant growth and body composition parameters together with related associations 68
6.4 Study strengths and limitations 71
6.5 Recommendations for future studies 71
6.6 Conclusion 72
REFERENCES 73
APPENDICES 82

List of tables

Table 2.1 Diagnostic criteria for the diagnosis of gestational diabetes mellitus using the oral glucose tolerance test 13

Table 2.2 Overview of anthropometric and body composition assessment for infants 20

Table 4.1 Characteristics of women screened for GDM 36

Table 5.1 Delivery outcomes of infants born to women with and without GDM, at birth until six months of age 41

Table 5.2 Anthropometry of infants born to women with and without GDM, at birth until six months of age 42

Table 5.3 Z-scores of infants presented according to maternal GDM status and sex of the baby, at birth until six months of age 44

Table 5.4 Body composition of infants born to women with and without GDM, at birth until six months of age 45

Table 5.5 Bivariate regressions for associations between independent exposure variables and birth outcomes 48

Table 5.6 Multiple linear regression models for associations between maternal and infants exposure variables and infant weight at birth 52

Table 5.7 Multiple linear regression models for associations between maternal and infants exposure variables and infant length at birth 53

Table 5.8 Multiple linear regression models for associations between maternal and infants exposure variables and infant head circumference 55

Table 5.9 Multiple linear regression models for associations between maternal andinfants exposure variables and infant fat mass index at birth 57

Table 5.10 Multiple linear regression models for associations between maternal and infants exposure variables and infant fat free mass index at birth 58

Table 5.11 Multiple linear regression models for associations between maternal and infant exposure variables and infant conditional weight 59

Table 5.12 Multiple linear regression models for associations between maternal and infant exposure variables and infant conditional length 60

Table 5.13 Associations related to conditional weight and length on infants in the first six months of life 61

Table 6.1 Summary of the research findings 64

List of figures

Figure 1.1 Conceptual framework showing possible pathways for infants born to mothers with diabetes during pregnancy 4

Figure 1.2 Link between the conceptual framework showing possible outcomes of infants born to mothers with diabetes and my study 5

Figure 2.1 A diagram representing the history of diabetes (below the centre bar), gestational diabetes (middle of the centre bar) and developmental over-nutrition hypothesis (top of the figure) by the International Association of the Diabetes in Pregnancy Study Group 10

Figure 2.2 Modified schematic representation of fluctuations in glucose levels during normal pregnancy and gestational diabetes mellitus 12

Figure 2.3The vicious cycle of maternal obesity and diabetes 14

Figure 2.4 The risk of developing non-communicable diseases in the mother and child, increases with each pregnancy affected by GDM 16

Figure 2.5 Maternal hyperglycemia modified according to Pederson's hypothesis 17

Figure 3.1 Soweto township 23

Figure 3.2 Chris Hani Baragwanath Academic Hospital 24

Figure 3.3 Length position for pregnant women 28

Figure 3.4 Photographic image of the air displacement plethysmography 31

Figure 4.1 Pregnancy study participants 35

Figure 4.2 Representing proportions of women not meeting the selective screening criteria at the hospital 37

Figure 4.3 Reported barriers to screening for GDM 38

Presentations

Ngobeni, M. *Gestational diabetes mellitus screening study*. Postgraduate students, Faculty of Health Sciences, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, 20 November 2015.

Ngobeni, M. *Gestational diabetes mellitus in women living in Soweto, Johannesburg*. Professional and research nurses working at Chris Hani Baragwanath Hospital, Faculty of Health Sciences, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, 17 June 2017.

Peer reviewed publications

Shelley Macaulay, Martha Ngobeni, David B. Dunger, Shane A. Norris. The prevalence of gestational diabetes amongst black South African women is a public health concern. Diabetes Research and Clinical Practice.2018; 139:278-87

List of abbreviation and acronyms

ADP	Air-displacement plethysmography
ANC	Antenatal Clinic
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
DM	Diabetes mellitus
DPHRU	Developmental Pathways for Health Research Unit
DXA	Dual-energy X-ray absorptiometry
GDM	Gestational diabetes mellitus
HAPO	Hyperglycaemia and adverse pregnancy group
HIV	Human immunodeficiency virus
IADPSG	International Association of Diabetes Pregnancy Study Group
LMIC	Low-to-middle-income countries
OGTT	Oral glucose tolerance test
NCD	Non-communicable diseases
REDCap	Research Electronic Data Capture
SES	Socio-economic status
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

CHAPTER ONE: Introduction

Introduction

This chapter provides background on gestational diabetes mellitus, infant growth, and body composition. It includes the conceptual framework adopted in the study, the problem statement, research question, aim and objectives.

1.1 Background

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance first recognised in pregnancy (1-3). This medical condition results in short- and long- term consequences such as obesity, cardiovascular diseases, and type 2 diabetes mellitus (T2DM) in the mother and child (4, 5).

Globally there has been an increase in the number of overweight and obese children including children under the age of five years (6). Childhood obesity can be traced back to influences earlier in life (7, 8). Moreover, infant growth patterns have been coupled with obesity in children and adults later in life (9). Therefore, infancy is a critical period in which catch up and rapid growth occurs in pre-term and full-term infants (10, 11). Determining body composition in infants can assist in understanding growth and adverse health outcomes across the lifespan (12). Cross sectional and longitudinal research studies that investigate the growth in children are important to provide insight in this regard.

1.2 Problem statement

Gestational diabetes mellitus is linked with adverse birth outcomes, including elevated body fat at birth (1). Furthermore, infants exposed to GDM are at a greater risk of having diabetes and grow up to developing other metabolic diseases later in life (1). According to the World Health Organization (WHO), about 38.2 million children below the age of five years in 2019 were overweight or obese in low-to-middle-income countries (LMIC) and in Africa there has been a 24% increase of overweight children since 2000 (13). Obesity is a definite public health concern, mostly in children younger than five years of age and has serious adverse health outcomes in childhood and adulthood (14-17). Therefore this is the preferred time for interventional studies to find solutions to deal with childhood obesity (16). The rise in obesity in children signifies the need to assess childhood body fat and how it will affect future health outcomes (18).

Growing evidence indicates that infant growth from childbirth up to the age of two years is a critical stage of development (19). During this period infants are likely to undergo rapid weight gain. In addition, early infant growth, especially infant weight gain, had been linked to childhood body weight followed by metabolic and heart related diseases in adulthood (16, 20-22).

Body composition plays a significant role in early infancy and predisposes the infant to developing metabolic diseases later in life. Precise measures of fat mass, using validated methods like the air displacement plethysmography (ADP) (15) are important for infants over a six months period (23) and are better than anthropometric measurements, which cannot segregate between fat mass and fat free mass (24).

The following section discusses the conceptual framework adopted by the study. The impact of obesity and over-nutrition on public health was addressed by Lawlar (Figure 1.1). The conceptual framework refers to maternal factors, such as diabetes and how they influence foetal growth. It highlights how prenatal exposure to diabetes results in the child being programmed to be bigger than normal which increases the risk of obesity throughout the life course (25).

Figure 1.2 highlights key points of the framework in relation to the current research study. Firstly, exposure to GDM and the influence on the child's birth outcomes in the short term. Secondly, the association between maternal influence, such as body mass index (BMI), and in addition specific to this research, maternal obstetric history and socio-economic status (SES), and birth outcomes. Lastly, the growth and body composition of children born from mothers with and without GDM over a six month period (26).

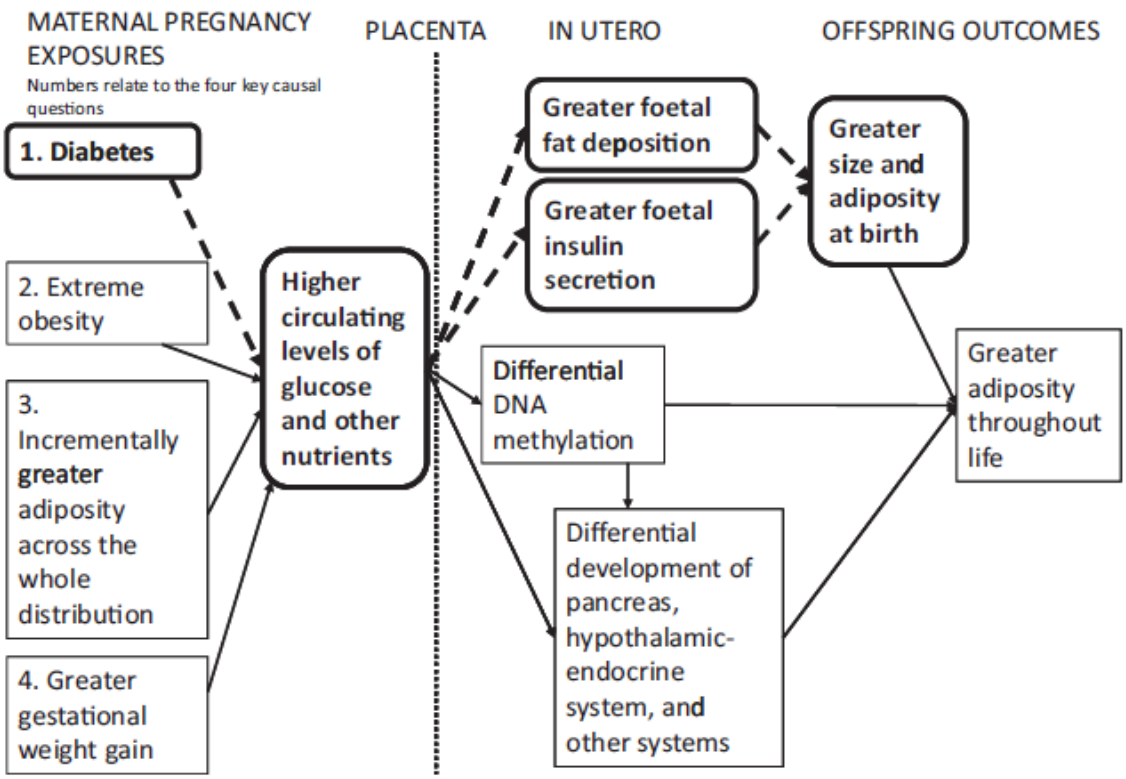

Figure 1.1 Conceptual framework showing possible outcomes of infants born to mothers with diabetes during pregnancy (25)

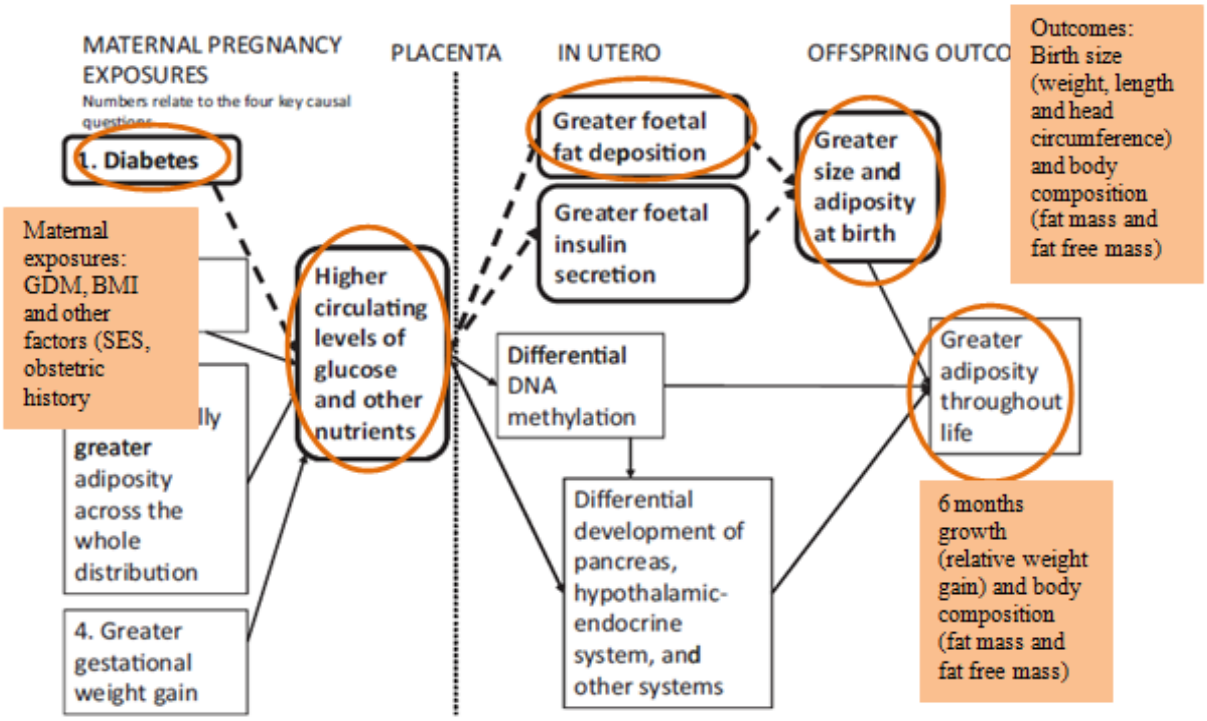

Figure 1.2 Link between the conceptual framework showing possible outcomes of infants born to mothers with diabetes (25) and the current study

1.3 Research questions

This study explored the following research questions:

- Are there any factors influencing the uptake of universal screening for GDM?
- What is the relationship between the growth and the body composition of infants born to mothers with GDM compared to those born to mothers without GDM?

1.4 Aim of the study

This study aimed to assess the uptake of universal screening for GDM and to explore the relationship between maternal factors and birth outcomes (growth and body composition) in infants born to mothers with and those without GDM.

1.5 Study objectives

The objectives of the study were:

1. To determine the uptake of universal screening and the effectiveness of selective screening for GDM
2. To compare anthropometric factors (comprising weight, length and head circumference) and the body composition (fat mass and fat free mass) at birth until six months of life between infants born to mothers with, and those without, GDM.
3. To determine the association between maternal obstetric history (number of previous pregnancies and previous births), maternal demographics (marital status, total number of years of formal education), human immunodeficiency virus (HIV) status, and BMI and infant birth outcomes (birth weight, length, head circumference, fat mass and fat free mass).

CHAPTER TWO: Literature review

Introduction

This chapter provides an outline of diabetes mellitus (DM) and GDM. The effect of maternal GDM status on infant development and body composition, and its consequences later in life, are also discussed.

2.1 The health burden of diabetes mellitus

Diabetes mellitus is defined as hypergylcemia due to insulin dysfunction (27) and it is a chronic medical condition, occurring in young and old people (28). The symptoms associated with DM are high glucose levels, excretion of diluted urine, continuous thirst (28), excessive eating, weight loss and impaired vision. Chronic diabetes affects numerous tissues including the eyes, kidneys, nerves, the heart and blood vessels (29).

There are four types of DM according to the WHO: Type 1 DM (T1DM), T2DM, other uncommon types of DM and GDM (30). Firstly, T1DM results from an autoimmune deficiency whereby beta cells are unable to secrete insulin. Secondly, T2DM is due to insulin resistance and relative insulin shortage. There are other rare types of DM such as genetic deficiencies of beta cell function or insulin action, exocrine pancreas ailments, and drug prompted DM. Lastly, there is GDM which starts or is recognised during pregnancy. However, there is a link between GDM and T2DM because they are both caused by insulin resistance and follow the same pathophysiology (30, 31).

The WHO reported a global increase in newly diagnosed cases of diabetes over the last three decades. The prevalence of DM in Africa is estimated to increase from 3.8% to 4.5% by 2030(28). An estimated escalation from 19.8 million to 41.5 million is expected between 2013 and 2035 in Africa (32). An increase in the estimated life expectancy, decrease in communicable diseases, and a shift towards urbanisation as well as lifestyle changes, contribute towards the risk of NCD (33, 34).

Diabetes mellitus is one of the medical conditions, along with other chronic diseases (including cardiovascular diseases, cancer, and metabolic syndrome), that adds a burden onto the health system of a country (34, 35). Overweight, as well as obesity, increase the risk of T2DM and cardiovascular-related diseases (31). Changes in lifestyle from healthy to poor eating habits has been found to contribute to people being overweight and obese (31).

2.1.1 Gestational diabetes mellitus

Globally, GDM arises in approximately 7% of pregnancies (36-38). Historically, GDM was first recognised in the early 1930s when studies found that diabetes differs between pregnant and non-pregnant women. In 1946, Hurwitz and Jensen performed the oral glucose tolerance test (OGTT) on 25 healthy pregnant females. They found that high glucose levels, which transpired during the second and third trimester, reverted to normal shortly after delivery (25). In 1954, several studies described the relationship between GDM and infant outcome (in relation to birth weight and body fat). In the 1960s, O'Sullivan *et al*., (39) reported the association between OGTT results during pregnancy and future risk of developing T2DM. In the 1980s the cut-off values for diagnosing GDM were modified (39). In addition, in 1980 Freinkel *et al*., (25) found that infants exposed to GDM had more body fat at birth than unexposed infants (Figure 2.1).

Evidence by the International Diabetes Federation suggest that about 131 million births are affected by abnormal glucose levels during pregnancy, of which 86% involve GDM (40). In addition, females born to mothers with GDM are likely to have GDM in their pregnancies. Furthermore infants exposed to GDM are likely to be obese, and develop T2DM and other metabolic illnesses later in life (40).

2.1.2 The rising prevalence of gestational diabetes mellitus

The utmost prevalence of GDM is in the South East Asia region at 24.2% (41). Limited studies have reported on the prevalence of GDM in Africa: 0% in Tanzania (42), 2.9% in Western Kenya (43), 8.3% in Rwanda (44) , 9.3% in Ghana and as high as 13.9 % in Nigeria (42). In South Africa the occurrence of GDM in a rural community in the Limpopo Province (1999-2000) was reported as 8.8% (45) and a prevalence of 9.1% was found among black South African females in urban Soweto (2013-2017) (46).

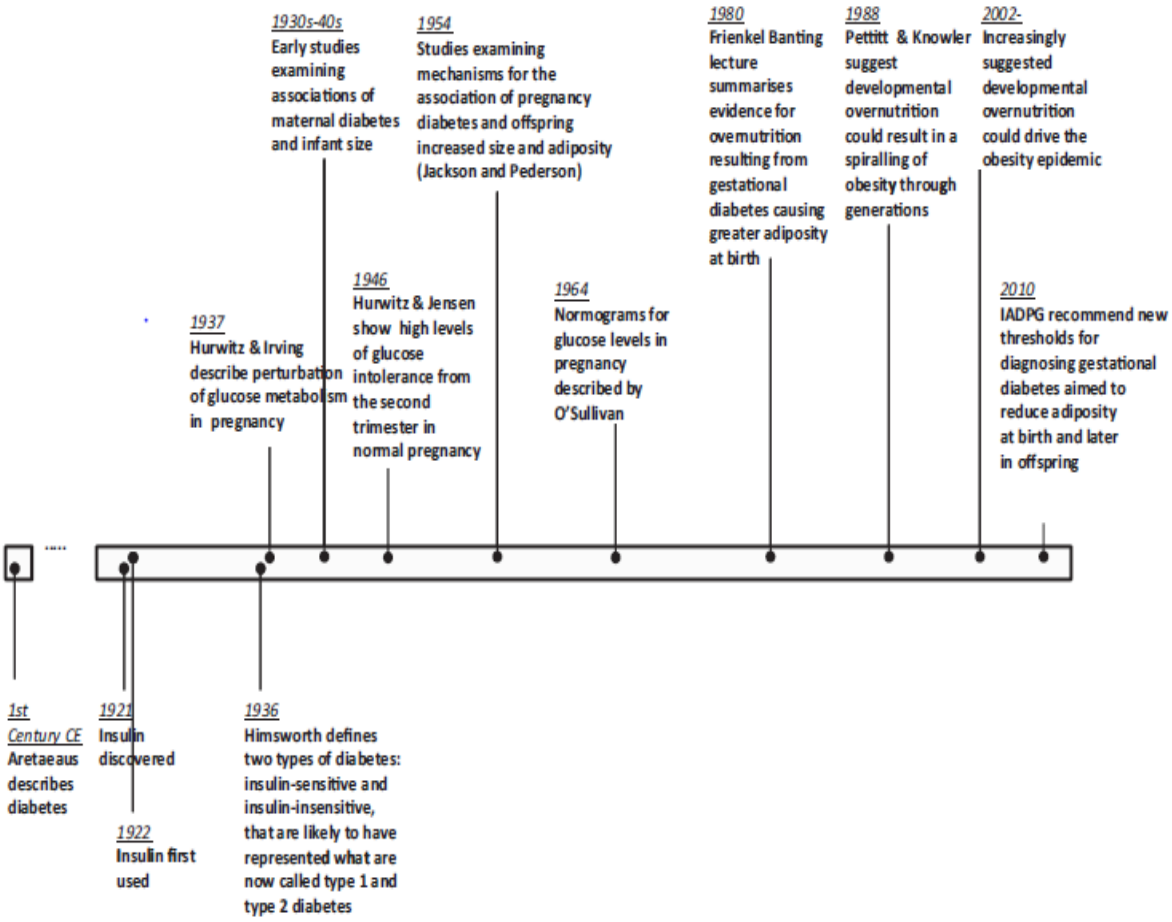

Figure 2.1 A diagram representing the history of diabetes (below the centre bar), gestational diabetes (above the bar in the middle of the figure) and the developmental over-nutrition hypothesis (above the bar at the top of the figure) by the International Association of the Diabetes in Pregnancy Study Group (25)

2.1.3 Pathophysiology of gestational diabetes mellitus

The main role of the beta cells in the pancreas is to synthesise and secrete insulin to normalise blood glucose levels. Insulin secretion is in response to elevated glucose levels to compensate for hyperglycaemia. In addition, insulin resistance arises when insulin secreted by the pancreas is incapable to stimulate the muscles and tissues to absorb glucose. Due to these events, the cycle of elevated blood glucose and beta cells dysfunction continues (4). The dysfunction of the beta cell leads to maternal GDM (47, 48). The beta cell and insulin levels in normal and GDM affected pregnancies are shown in Figure 2.2. As maternal glucose crosses the placenta, when maternal glucose levels are high, foetal insulin production increases thereby promoting insulin-mediated fat storage (49).

During pregnancy, foetal growth is accompanied by a growing placenta under the influence of hormones such as oestrogen, progesterone, cortisol and placental lactogen which circulate in the maternal blood (10, 50, 51). Furthermore, there is a reduction in maternal insulin sensitivity as the pregnancy progresses. At birth, placental production stops and so do the effects of GDM, which strongly suggest hormonal change may be responsible for the development of GDM (52).

Catalano *et al.*, (53) indicated a decline of 50-60% insulin sensitivity as the pregnancy progresses in pregnant women with and those without GDM. But in women with GDM the insulin sensitivity was due to factors that existed prior to pregnancy compared to women without GDM (53). A subsequent study indicated that maternal glucose levels are positively linked with infant adiposity at childbirth and in later childhood (54). Other findings from the Pima Indian population, have supported the relationship between maternal diabetes and the danger of the infant of having T2DM in the adolescents and adulthood (55, 56). In South Africa there are no studies that have explored maternal GDM and adolescent health.

2.1.4 Diagnostic criteria for gestational diabetes mellitus

Early identification of GDM may reduce complications for the mother and developing foetus (57). Screening for maternal GDM is performed during the second trimester (between 24 to 28 weeks of foetal development) using an OGTT (58, 59). This is the period during which maternal glucose levels naturally peak (60). Currently, there are no standard diagnostic criteria used to test for GDM (Table 2.1) (61). The diagnostic criteria have changed several times over the years, thus posing a challenge when comparing different studies. For example, a Nigerian study found the commonness of GDM to vary in the same people depending on the diagnostic criteria applied; when the 1999 WHO, 2013 WHO, and the International Association of Diabetes Pregnancy Study Group (IADPSG) criteria were applied the prevalence of GDM was 3.8%, 8.1 %, and 8.6 % respectively (62). Regardless of the different diagnostic criteria applied, it is important to screen pregnant women and to conduct interventional studies to reduce the effects of GDM (63, 64).

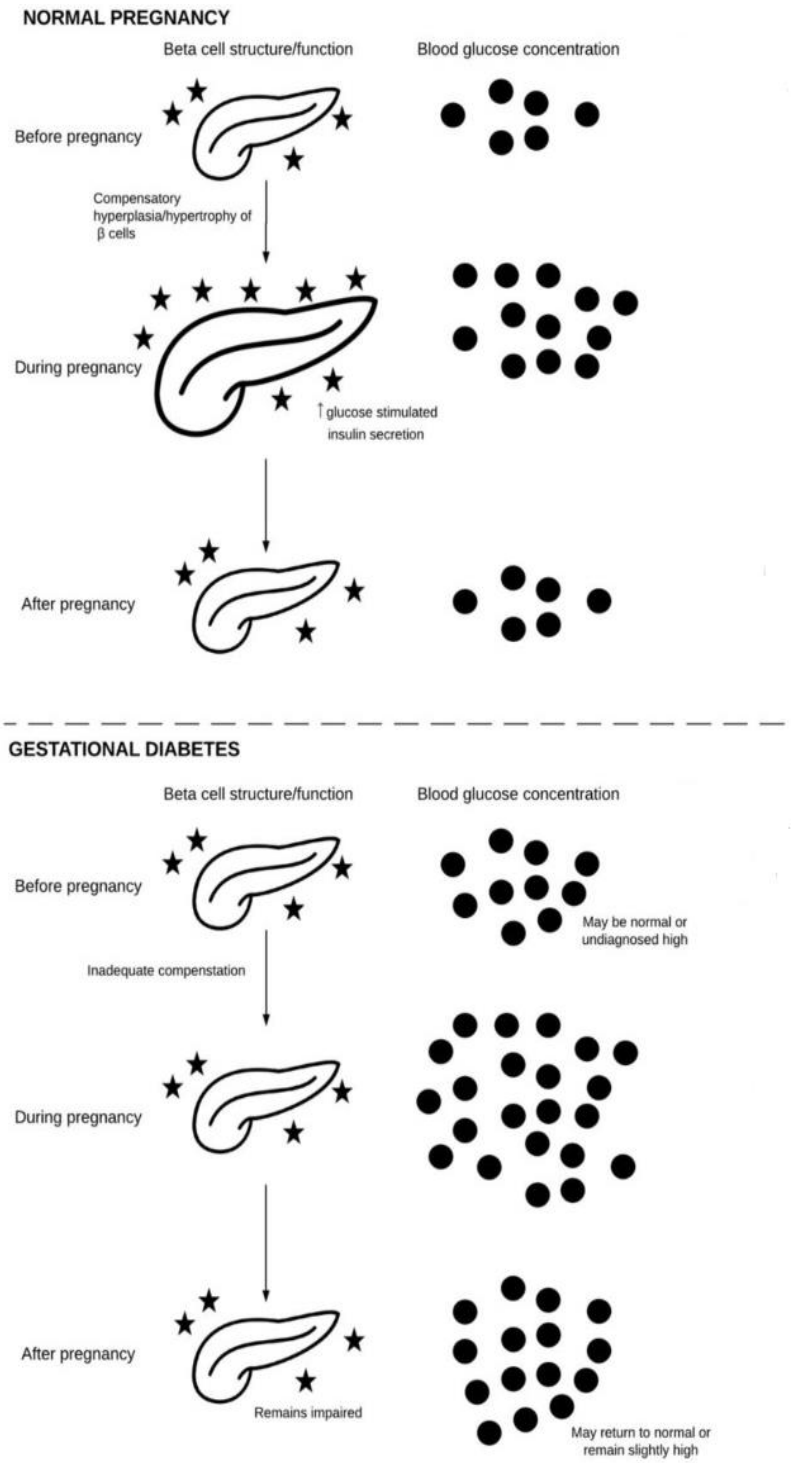

Figure 2.2 Modified schematic representation of fluctuations in glucose levels during normal pregnancy and gestational diabetes mellitus (4)

Table 2.1 Diagnostic criteria for the diagnosis of gestational diabetes mellitus using the oral glucose tolerance test (4)

Criteria	Pregnancies	Timing of OGTT	Steps	Glucose Load (g)	Glucose Threshold (mmol/L)			
					Fasting	1 h	2 h	3 h
O'Sullivan, 1964	All	24–28 weeks	2	100	5.0	9.2	8.1	6.9
WHO, 1999	All	24–28 weeks	1	75	7.0	—	7.8	—
American Diabetes Association (ADA), 2004	High and medium risk	14–18 weeks for high risk, 28–32 weeks for medium risk	2	100	5.3	10.0	8.6	7.8
National Institute for Health and Care Excellence (NICE), 2015	High risk	As early as possible	1	75	5.6	—	7.8	—
IADPSG, 2010 WHO, 2013 ADA, 2016	All	24–28 weeks	1	75	5.1	10.0	8.5	—

2.1.5 Treatment for gestational diabetes mellitus

The ultimate goal in treating GDM is to control maternal blood glucose levels (65). The first approach to managing GDM is using lifestyle interventions such as dietary changes, as advised by a dietician, and physical activity (65, 66). If glucose levels are not controlled after making dietary or physical changes, pharmacological treatment is implemented (67, 68). Approximately 10-20 % of females with GDM are treated with insulin or medication. Such interventions can prevent the effects of GDM exposure to the child and disrupt the onset of T2DM in females with GDM (69). Insulin is unfavourable, because it requires daily injections, is expensive and has to be stored correctly (70). In comparison to insulin, metformin is preferred in controlling glucose levels for GDM women (70). Several countries use metformin to lower maternal glucose levels, and it has been proven to be effective (71, 72). Metformin acts by elevating insulin sensitivity and reducing the production of glucose. In pregnant women, metformin reduces insulin resistance, which decreases glucose levels and subsequently reduces glucose levels in the growing foetus. Consequently this mechanism, results in a decline in maternal glucose levels and the problems related with GDM are reversed (73, 74).

2.1.6 Barriers to screening for gestational diabetes mellitus

The importance of early identification and intervention for GDM to prevent adverse health outcomes in the mother and child is necessary. Hocaoglu et al., 2019 reported on reasons why women were reluctant to do the OGTT in Turkey, some thought the test was harmful to the baby, not necessary, unpleasant test or their doctor did not raise it as a concern to perform the

test (38). In another study barriers such as cultural or social barriers, (pregnant women are expected to gain weight and eat sweets), role of women in society (expected to be busy with mainly household chores), pregnant woman's health is not perceived to be important (need to spent money and buy healthy food for her), and the distance travelled to health care facilities (75). Whereas in systematic review on low- and middle- income countries, some of the barriers identified were pregnant women that fasted overnight, test takes long and insufficient testing equipment in those areas (2).

2.1.7 Inter-generational consequences of gestational diabetes mellitus

Barker *et al*., (76) proposed the "developmental origins of health and adult disease" theory which speaks of the origin of several diseases in adults originating early in life. In 1944, a Dutch cohort showed that maternal under-nutrition during pregnancy was related with increased risk of cardio-metabolic disorders in the child. Several studies have shown that the *in utero* environment affects the development of foetal organs and tissues (76), and is associated with the danger of developing metabolic diseases later in life.

In women with GDM, the foetus is affected by the *in utero* environment, resulting in gene expression changes in the foetus through epigenetic programming (77). These epigenetic alterations prompt the child to developing diabetes in adulthood. In addition, women with mildly or severely high glucose levels are at increased risk for developing GDM and other metabolic diseases in their later years, and so the cycle progresses to the subsequent generation. This cycle of diabetes is known as, "trans-generational transmission" (Figure 2.3) (52). Specifically, female infants born to mothers with GDM are likely to develop GDM when they are pregnant and the cycle continues to their children (17, 78). In the 1980s, the "fuel-mediated teratogenesis" concept was introduced which proposes that maternal over-nutrition leads to high insulin levels in the developing foetus and causes the child to be at danger of being diabetic and obese later in life (79, 80).

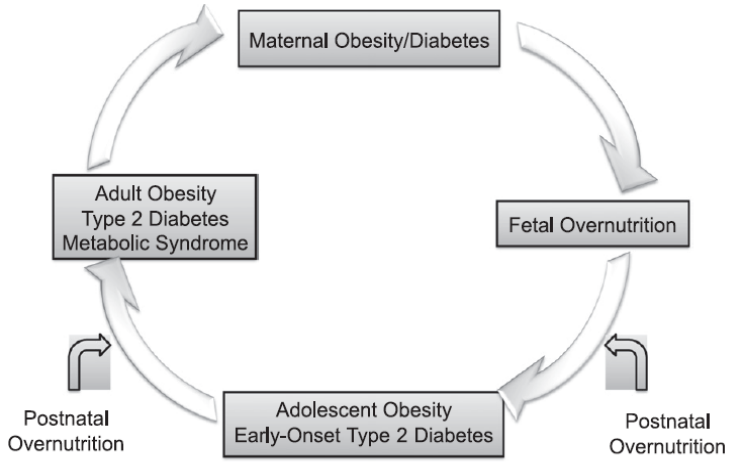

Figure 2.3 The vicious cycle of maternal obesity and diabetes (81)

2.1.8 Risk Factors related with gestational diabetes mellitus

In South Africa, the application of selective screening of GDM is centred on the existence of risk factors (82, 83) which is also practiced in some developed countries (84)**.** Selective screening for GDM is performed in various hospitals (57) and several studies (63, 70, 82, 83) have mentioned risk factors associated with GDM:

- BMI > 30 kg/m^2
- Pregnancy-induced or chronic high blood pressure
- Formerly given birth to a macrosomic (≥ 4 kg) baby
- Formerly had GDM
- Former stillborn
- In the past a family member had diabetes
- Belonging to a particular ethnic group (e.g., African American, Hispanic)

2.1.9 Health related adverse events of gestational diabetes mellitus

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study reported that maternal diabetes is linked to foetal and postnatal complications (56). Some of these complications include pregnancy related high blood pressure, preterm delivery, polyhydramnios, macrosomia (birth weight ≥ 4 kg) , stillbirth and intrauterine death (85). In addition, infants exposed to GDM are likely to have jaundice, hypoglycaemia, distress at birth and respiratory distress condition (86). Children exposed to GDM *in utero* are likely to be overweight or obese, have

more abdominal fat, high blood pressure, insulin resistance and weakened glucose tolerance, and are at risk of developing T2DM and heart-related ailments later in life (87).

Even if most females with GDM revert back to normal glucose metabolism after giving birth, approximately 10% of them are diagnosed with T2DM after giving birth, while 20-60% of them are expected to develop T2DM within five years after giving birth (56, 88). In addition, there is greater risk of NCD in the mother and child following one or more GDM pregnancies, Figure 2.4 (89). Therefore, interventional studies are important to identify GDM quickly and to carefully evaluate the dangers for GDM in order to stop further complications in the mother and child (79).

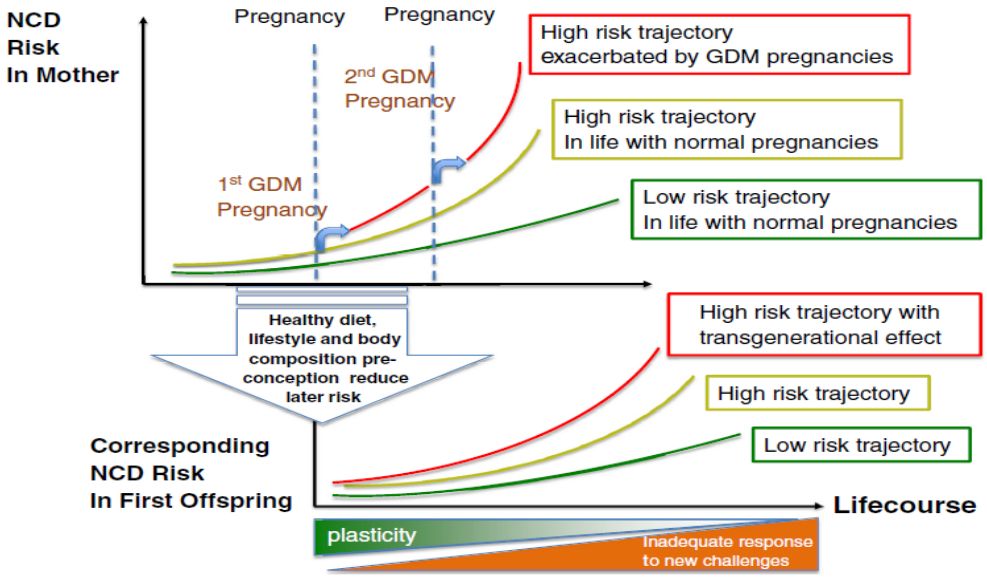

Figure 2.4 The risk of developing non-communicable diseases in the mother and child, increases with each pregnancy affected by GDM (89)

2.1.10 Risk of macrosomia with gestational diabetes mellitus exposure

Macrosomia is well-defined as a birth weight ≥ 4 kg or above the 90th percentile respectively (90, 91) and occurs in approximately 15% - 45% of GDM affected pregnancies (50, 92, 93). Ultrasonographic assessments are performed to estimate foetal growth; however this method is not precise (error of 10-15%) (94). A foetus exposed to GDM is at risk of being macrosomic and having shoulder dystocia at birth. It is also in danger of having hereditary defects and or being stillborn. Immediately after delivery the child is at risk of complications such as respiratory distress syndrome, hypoglycaemia, hyperbilirubinemia and reduced anaemic blood

levels (95). In the long-term, as previously mentioned, macrosomia may result in a greater danger of developing T2DM, obesity and other metabolic ailments (92, 96).

2.1.11 Pathophysiology of macrosomia

In the 1950s the Pedersen hypothesis explained the pathophysiology of macrosomia (Figure 2.5). Maternal hyperglycaemia causes foetal insulin levels to increase, leading to high foetal glucose levels which is then kept as body fat or adipose tissue in the growing foetus. Whilst maternal glucose is able to cross the placenta, maternal insulin is unable to do so. Glucose therefore accumulates in the developing foetus causing the foetal pancreas to secrete more insulin. Hyperinsulinemia and hyperglycaemia favours the storing of foetal fat and protein resulting in macrosomia (52). Organs such as the liver, heart and ventricular septum also enlarge because of cellular hypertrophy and hyperplasia. The enlarged organs contribute to the total body composition, and therefore high birth weight (97).

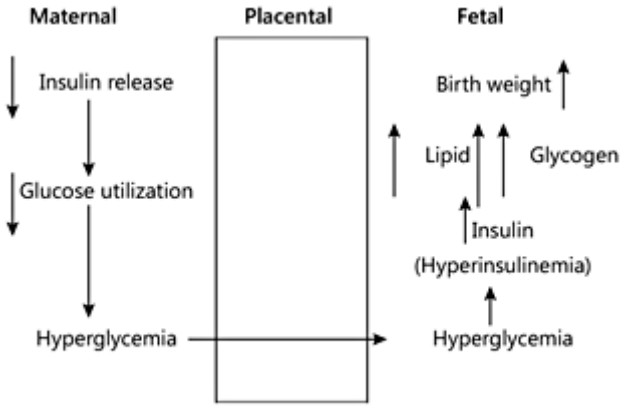

Figure 2.5 Maternal hyperglycaemia modified according to Pederson's hypothesis (52)

2.2 Early infant growth and adiposity

From the third trimester during pregnancy onwards there is a substantial surge in body fat which peaks at about six months after birth (98). Other studies (99, 100) showed that at birth, infants born to mothers with GDM had higher weights compared to infants born to mothers without GDM, while at two weeks after birth there was no significant difference in weight between the two groups. In contrast, other studies showed there was no significant variation in the birth weight between infants exposed and those not exposed to GDM (50, 101-103). A study led by Durnwald *et al.,* (87) found no significant difference in fat mass and percentage

of body fat in infants exposed to GDM compared to unexposed infants. In the same study, maternal GDM status and gestational age were significantly related with fat mass (101). In a study by Brumbaugh *et al.,* (99) there was no statistical difference in the fat mass and fat free mass of infants exposed and unexposed to GDM. Lastly Catalona *et al.,* (104) found infants exposed to GDM had significantly more fat mass and percentage of body fat but less fat free mass while no significant differences in birth weight and length in infants exposed to GDM compared to infants unexposed to GDM was observed.

Several studies have revealed that infants exposed to GDM are likely to have slower weight gain in the first six months of life compared to infants not exposed to GDM (105, 106). There are, however, conflicting results in the literature, whereby some researchers have shown that infants whose mothers had GDM have less weight gain and length gain in the first three months of life, and more weight gain after six months of life, compared to infants born to mothers without GDM (105, 107, 108).

2.3 Infant body composition

Body composition provides information regarding the nutritional status of the child and then guides nutritional guidelines provided by the health professional (109). There are simple and complex methods used to determine body composition (109). Anthropometric measurements (including skinfolds) are widely used to estimate adiposity because they are simple and inexpensive (24, 110). A disadvantage of anthropometric measurements is the inability to precisely distinguish between fat mass and fat free mass (24). Other methods like the dual energy X-ray absorptiometry (DXA), deuterium, and magnetic resonance imaging are not widely used due to their price, radiation exposure for DXA and availability (24). Presently, the ADP machine known as the PEAPOD is the gold standard technique used to measure infant body composition in the first six months of life (15). However, it is not easily available, and it is costly. The advantage of this method is that there is no exposure to radiation and measurements are not affected by the infant's movement (111). An overview of the different approaches used to measure body composition are presented in Table 2.2 (11).

Body mass index has been used to define obesity, yet it is not an accurate method to determine body fat, since high BMI may be due to muscle mass and not body fat (15). Nonetheless, weight-for-length and BMI-for-age are anthropometric measures used to diagnose overweight and obesity in school children or adolescents but not in infants (111).

Table 2.2 An overview of anthropometry and body composition assessments for infants (9)

Method	Advantages	Disadvantages
Weight	Minimal equipment needed Applicable in a variety of settings	Not a direct measure of body composition
Body circumferences	Ease of measurement Minimal equipment needed	Not widely used in infants Reference values for infants are lacking
Skinfolds	Minimal equipment needed Non-invasive	Investigator must be highly trained Limited validation of conversion equations In diverse population
Dual energy X-ray absorptiometry (DXA)	Able to differentiate fat tissue from lean tissue Applicable for regional and whole-body assessments	Radiation exposure, although minimal Lack of availability due to high cost Limited use in previous research
Computed tomography (CT)	Regional body assessment Accurately assesses body composition, body fat distribution, internal fat deposition, and organ site	Expensive Time-consuming procedures High radiation exposure
Magnetic resonance imaging (MRI)	Regional body assessment Accurately assesses body composition, body fat distribution, internal fat deposition, and organ site No radiation exposure	Expensive Time consuming procedure Inaccuracy among infants < 6 months of age
Air displacement plethysmography (ADP)	Commercial device available (PEA POD) Accurate and reliable measure of fat mass and fat-free mass	Expensive Lack of portability
Bioelectrical impedance (BIA)	Noninvasive Portable Utilised in clinical settings	Inaccuracy concerns in infants
Dilution (deuterium or 18 O)	Applicable for total body water and hydration Assessment	Associated with accuracy errors Not utilised in clinical or applied settings
Ultrasonography	Acceptable accuracy Preferred by mothers to MRIs	Limited use in previous research

2.3.1 Fat mass and fat free mass of infants exposed to gestational diabetes mellitus

An upsurge in the amount of fat in children and adults has been found to be related with an increase in health dangers such as heart related metabolic disorders (106, 112). Numerous studies have shown that infants exposed to GDM have higher birth weight due to the greater amount of body fat (113, 114). Some studies have shown that infants exposed to GDM had greater fat mass compared to unexposed infants (101, 115, 116). Conflicting results by Naeye *et al.*, (117) found an increase in fat free mass in large infants exposed to GDM during pregnancy. Uebel *et al.*, (106) found greater abdominal fat in infants exposed to GDM compared to those who had not been exposed. Several studies found infants exposed to GDM during pregnancy were born with normal body fat but later in life the same children were found to be overweight with excess body fat (118, 119).

2.4 Risk of obesity and gestational diabetes mellitus in the South African context

South Africa is a diverse country in terms of ethnicity, demographic factors, cultural beliefs and disease risks. In addition, environmental influences together with genes, are determinants of infant and childhood growth (120). South Africa is experiencing the double burden of childhood stunting and obesity (121). Inversen *et al*., (122) reported on 1512 children, between the age one and five years, according to the 2006 WHO growth standards, that 20.1% were stunted, 6.8% were underweight, 20.6% were overweight and 9.5 were obese. However, there has been an increase in obesity due to urbanisation and consumption of foods high in fat, sugar, and salt (123-126). In addition, 28% of children between the ages of six and 12 years were reported to be overweight increasing their dangers of having NCD later in life (121).

A study of black South African women showed that the commonness of GDM is increasing in this population (46) and it relates to the intergenerational cycles of diabetes. There are several ways to curb the continuous cycle caused by GDM, either before conception, during pregnancy and/or in the infancy period, and therefore minimise the risk of long term complications (40). In South Africa selective screening for GDM is not a standard clinical practice in all health facilities, however it is done at Chris Hani Baragwanath Academic Hospital (CHBAH) and universal screening has been offered on a research basis (46).

2.5 Study Motivation

To the best of my understanding, there have been no studies in South Africa that have assessed longitudinal body composition in infants born to mothers with and without GDM. Pregnancy is a critical period for the mother and the growing foetus as it can have lasting impact on the health of the mother and child. Women need to be aware of the physical changes that accompany pregnancy and the physiological aspect. The food items a woman consumes is converted to glucose which gets transported to the foetus via the placenta. This study contributes to the research gap on the need for effective screening for GDM thus addressing the standard practice and how exposure to GDM affects the baby in the short term. The importance of assessing infant body composition is necessary in the research field and health sector to understand the risk of GDM on early infant growth.

CHAPTER THREE: Methodology

Introduction

This chapter reports on the study participants and location. The study material, methods and inclusion and exclusion criteria of the participants are defined. The reliability and validity of the data collected are discussed together with the statistical analyses performed.

3.1 Study population and setting

Three thousand six hundred and fifty-six (3656) pregnant women were enrolled from the Foetal Medicine Unit (FMU) and Antenatal Clinic (ANC) of the CHBAH and invited to participant in the study. Data collection was conducted at the MRC/WITS Developmental Pathways for Health Research Unit (DPHRU) located on the CHBAH property in Soweto, Johannesburg.

3.1.1 Soweto

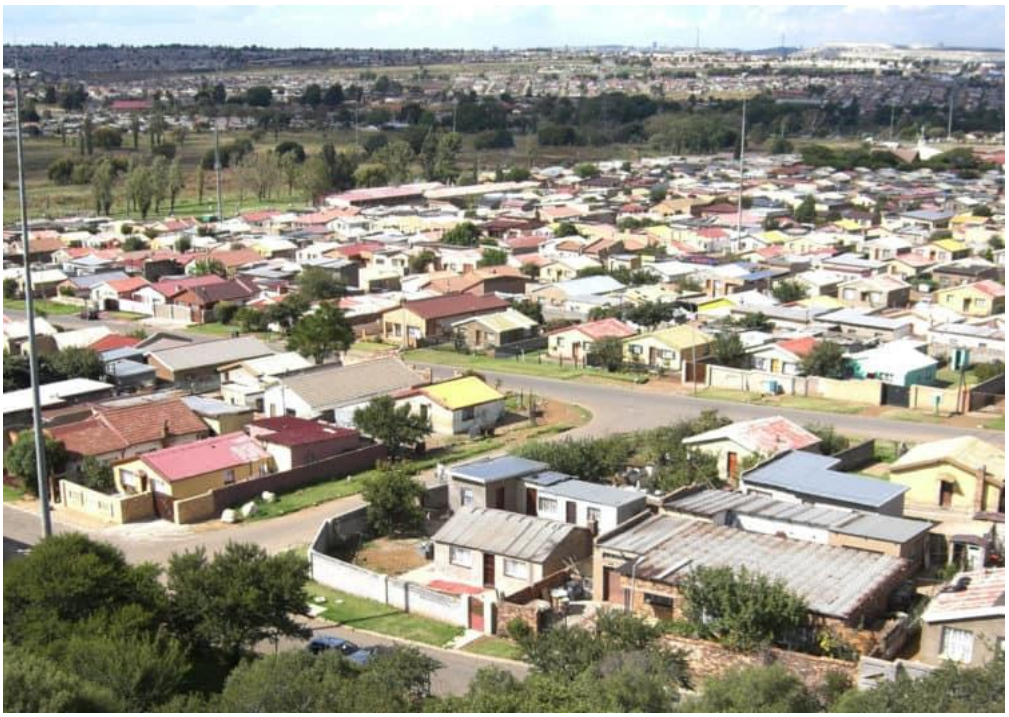

Figure 3.1 Soweto township (127)

The urban township ‘South Western Township’ (Figure 3.1), known by its acronym Soweto is in Johannesburg, South Africa. The township was started in the 1930s during the apartheid era, when South Africans were categorised as either black, white, Indian, or coloured and were

separated geographically. The majority of people living in Soweto are black South Africans. The population of Soweto is estimated to be 1.3 million (128).

3.1.2 Chris Hani Baragwanath Academic Hospital



Figure 3.2 Chris Hani Baragwanath Academic Hospital (127)

The CHBAH (Figure 3.2) is the third largest hospital in the world and is located in Soweto, Johannesburg. It serves the people of Soweto and those from the surrounding areas and neighbouring countries. Pregnant women are referred from the district hospitals and local clinics to this tertiary hospital as its ANC is able to care for patients with high risk medical conditions. All pregnant women at CHBAH undergo at least one dating ultrasound scan (46). Pregnant women undergo a several procedures at the ANC, such as urine dipstick testing, blood pressure monitoring, blood taking for various medical tests, and weight and height measurements. However, selective screening based on risk factors is applied to find women at risk of having GDM. Those identified as high risk then undergo an OGTT**.** The screening criteria used by the hospital to identify women at risk for GDM are as follows (129):

- Random blood glucose ≥ 8mmol/l, but < 11mmol/l
- Positive glucose urine-strip results, on two antenatal clinic visits
- History of stillbirth

- History of large for gestational age baby (≥ 4 kg)
- History of gestational diabetes mellitus
- Immediate family with diabetes
- Polyhydramnios with or without abnormalities
- Regular infections, e.g., urinary tract infection, vaginal thrush

The hospital uses the WHO 2013 criteria (127) to diagnose GDM. According to the criteria, the diagnosis of GDM is made if one value of plasma glucose concentration equals or surpasses the threshold ranges of 5.1 - 6.9 (fasting glucose), ≥ 10.0 (one-hour post-glucose load), and 8.5 - 11.0 (two hours post-glucose load) after performing a two-hour 75g OGTT.

3.2 The pregnancy study inclusion criteria

Pregnant women who had been referred to CHBAH from district hospitals and local clinics in Soweto and the surrounding areas (Orange Farm and Lenasia) were asked to join in the study, on condition that they met the study inclusion criteria. The inclusion criteria for this study involved women being less than 20 weeks pregnant black South African (ethnicity verbally reported), 18 years of age or older and expecting singleton babies that were, naturally conceived. Furthermore, no foetal abnormalities could have been detected and the women could not have T1DM or epilepsy (epilepsy medication influences glucose breakdown in the body).

3.2.1 Recruitment of the pregnant women

Universal screening which took place from the 1st of June 2013 until the 30 April 2017 was offered to every pregnant woman who met the inclusion criteria. An information sheet (Appendix A) used by the research assistants explained the importance of testing for GDM and how the condition can affect the unborn baby. In addition, a simplified GDM pamphlet was given to each woman at the clinic (Appendix B). The pamphlet defined the differences between overt diabetes and GDM. The causes, risk factors and symptoms of GDM were detailed and the pamphlet also stated that GDM can be managed by diet, exercise, blood glucose monitoring, and as a last resort, medication. Participants were recruited when they were less than 20 weeks pregnant at ANC and booked to have the OGTT performed during week 24 of pregnancy thus giving them a four-week leeway (between 24-28 weeks) if they had to reschedule their appointment. Appointments for the OGTT were confirmed one week in advance which allowed for rescheduling.

3.2.3 Questionnaires

Each pregnant woman was asked a series of questions to obtain information on obstetric medical history, such as previous births and number of previous pregnancies, previous macrosomic babies (Appendix C), demographics and socioeconomic status (SES) (Appendix D). The SES questions asked whether women were married or not, if they were educated or not and to what extend and the household environment (water source, house ownership, type of house and ownership of household assets such as a television, refrigerator, washing machine and cell phone). A participant's HIV status was not tested at DPHRU but was recorded from the ANC card. The participants were contacted telephonically after delivery to complete a delivery and birth outcome questionnaire (Appendix E).

3.2.3 Specimen collection

At the OGTT visit, a urine dipstick test was performed and bloods for glucose testing were taken during the OGTT. A laboratory sheet was used to record the different blood collection times, as well as the urine dipstick test results (any signs of infection, protein, traces of blood or glucose) (Appendix F).

3.2.4 Oral glucose tolerance test procedure

A 75g two-hour OGTT was administered after a participant had fasted for a minimum of 10 hours. If the participant had eaten or drunk anything other than water, the OGTT was rescheduled. Before blood collection, finger prick (capillary) fasting glucose levels (glucometer, ACCU-CHEK Active, Roche, Indianapolis. USA) were measured. If the glucose was < 7mmol/L the nurse proceeded with the OGTT. In cases where the glucose was ≥ 7mmol/L, the fasted participant was referred to the ANC at CHBAH for further managing (possible overt diabetes). Research nurses mixed the 75g glucose powder, with 250 ml of warm water. The solution was then allowed to rest for a few minutes to cool down. The blood taking arm area was cleaned with an alcohol swab, the cannula placed in the vein, and the 3-way stopcock attached and secured with a tape. The research nurse attached the vacutainer tube holder to the luer adaptor, placed it into the 3-way stopcock and opened the tap. A fasting blood glucose sample was drawn into the grey 5ml blood collection tubes and gently inverted. Grey top blood collection tubes contain fluoride and oxalate to prevent glucose from breaking down.

Using a 10 ml syringe, the 3-way stopcock was filled with ± 2ml of saline during blood taking intervals to prevent blood clothing on the vein. The time when the baseline blood samples were taken was recorded. The stopwatch was started as soon as the participant started drinking the glucose solution. The participant was asked to finish the glucose solution within 5 minutes. Around ± 5 ml of blood was collected at 30 minutes, 60 minutes and 120 minutes after glucose intake. The blood samples were placed on ice and sent to the laboratory for processing.

3.2.5 Gestational diabetes mellitus diagnostic criteria

The WHO 2013 diagnostic criteria (127) were applied to diagnose GDM. According to the criteria, the diagnosis of GDM was made if one value of plasma glucose equalled or exceeded the threshold for fasting bloods of 5.1-6.9mmol/l, at one hour ≥ 10.0 mmol/l and at two hours 8.5-11.0 mmol/l after performing the 75g OGTT. Overt diabetes was diagnosed as a fasting plasma glucose level ≥ 7 mmol/l or a two hour plasma glucose ≥ 11 mmol/l (130). Women who tested positive for GDM were referred to the Obstetric Diabetes Clinic at CHBAH for further managing.

All blood samples were processed at the DPHRU laboratory using the centrifuge (MPV 351e med instruments). The Clinical Laboratory Standard institution document EP15 was used to check precision of the Radox RX Daytons Chemistry Analyzer. Analyses of 150 randomly selected samples were repeated to test for reliability. The coefficient of variation was 2.3%.

3.2.6 A sub-study: Barriers to the uptake of universal screening

A total of 137 women post-delivery were contacted and interviewed telephonically to find out why they did not attend the GDM screening study.

3.2.7 Pregnant women anthropometric measures

Anthropometric measurements were taken at the OGTT appointment. Maternal weight and height were measured using calibrated instruments and thereafter BMI was calculated as weight (kg) over height (m) squared. The WHO classification was used to define underweight (<18.5 kg/m^2), normal weight (≥ 18.5-24.9 kg/m^2), overweight (≥25-29.9 kg/m^2) and obese ≥30 kg/m^2) (131).

3.2.7.1 Adult weight

The participants were weighed wearing minimal clothing. Weight was measured to the nearest 0.1 kg using a calibrated scale (SECA 877 Hamburg, Germany). When the participant stepped on the scale, the weight was read and recorded to one decimal place on a data collection sheet.

3.2.7.2 Adult height

Height was measured to the nearest 0.1 cm using a stadiometer (SECA, Stadiometer 264 Hamburg, Germany) with participants were asked to take off shoes. The participant was made to stand with her back against the measuring rod, feet slightly apart, knees straightened, arms and shoulders relaxed (Figure 3.3). The head was positioned in the Frankfort horizontal position the peak point of the external auditory canal and the lowest side-line of the left orbit in line. The head piece was then moved downwards till it touched the top of the participant's head and the participant was asked to take a deep breathe in to straighten the spine for standing height position.

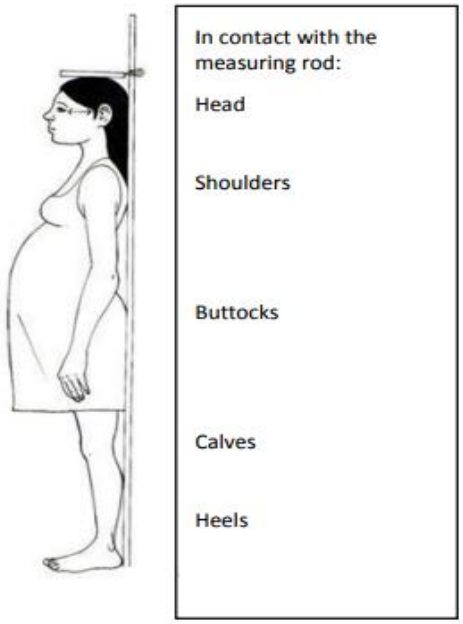

Figure 3.3 Height position for pregnant woman (132)

3.3 Follow up of infant mother pairs

An overall of 131 mothers and their babies were randomly selected after delivery from May 2016 to October 2017 for the longitudinal case-control study. The case group consisted of 22 mother-infant pairs of which the mother had been identified to have GDM during her recent

pregnancy with the child. The control group consisted of 110 mother-infant pairs in which the mothers were diagnosed as not having GDM during their recent pregnancies. The mothers gave written consent for their infants to be part of the study (Appendix G and Appendix H; case and control information and consent sheets respectively).

The infants were followed up from day one to day 33 of life and then seen once a month until they were six months old. The data collection follow-up time points were coded as follows: 1) ≤ 33 days, 2) 34 to 54 days, 3) 55 to 73 days, 4) 74 to 111 days, 5) 112 to 138 days, 6) 139 to 164 and 7) ≥ 165 days. Neonates who had been admitted to the Neonatal Intensive Care Unit at CHBAH after birth for a period of four days or more were excluded from the study.

3.3.1 Infant anthropometry

Standard procedures were followed when taking infant anthropometric measurements (Appendix J). Infants' clothes, waist/neck bands and shoes were removed. Weight was measured to the nearest 1000 g; length was measured to the nearest 0.1 cm and head circumference was measured to a precision of 1 mm.

3.3.2.1 Infant weight

Babies were weighed according to the standardised techniques using a weighing scale (SECA 376, London, UK). The scale was turned on and a paper towel was placed on the surface to protect the baby from direct contact with the cold surface of the scale. The baby had to have stopped moving before the hold button was pressed and the weight was measured and recorded. If the baby did not lie still on the scale, he/she was removed from the scale and the mother of the baby had to calm the baby before measurements were attempted. A delivery weight of ≥ 4 kg was defined as macrosomia (133) although the gestational age varied (91).

3.3.2.2 Infant length

Infant head-heel length was measured with an infantometer (Harpenden 98.702 infantometer, Britain) which was perpendicularly fixed headboard and a removable footboard against the horizontal board. The infantometer was placed on a flat surface and a soft paper towel was placed on the horizontal board. The research assistant stood in front of the infantometer, positioned the head and ensured that it touched the headboard. The head needed to be centralised against the headboard. The head was positioned so that the upright line from the ear

canal to the lower edge of the eye socket was perpendicular to the parallel board, (Frankfort Vertical Plane). The lead person taking the measurements stood to the side to keep the baby's legs composed and to make straight the knees. The footboard was moved towards the baby, making sure that it touched the bottom of the heels. The heels were centralised on the food board. A reading was then recorded.

2.3.2.3 Infant head circumference

A non-elastic metallic measuring tape (2 m longand0.7 cm wide) was used measure the infant head circumference. A research assistant held the baby on her lap while in a seated position. The tape was placed above the eyebrows and on the most protruding portion of the back of the head. As soon as the tape was correctly positioned, it was pulled tightly enough to flatten the hair but not hurt the infant. Tape measurements were read on either side, away from the research assistant's abdomen and chest. A reading was recorded, and measurements were repeated by a second person.

2.3.2.4 Z- scores

The z-scores were characterised according to the WHO guidelines as stunted, wasted or underweight if their weight-for-age z-scores (zweight) and length-for-age z scores (zlength) were less than -2 (90). Overweight was defined as BMI z-score (zBMI) +1 and obese was well-defined as zBMI +2 (134). The head circumference-for-age (zhead circumference) was also calculated.

3.4 Infant body composition

Infant body composition was evaluated from birth until six months of age or when a maximum weight of 8 kg was reached by the whole-body ADP called the PEAPOD (Cosmed, USA) (Figure 3.4). The results were interpreted as the body volume of a participant's body composition. This method of determining the body composition has been validated against the other available methods to measure body composition. Body size was determined by the Boyle's Law equations, which state that at a steady temperature, volume (V) and pressure (P) are inversely related: PI / P2 = V2 / V1

Where P1 and P2 represent the pressure prior to and after the infant was positioned inside the PEAPOD machine , respectively and V1 and V2 are volumes prior to and after the infant placement into the machine, respectively (135).

The PEAPOD quality check or standardisation was done once every morning before any scans were conducted. A calibration cylinder or phantom was used to standardise the machine volume and a 5000g weight was used to standardise the machine scale (136).



Figure 3.4 Photographic image of the air displacement plethysmography

The gestational age, childbirth date, sex and length were captured into the computer system of the PEAPOD machine. All clothing was removed from an infant including the diaper, earrings and beads around the waist or neck. A standard tight-fitting wig cap was placed on each infant's head to prevent air from being trapped in between the hair, when measuring body volume and body weight. For the neonatal visit, the umbilical cord peg and name or hospital tag were calibrated against the body weight and body volume measurements. The infant was placed in the PEAPOD chamber and body size measurements were recorded. The full body assessment took about two minutes. The radiographer or trained student watched the baby through the glass space and the chamber entrance opened automatically at any time if the baby was unsettled, uncomfortable or restless during the scan. Body density was converted to fat percentage using Fomon *et al*., (137) equations.

3.5 Reliability and validity of results

To ensure reliability of the results, an assessment validation was performed prior to the study and during data collection. All anthropometry measurements were performed by the student

with the assistance of a research assistant. Interpersonal variability was tested and checked for technical error of measurement between the two measures. The same measuring technique was applied by all research assistants. Standardisation took place every three months for weight, length and head circumference measurements. To ensure accuracy, calibration of all instruments (scale, infantometer and PEAPOD) was performed daily during data collection. The scale was calibrated using different weights (0.5 kg, 1 kg, 2 kg, and 5 kg). Two aluminium metallic rods (40 cm and 75 cm) were used to calibrate the infantometer.

3.6 Data cleaning and preparation

The Research Electronic Data Capture (REDCap) was used to captured data and all coding was done in REDCap (138). All errors and missing data were rectified unless participants could no longer be contacted. Missing data were excluded when z-scores were calculated. For data analysis, some variables were re-coded, and some continuous variables were converted to categorical variables. STATA version 14 (Stata Corporation, College Station, Texas, USA) was used to merge datasets.

3.7 Statistical analysis

Data were analysed using STATA version 14 (Stata Corporation, College Station, Texas, USA)**.** The Skewness-kurtosis test was used to test for normality of all continuous variables. The means ± standard deviations were calculated for maternal age, infant birth weight and length until six months of age. Continuous variables were compared using the Student's t-test (two independent variables). Data that were not normality distributed were presented as median (interquartile range) and were compared using the Wilcoxon rank-sum test (Mann- Whitney-U test). Frequencies and proportions were calculated for all categorical variables. Categorical variables were compared using the Chi-square test. A p-value of $p < 0.05$ was considered statistically significant. To determine associations' linear regression analysis was used for maternal and infant exposure variables and birth outcomes (weight, length, head circumference, fat mass index and fat free mass index). Multivariate models were specified *a priori* based on literature between exposures and infant outcomes, significant associations, and beta values of 0.2 onwards on the bivariates. The following z scores: zweigh, zlength, zhead circumference and zBMI were calculated using our own study population mean and standard deviation at various time points. The conditional weight and length were generated between two points (Appendix J) by regressing the weight at each age on all the previous weight

measures adjusting for the present length (139) and therefore showing the rate of weight gain. In addition, conditional length was defined as present length accounting for previous lengths (140).

3.8 Ethics Clearance

All the data collected from the participants were treated as confidential. Ethics approval for this Masters project was obtained from the Human Research Ethics Committee (HREC) (Medical) at the University of the Witwatersrand, certificate number: M150461, (Appendix K).

CHAPTER FOUR: Results **-** Uptake of universal screening and the effectiveness of selective screening for gestational diabetes mellitus

Introduction

This chapter provides an overview of the characteristics of the women with and without GDM who were included in this study. The risk factors used to selectively screen for GDM at CHBAH in women with GDM are also presented. In addition, reasons are given as to why women declined the research universal screening. The statistical analyses comparing the two the groups are presented as well.

4.1 Characteristics of women screened for gestational diabetes mellitus

An overall of 3656 women decided to participate in the study and were then booked for an OGTT appointment when they were 24-28 weeks pregnant after giving informed consent. A total number of 2009 pregnant women underwent an OGTT, 1906 pregnant women had complete reading and were counted in the study. Fifty seven percent (2100/3656) of the pregnant women took up the offer of the universal screening. Forty three percent of pregnant women (1556/3656) declined the universal screening for GDM (46), (Figure 4.1).

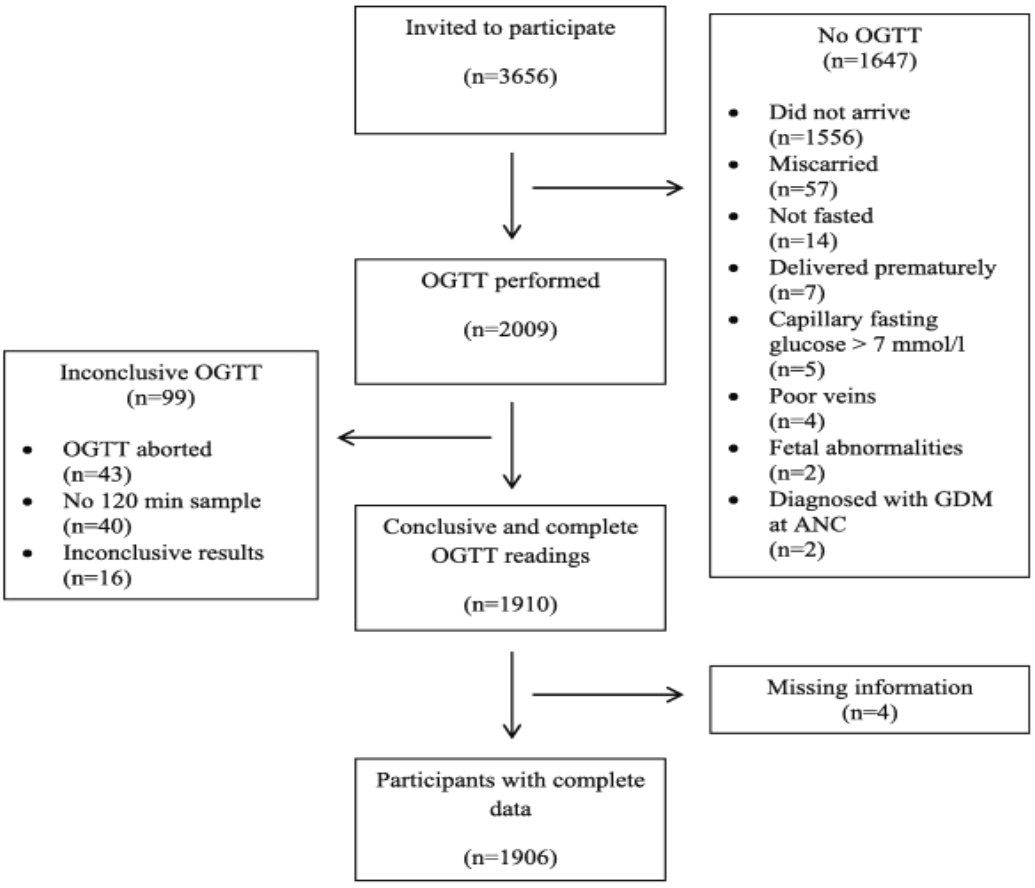

Figure 4.1 Pregnant study participants (46)

The characteristics of the women screened for GDM are presented in Table 4.1. The study population consisted of 174 pregnant women who tested positive for GDM and 1732 pregnant women who tested negative for GDM resulting in 9.1% prevalence of GDM amongst the study participants (46).

Women with GDM were significantly older than women without GDM (p = 0.007). There was a significant difference in the maternal BMI categories between the women with and without GDM. Many women with GDM underwent the OGTT procedure between 27-28 weeks while women without GDM underwent the OGTT between 25-26 weeks. In addition, 22% of women without GDM underwent testing at ≤ 24 weeks gestation compared to 16% of women with GDM. Lastly, in both groups 3% of the women tested at 29 weeks and above.

Table 4.1 Characteristics of women screened for GDM

Variables	Total women (n = 1906)	Women with GDM (n = 174)	Women without GDM (n= 1732)	p-value
Age (years)	36.00 (35.00-39.00)	31.00 (27.00-36.00)	30.00 (25.00-34.50)	**0.007**
BMI				
Normal (≤24.9 kg/m^2)	395 (20)	26 (15)	369 (21)	**0.004**
Overweight (25-29.9kg/m^2)	606 (32)	45 (26)	561 (33)	
Obese (≥ 30 kg/m^2)	905 (47)	103 (59)	796 (46)	
Previous pregnancies				
None	230 (12)	15 (9)	215 (12)	0.078
One or two	1191(62)	104 (60)	1084 (63)	
Three or more	485 (25)	55 (32)	427 (25)	
Previous births				
None	494 (26)	40 (23)	453 (26)	0.183
One or two	1237 (65)	123 (71)	1109 (64)	
Three or more	175 (9)	11 (6)	164 (10)	
Weeks pregnant at OGTT				
≤ 24 weeks	402 (21)	27 (16)	374 (22)	**0.002**
25-26 weeks	867 (45)	67 (39)	797 (46)	
27-28 weeks	574 (30)	74 (43)	499 (29)	
≥ 29 weeks	63 (3)	6 (3)	56 (3)	
HIV status				
Negative	1309 (67)	115 (66)	1190 (69)	0.439
Positive	597 (31)	59 (34)	536 (31)	
Family history of diabetes (n = 1094)				
No	1423 (75)	118(68)	1305 (76)	**0.022**
Yes	475 (25)	56 (32)	419 (24)	
Previous macrosomic baby, ≥ 4kg (n = 1904)				
No	1808 (95)	165 (95)	1643 (95)	0.779
Yes	90 (5)	9 (5)	81 (5)	
History of stillbirth (n = 1769)				
No	1626 (92)	147 (88)	1473 (92)	0.055
Yes	143 (8)	20 (12)	123 (8)	
Polyhydramnios (n = 727)				

	No	723 (99)	81 (100)	642 (99	0.478
	Yes	4 (1)	0	4 (1)	
Urinary samples					
Urinary tract infection (n= 733)					
	No	691 (94)	81(99)	610 (94)	0.062
	Yes	42 (6)	1 (1)	41 (6)	
Leukocytes (n = 1850)					
	No	1744 (94)	157 (94)	1581 (94)	0.889
	Yes	106 (6)	10 (6)	96 (6)	
Protein (n= 1853)					
	No	1847 (100)	167 (99)	1674 (100)	0.519
	Yes	6 (0)	1 (1)	5 (0)	
Glucose (n = 1853)					
	No	1852 (100)	167 (100)	1679 (100)	0.753
	Yes	1 (0)	0 (0)	1 (0)	

Significant results are represented in bold ($p < 0.05$). Data are summarised as median (interquartile ranges) or n (%)

4.2 Effectiveness of selectively screening of women for GDM at Chris Hani Baragwanath Academic Hospital

The study also assessed how effective the selective screening criteria used by CHBAH is in identifying women with GDM. A total of 86/174 (49%) women would have been detected by the selective screening but of those numbers 88/174 (51%) would have been missed by the selective screening procedure because of the absence of GDM related risk factors (Figure 4.2).

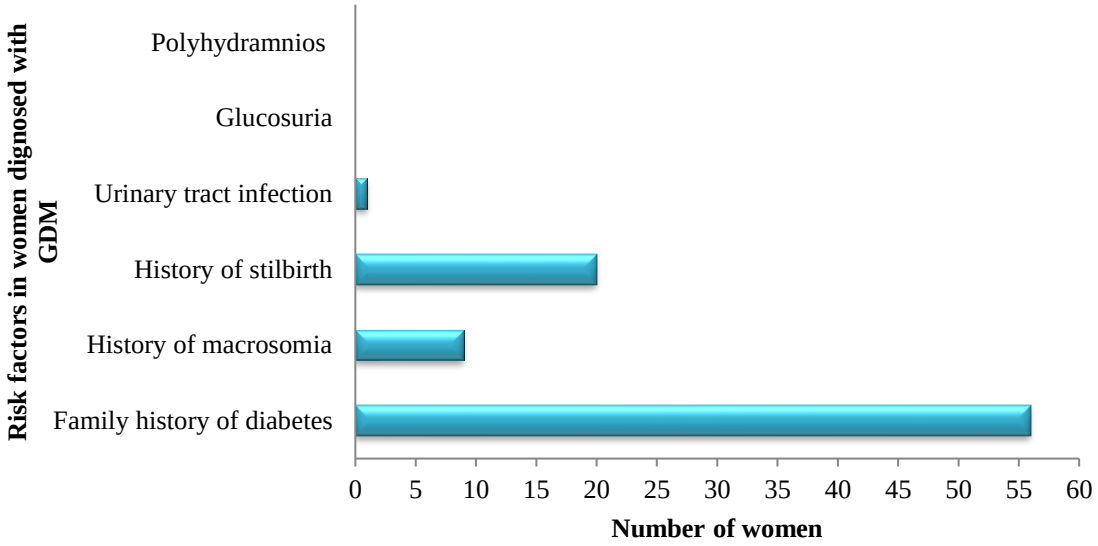

Figure 4.2 The number of women diagnosed with GDM who presented with risk factors that would have warranted selective screening for gestational diabetes mellitus at CHBAH

4.3 Barriers to the uptake of universal screening for GDM

In the sub-study, a total of 137 pregnant females were contacted post the OGTT and they gave various reasons as to why they chose not to attend their OGTT appointment. The reasons are summarised in Figure 4.3.

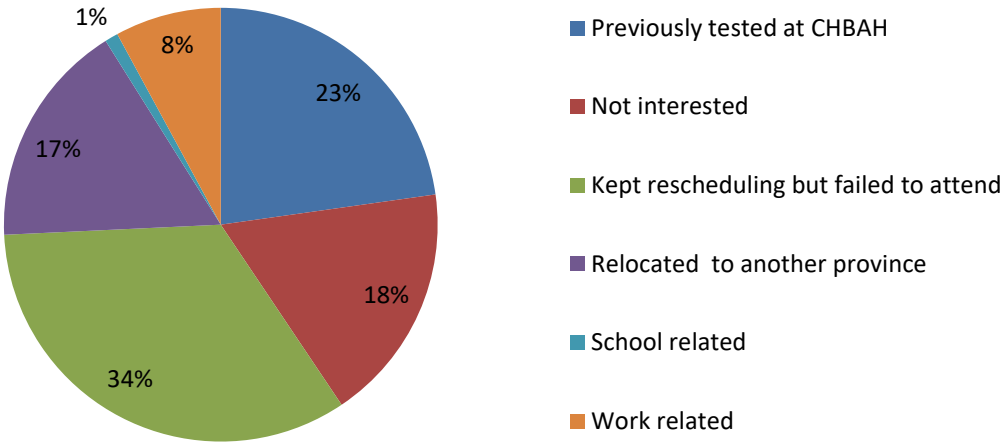

Figure 4.3 Illustrates the reasons for declining universal screening

CHAPTER FIVE: Results **-** Longitudinal follow-up of infants

Introduction

This chapter presents results of the mother-infant pairs who were monitored at birth until six months of life. Firstly, the delivery outcomes are described, followed by anthropometric, z-scores and body composition measurements of the infants. Bivariate and multiple linear regressions analyses were performed to establish associations of infant exposures to GDM and maternal and infant outcomes.

5.1 Maternal and infant characteristics

5.1.1 Delivery outcomes

In Table 5.1, the study participants consisted of 22 infants exposed to GDM and 110 infants unexposed to GDM. The median (interquartile ranges) gestational age was 38 (37.00-39.00) weeks for women with GDM and 39 (38.00-40.00) weeks for women without GDM ($p = 0.002$). The majority of the mothers with GDM had a vaginal delivery (59%) while 41% delivered via caesarean session. The weight to length ratio was the same for both groups. The infants born from mothers with had lower BMI values compared to infants born to mothers without GDM.

Table 5.1 Delivery outcomes of infants born to women with and without GDM

Characteristics	Total participants (n=132)		Infants of mothers with GDM(n=22)		Infants of mothers without GDM (n=110)		p-value
Gestational age at delivery (weeks)		38.00 (38.00 -40.00)		38.00 (37.00 - 39.00)		39.00 (38.00 - 40.00)	**0.002**
Neonatal sex							
Male	72	55%	11	50%	61	55%	0.242
Female	60	45%	11	50%	49	45%	
Mode of delivery							
Vaginal	63	48%	13	59%	50	45%	0.639
Caesarean session	69	52%	9	41%	60	55%	
Infant anthropometry at birth, ≤ 33 days							
Weight (g)	131	3459.78 ± 591.85	22	3396.86 ± 501.66	109	3472.48 ± 609.70	0.587
Length (cm)	131	49.41 ± 3.28	22	49.64 ± 3.17	109	49.37 ± 3.32	0.721
Head circumference (cm)	111	35.38 (34.65 - 36.40)	22	35.15 (34.90 - 35.60)	108	35.48 (34.63 - 36.4)	0.360
BMI (kg/m^2)	131	14.14 ± 1.85	21	13.85 ± 1.62	110	14.20 ± 1.89	0.431
Weight for length (kg/cm)	131	0.98 ± 0.19	21	0.07 ± 0.01	110	0.07 ± 0.01	0.477
Infant body composition at birth, ≤ 33 days							
Fat mass (kg)	101	0.52 (0.34 - 0.67)	16	0.54 (0.38 - 0.66)	85	0.51(0.33 - 0.70)	0.723
Fat free mass (kg)	101	2.82 (2.59 - 3.13)	16	2.79 (2.60 - 2.96)	85	2.82 (2.59 - 3.16)	0.413
Fat mass index (kg/cm^2)	125	3.80 ± 2.14	22	4.47 ± 2.14	103	4.52 ± 2.68	0.940
Fat free mass index (kg/cm^2)	125	12.14 ± 3.67	22	16.21 ± 5.13	103	15.37 ± 3.89	0.388

Significant results are represented in bold ($p < 0.05$). Data are summarised as n (%), median (interquartile ranges) and mean ± standard deviation.

5.1.3 Anthropometry outcomes

The findings show that body weight increased non-significantly from birth until six months in all infants, Table 5.2. The mean BMI of all infants shortly after birth was 16.44 kg/cm^2 and was 17.97 kg/cm^2 at around six months of age. There were no significant differences in any of the anthropometric measures including, weight, length and head circumference in infants exposed to GDM compared to those unexposed to GDM.

Table 5.2 Anthropometric measurements of infants born to women with and without GDM, at birth until six months of age

Infant anthropometry		Total participants (n=131)		Infants of mothers with GDM (n=22)		Infants of mothers without GDM (n=109)	p-value
Infant anthropometry at birth							
Birth weight (g) at ≤ 33 days	131	3459.78 ± 591.85	22	3396.86 ± 501.66	109	3472.48 ± 609.70	0.587
Birth length (cm)	131	49.41 ± 3.28	22	49.64 ± 3.17	109	49.37 ± 3.32	0.721
Birth head circumference (cm)	111	35.38 (34.65 - 36.40)	22	35.15 (34.90 - 35.60)	108	35.48 (34.63 - 36.4)	0.351
Weight (g)							
34 - 54 days	111	4732.40 ± 636.99	21	4551.43± 570.09	90	4774.62 ± 647.26	0.149
35 - 73 days	106	5222.08 ± 697.54	19	5098.16 ± 656.78	87	5249.14 ± 706.85	0.395
74 - 111 days	118	5956.14 ± 744.59	22	5940.68 ± 745.56	96	5959.68 ± 748.23	0.915
112- 138 days	113	6557.41 ± 810.89	18	6349.72 ± 616.84	95	6596.76 ± 839.54	0.238
139 - 164 days	106	7050.85 ± 954.29	19	7000.79 ± 852.01	87	7061.78 ± 979.41	0.802
≥ 165 days	113	7385.36 ± 1180.36	19	7401.58 ± 853.25	94	7382.09 ± 1239.73	0.948
Length (cm)							
34 - 54 days	111	53.66 ± 2.68	21	52.87 ± 1.50	90	53.85 ± 2.86	0.132
35 - 73 days	106	55.04 ± 2.34	19	54.44 ± 2.08	87	55.16 ± 2.39	0.226
74 - 111 days	118	58.25 ± 2.91	22	57.93 ± 1.86	96	58.33 ± 3.11	0.654
112- 138 days	113	60.62 ± 3.53	18	60.14 ± 1.86	95	60.71 ± 3.76	0.518
139 - 164 days	106	63.06 ± 4.20	19	62.36 ± 1.96	87	63.21 ± 4.53	0.425
≥ 165 days	113	64.42 ± 2.82	19	64.04 ± 1.88	94	64.49 ± 2.98	0.511
Body mass index (kg/cm^2)							
34 - 54 days	111	16.44 ± 2.05	21	16.26± 1.64	90	16.48±2.14	0.651
35 - 73 days	106	17.24 ± 2.42	19	17.24 ± 2.42	87	17.24 ± 1.97	0.999
74 - 111 days	118	17.57 ± 1.94	22	17.70 ± 2,01	96	17.54 ± 1.95	0.724
112- 138 days	113	17.89 ± 2.01	18	17.56 ± 1.50	95	17.95 ± 2.10	0.451
139 - 164 days	106	17.77 ± 2.09	19	17.99 ± 1.92	87	17.73 ± 2.12	0.617
≥ 165 days	113	17.97 ± 1.999	19	18.06 ± 2.04	94	17.95 ± 1.99	0.834
Head circumference (cm)							
34 - 54 days	111	38.10 (37.40 - 38.9)	21	38.10 (37.35 - 38.40)	90	38.10 (37.40 - 38.95)	0.557
35 - 73 days	106	39.05 (38.25 - 39.80)	19	39.10 (37.85 - 39.55)	87	39.00 (38.25 - 39.85)	0.705
74 - 111 days	117	40.35 (39.4 - 41.20)	21	40.45 (39.40 - 41.00)	96	40.25 (39.40 - 41.33)	0.683
112- 138 days	113	41.30 (40.45 - 42.15)	18	41.33 (40.45 - 42.15)	95	41.25 (40.45 - 42.25)	0.972
139 - 164 days	106	42.18 (41.40 - 43.20)	19	42.20 (41.35 - 43.15)	87	42.15 (41.40 - 43.25)	0.751
≥ 165 days	112	43.02 (42.08 - 43.98)	19	43.10 (42.3 - 43.70)	93	42.85 (42.05 - 44.10)	0.963

Significant results are represented in bold ($p < 0.05$). Data are summarised as median (interquartile ranges) or mean ± standard deviation

5.1.4 Infants z-scores

The BMI-for-age, weight for age, length for age and head circumference for age z-scores of infants exposed to GDM and those unexposed to GDM are presented in Table 5.3. At birth, the mean zBMI was - 1.29 for the infants exposed to GDM and -1.15 for infants unexposed to GDM, respectively. The zlength ($p = 0.012$) difference between males and females was statistically significant ($p = 0.012$). Between 139 to 164 days postpartum, females had higher mean values of zlength compared to males ($p = 0.015$).

5.1.5 Body composition outcomes

In Table 5.4 results show there were no differences in the increase in percentage body fat from birth until approximately three months in both groups of infants. The median percentage fat free mass decreased from birth until four months in both groups of infants, thereafter it increased until six months. The mean fat mass index decreased by 0.23 kg at six months in infants exposed to GDM compared to an increase from 1.72 kg in infants not exposed to GDM during the first six months of life. There were no statistically significant differences in body composition between infants of women with and those without GDM at birth until six months of age.

Table 5.3 Z-scores of infants according to maternal GDM status and sex, at birth until six months of age

Infant z-scores	GDM status					Neonatal sex				
		Infants of mothers with GDM (n = 22)		Infants of mothers without GDM (n = 110)	P- values		Females (n = 60)		Male (n = 71)	P-values
≤ 33 days										
zBMI	21	-1.29 ± 1.68	110	-1.15 ± 0.79	0.431	60	-1.22 ± 0.81	71	-1.12 ± 0.75	0.454
Zweight	21	-1.50 ± 0.33	110	-1.45± 0.39	0.585	60	-1.41 ± 0.40	71	-1.50 ± 0.36	0.189
Zlength	21	-1.35 ± 0.53	110	-1.37 ± 0.55	0.881	60	-1.23 ± 0.59	71	-1.47 ± 0.59	**0.012**
zhead circumference	21	-1.55 ± 0.44	109	-1.49 ± 0.47	0.594	59	-1.44 ± 0.45	71	-1.55 ± 0.48	0.195
34-54 days										
zBMI	21	-0.28 ± 0.69	90	-0.19 ± 0.89	0.650	53	-0.17 ± 0.95	58	-0.24 ± 0.77	0.633
Zweight	21	-0.75 ± 0.37	90	-0.61 ± 0.42	0.149	53	-0.60 ± 0.40	58	-0.67 ± 0.42	0.342
Zlength	21	-0.79 ± 0.48	90	-0.62 ± 0.48	0.132	53	-0.62 ± 0.48	58	-0.69 ± 0.41	0.394
zhead circumference	21	-0.64 ± 0.31	90	-0.59 ± 0.37	0.610	53	-0.59 ± 0.34	58	-0.61 ± 0.38	0.723
55-73 days										
zBMI	19	0.13 ± 1.01	87	0.17 ± 0.83	0.999	46	0.02 ± 0.84	60	0.21 ± 0.87	0.252
Zweight	19	-0.40 ± 0.42	87	-0.31 ± 0.45	0.395	46	-0.30 ± 0.42	60	-0.34 ± 0.47	0.621
Zlength	19	-0.52 ± 0.34	87	-0.40 ± 0.40	0.226	46	-0.32 ± 0.37	60	-0.51 ± 0.39	**0.012**
zhead circumference	19	-0.31 ± 0.33	87	-0.27 ± 0.43	0.768	46	-0.24 ± 0.35	60	-0.31 ± 0.45	0.370
74 - 111 days										
zBMI	22	0.32 ± 0.84	96	0.25 ± 0.81	0.724	56	0.26 ± 0.79	62	0.27 ± 0.85	0.956
Zweight	22	0.13 ± 0.48	96	0.15 ± 0.48	0.914	56	0.20 ± 0.46	62	0.11 ± 0.49	0.296
Zlength	22	0.01 ± 0.31	96	0.12 ± 0.52	0.564	56	0.17 ± 0.41	62	0.06 ± 0.54	0.196
zhead circumference	21	0.14 ± 0.33	96	0.21 ± 0.59	0.553	56	0.29 ± 0.67	61	0.12 ± 0.41	0.112
112 - 138 days										
zBMI	18	0.26 ± 0.63	95	0.42 ± 0.89	0.451	53	0.52 ± 0.87	60	0.29 ± 0.81	0.165
Zweight	18	0.40 ± 0.40	95	0.56 ± 0.54	0.237	53	0.62 ± 0.55	60	0.46 ± 0.49	0.108
Zlength	18	0.43 ± 0.31	95	0.52 ± 0.63	0.528	53	0.52 ± 0.56	60	0.49 ± 0.62	0.784
zhead circumference	18	0.51 ± 0.36	95	0.54 ± 0.42	0.760	53	0.56 ± 0.39	60	0.51 ± 0.43	0.558
139 - 164 days										
zBMI	19	0.44 ± 0.80	87	0.33 ± 0.89	0.617	54	0.25 ± 0.91	52	0.45 ± 0.83	0.238
Zweight	19	0.82 ± 0.55	87	0.86 ± 0.63	0.802	54	0.91 ± 0.60	52	0.79 ± 0.63	0.295
Zlength	19	0.80 ± 0.33	87	0.94 ± 0.76	0.424	54	1.08 ± 0.86	52	0.75 ± 0.43	**0.015**
zhead circumference	19	0.79 ± 0.40	87	0.88 ± 0.62	0.490	54	0.94 ± 0.69	52	0.80 ± 0.44	0.233
≥ 164 days										
zBMI	19	0.47 ± 0.85	94	0.43 ± 0.83	0.834	54	0.50 ± 0.79	59	0.38 ± 0.89	0.444
Zweight	19	1.08 ± 0.55	94	1.13 ± 0.71	0.755	54	1.19 ± 0.70	59	1.06 ± 0.67	0.312
Zlength	19	1.08 ± 0.31	94	1.15 ± 0.50	0.520	54	1.17 ± 0.47	59	1.12 ± 0.47	0.588
zhead circumference	19	1.06 ± 0.38	93	1.03 ± 0.83	0.854	53	1.11 ± 0.46	59	0.96 ± 0.97	0.294

Significant results are represented in bold ($p < 0.05$). Data are summarised as median (interquartile ranges) and mean ± standard deviation.

Table 5.4 Body composition of infants born to women with and without GDM, at birth until six months of age

Body Composition		All (n=101)		Infants of women with GDM (n=22)		Infants of women without GDM (n=91)	p-value
Birth fat mass %	101	15.20 (11.80 - 18.10)	16	16.75 (12.15 - 18.85)	85	15.10 (11.70 - 17.90)	0.434
Birth fat free mass %	101	84.80 (81.9 - 88.20)	16	83.25 (81.15 - 83.25)	85	84.90 (82.10 - 88.30)	0.435
Birth fat mass (kg)	101	0.52 (0.34 - 0.67)	16	0.54 (0.38 - 0.66)	85	0.51(0.33 - 0.70)	0.724
Birth fat free mass (kg)	101	2.82 (2.59 - 3.13)	16	2.79 (2.60 - 2.96)	85	2.82 (2.59 - 3.16)	0.413
Fat mass %							
34 - 54 days	62	22.70 (20.10 - 25.60)	11	20.70 (17.40 - 26.10)	51	22.90 (20.30 - 25.60)	0.249
35 - 73 days	62	24.75 (21.90 - 27.70)	13	25.00 (21.60 - 27.70)	49	24.70 (23.20 - 27.40)	0.717
74 - 111 days	61	27.50 (24.30 - 30.00)	8	25.40 (24.55 - 27.85)	53	27.50 (24.10 - 30.30)	0.474
112 - 138 days	58	27.10 (23.80 - 29.90)	9	26.80 (25.30 - 28.70)	49	27.10 (23.60 - 30.00)	0.906
138 - 164 days	46	26.10 (22.60 - 29.10)	9	25.20 (23.70 - 28.60)	37	26.50 (22.60 - 29.80)	0.533
≥ 165 days	35	25.30 (22.40 - 28.20)	6	24.80 (23.00 - 28.30)	29	25.40 (22.40 - 28.00)	0.896
Fat free mass %							
34 - 54 days	62	77.30 (74.40 - 79.90)	11	79.30 (73.90 - 82.60)	51	77.10 (74.40 - 79.70)	0.249
35 - 73 days	62	75.25 (72.30 - 78.10)	13	75.00 (72.30 - 78.40)	49	75.30 (72.60 - 76.80)	0.717
74 - 111 days	61	72.50 (70.00 - 75.70)	8	74.60 (72.15 - 75.45)	53	72.50 (69.70 - 75.90)	0.474
112 - 138 days	58	72.90 (70.10 - 76.20)	9	73.20 (71.30 - 74.70)	49	72.90 (70.00 - 76.40)	0.906
138 - 164 days	46	73.90 (70.90 - 77.40)	9	74.80 (71.40 - 76.30)	37	73.50 (70.20 - 77.40)	0.533
≥ 165 days	35	74.70 (71.80 - 77.60)	6	75.20 (71.70 - 77.00)	29	74.60 (72.00 - 77.60)	0.896
Fat mass (kg)							
34 - 54 days	62	1.04 (0.84 - 1.28)	11	0.89 (0.77 - 1.28)	51	1.05 (0.91 - 1.32)	0.185
35 - 73 days	62	1.25 (1.09 - 1.54)	13	1.25 (0.91 - 1.54)	49	1.26 (1.12 - 1.54)	0.383
74 - 111 days	61	1.64 (1.37 - 1.90)	8	1.47 (1.38 - 1.66)	53	1.65 (1.37 - 1.91)	0.276
112 - 138 days	58	1.71 (1.48 - 2.02)	9	1.69 (1.61 - 1.90)	49	1.73 (1.48 - 2.04)	0.675
138 - 164 days	46	1.76 (1.54 - 2.00)	9	1.75 (1.54 - 1.83)	37	1.77 (1.55- 2.05)	0.589
≥ 165 days	35	1.76 (1.46 - 2.08)	6	1.75 (1.64 - 2.08)	29	1.76 (1.46 - 2.07)	0.965
Fat free mass (kg)							
34 - 54 days	62	3.61 (3.27 - 3.84)	11	3.52 (3.21 - 3.67)	51	3.63 (3.27 - 3.88)	0.315
35 - 73 days	62	3.87 (3.51 - 3.34)	13	3.75 (3.44 - 3.90)	49	3.90(3.66 - 4.25)	0.052
74 - 111 days	61	4.25(4.06 - 4.55)	8	4.22 (4.15 - 4.36)	53	4.25(4.06- 4.57)	0.669
112 - 138 days	58	4.75 (4.47 - 4.98)	9	4.62(4.46 - 4.73)	49	4.76 (4.53 - 5.00)	0.233
138 - 164 days	46	5.01 (4.74 - 5.43)	9	5.12 (4.90 - 5.22)	37	5.08 (4.72 - 5.43)	0.879
≥ 165 days	35	5.33 (4.86 - 5.64)	6	5.28 (5.06 - 5.33)	29	5.34 (4.86 - 5.65)	0.569
Fat mass index (kg/cm ^{2})							
34 - 54 days	106	4.66 ± 2.26	21	3.10 ± 1.87	85	4.82 ± 2.33	0.136
35 - 73 days	101	4.07 ± 2.28	19	4.08 ± 1.92	82	4.07 ± 2.37	0.986
74 - 111 days	113	3.71 ± 1.98	22	3.27 ± 1.58	91	3.81 ± 2.06	0.251
112 - 138 days	109	3.28 ± 1.77	18	3.13 ± 1.53	91	3.31 ± 1.82	0.692
138 - 164 days	102	3.21 ± 1.65	19	3.01 ± 1.44	83	3.25 ± 1.70	0.556
≥ 165 days	109	3.08 ± 1.61	19	2.83 ± 1.31	90	3.13 ± 1.66	0.458

Fat free mass index (kg/cm ^{2})							
34 - 54 days	106	14.16 ± 3.28	21	13.49 ± 3.09	85	14.33 ± 3.32	0.297
35 - 73 days	101	12.70 ± 3.13	19	12.70 ± 2.54	82	12.70 ± 3.27	1.000
74 - 111 days	113	11.74 ± 2.82	22	11.01 ± 2.39	91	11.92 ± 2.90	0.174
112 - 138 days	109	10.56 ± 2.61	18	10.12 ± 2.34	91	10.64 ± 2.66	0.442
138 - 164 days	102	10.06 ± 2.44	19	9.67 ± 1.93	83	10.14 ± 2.55	0.450
≥ 165 days	109	9.75 ± 0.23	19	9.31 ± 1.89	90	9.85 ± 2.46	0.371

Significant results are represented in bold ($p < 0.05$). Data are summarised as median (interquartile ranges) or mean ± standard deviation.

5.2 Bivariate associations

Maternal and infant measures associated with birth outcomes, including weight, length, head circumference, fat mass index, fat free mass index, conditional weight and conditional length analysis are presented in Table 5.5.

5.2.1 Weight related associations

In Table 5.5, higher maternal age was positively associated with infant weight. Maternal obesity ($\beta = 399.03$, 95% CI: 90.42, 554.59, $p = 0.012$), previous baby ≤ 4 kg at birth ($\beta = 428.86$, 95% CI: 49.36, 808.36, $p = 0.027$) and gestational age ($\beta = 150.59$, 95% CI: 67.01, 234.17, $p < 0.001$) at delivery were positively associated with an increase in birth weight. Maternal age, BMI, previous pregnancies, marital status, education level, gestational age and neonatal sex were positively associated with the birth weight.

5.2.2 Length related associations

In Table 5.5, gestational age was significantly associated with the length of infants ($\beta = 150.59$, 95% CI: 67.01; 234.17, $p < 0.001$). The length of the baby was non-significantly positively associated with the following confounders: maternal age, BMI, GDM status, HIV status, previous pregnancies, previous birth and baby ≥ 4 kg at birth, marital status, and the highest level of education.

5.2.3 Head circumference related associations

Despite results being statistically non-significant in Table 5.5, the following confounders were positively associated with the infants' head circumference: overweight and obese mothers, previous pregnancies (less than two), previous births (less than two), educational status and gestational age at delivery. In contrast maternal age, GDM status, HIV status, and neonatal sex were negatively associated with the head circumference at birth.

5.2.4 Fat mass index related associations

In Table 5.5, female infants at birth had significantly greater fat mass (β = 0.96, 95% CI: 0.06; 1.87, $p < 0.05$) compared to male infants. For every unit increase in fat mass index, the gestational age decreased by 0.04 weeks (95% CI: 0.64; 0.57). None of the other maternal confounders (maternal age, BMI, marital status and education) were significantly associated with infant fat mass index. There was a negative association between women with GDM and fat mass index.

5.2.5 Fat free mass index related associations

In Table 5.5, the birth outcome results shown that maternal age was positively non-significantly associated with fat free mass index. Women with one or two and three or more previous births were all non-significantly associated with the fat free mass index. The gestational age at delivery was found to be negatively non-significantly associated with the fat free mass index. The other additional unadjusted confounders (maternal age, GDM status, BMI, HIV status, educational status and neonatal sex) were non-significantly positively associated with fat free mass index.

Table 5.5 Bivariate regressions for associations between independent maternal and infant exposure variables and birth outcomes

Variables	Weight (kg) Coef. (95% CI) p-value	Length (cm) Coef. (95% CI) p-value	Head circumference (cm)Coef. (95% CI) p-value	Fat mass index (kg/cm^2) Coef. (95% CI) p-value	Fat free mass index (kg/cm^2) Coef. (95% CI) p-value	Conditional weight (kg) Coef. (95% CI) p-value	Conditional length (cm) Coef. (95% CI) p-value
Maternal age (years)	5.95 (-11.69; 23.60)	0.04 (-0.05; 0.14)	-0.00 (-0.04; 0.04)	0.02 (-0.06; 0.01)	0.01 (-0.12; 0.14)	-0.05 (-0.08; -0.02) *	- 0.01 (- 0.04; 0.02)
Maternal GDM status							
Negative	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Positive	-75.61(-350.05; 198.82)	0.28(01.25; 1.80)	- 0.19 (- 0.82; 0.45)	-0.5 (-1.25; 1.16)	0.84 (-1.08; 2.76)	- 0.24 (- 0.73; 0.24)	- 0.29 (- 0.77; 0.19)
Maternal BMI categories							
Normal weight (kg/m^2)	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Overweight (kg/m^2)	222.38 (-109.83; 554.59)	0.80 (-1.08; 2.69)	0.19 (- 0.58; 0.96)	0.83 (-0.68; 2.33)	1. 33 (-1.06; 3.73)	- 0.07 (- 0.73; 0.58)	0.05 (- 0.59; 0.69)
Obese (kg/m^2)	399.03 (90.42; 707.64) *	0.99 (- 0.76; 2.75)	0.71(- 0.00; 1.42)	0.70 (-0.69; 2.08)	0.83 (-1.38; 3.04)	- 0.30 (- 0.91; 0.32)	0.33 (- 0.28; 0.93)
HIV status							
Negative	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Positive	2.47 (-222.14; 227.08)	0.37 (- 0.87; 1.62)	- 0.16 (- 0.67; 0.36)	0.63 (-0.36; 1.63)	1.37 (-0.20; 2.95)	- 0.55 (- 0.95; -0.15) *	- 0.07 (- 0.47; 0.34)
Marital status							
Single	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Co-habiting/ married	99.54 (-117.22; 316.31)	0.57 (- 0.63; 1.77)	- 0.19 (- 0.69; 0.30)	0.45 (-0.54; 1.43)	-0.25 (-1.82; 1.34)	-0.02 (- 0.42; 0.39)	- 0.01 (- 0.41; 0.38)
Previous pregnancies							
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref
One or two	112.92 (-249.23; 475.07)	0.01 (-1.99; 2.02)	0.02 (- 0.82; 0.85)	-0.88 (-2.477; 0.70)	-1.69 (-4.21; 0.82)	0.19 (- 0.49; 0.87)	- 0.41 (-1.07; 0.26)
Three or more	104.04 (-300.45; 508.53)	0.81 (-1.43; 3.05)	- 0.13 (-1.06; 0.80)	-0.62 (-2.39; 1.15)	-0.85 (-3.66; 1.96)	0.36 (- 0.41; 1.13)	- 0.66 (-1.41; 0.09)
Previous births							
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref
One or two	232.79 (-8.87; 474.46)	0.50 (- 0.85; 1.86)	0.17 (- 0.39; 0.73)	0.61 (-0.48; 1.70)	0.71 (-1.03; 2.45)	- 0.45 (- 0.51; 0.41)	- 0.34 (- 0.78; 0.10)
Three or more	220.02 (-144; 584.05)	1.10 (- 0.94; 3.14)	-0.07 (- 0.92; 0.77)	1.51 (-0.10; 3.12)	2.30 (-0.27; 4.87)	0.23 (- 0.43; 0.90)	- 0.86 (-1.50; -0.22) *
Previous baby ≥ 4kg							
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	428.86 (49.36; 808.36) *	0.39(-1.76; 2.53)	0.17(- 0.72; 1.05)	0.69 (-1.09;2.46)	0.24 (-2.59; 3.08)	0.08 (- 0.59; 0.75)	- 0.09 (- 0.75; 0.57)

Highest level of education							
No schooling/ primary school	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Secondary school	401.67 (-127.97; 931.31)	0.93(-2.05; 3.91)	0.75 (- 0.48; 1.98)	1.10 (-0.34; 4.34)	2.92 (-0.81; 6.65)	0.14 (-1.05; 1.33)	- 0.10 (-1.27; 1.07)
Tertiary education	155.21(-404.05; 714.46)	0.03 (-3.12; 3.18)	0.48 (- 0.82; 1.78)	2.32 (-0.16; 4.80)	3.60 (-0.35; 7.56)	0.30 (- 0.94; 1.54)	0.12 (-1.10; 1.35)
Gestational age at delivery (weeks)	150.59 (67.01; 234.17) *	1.01(0.56; 1.45) **	0.19 (- 0.01; 0.38)	0.29 (-0.09; 0.66)	-0.04 (-0.64; 0.57)	0.03 (- 0.14; 0.20)	0.05 (- 0.12; 0.22)
Neonatal sex							
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	71.74 (-140.64; 284.12)	- 0.20 (-1.37; 0.96)	- 0.11(- 0.59; 0.38)	0.96 (0.06; 1.87) *	0.57 (-0.90; 2.03)	- 0.27 (- 0.67; 0.12)	- 0.27 (- 0.67; 0.12)

Significant p-values at $p < 0.05$ presented as *, (Ref) is the reference category.

5.2.6 Conditional weight related associations

In Table 5.5 higher maternal age was negatively associated with infant conditional weight (β = 0.05, 95% CI: -0.08; -0.02, p = 0.002). There was a significant difference in HIV positive women compared to HIV negative women (β = 0.05, 95% CI: -0.95; -0.15, p = 0.008) in relation to the infant conditional weight. None of the other confounders (maternal GDM status and BMI, marital status, previous births, history of macrosomic babies, educational status, and neonatal sex) were significantly associated with the infant conditional weight.

5.2.7 Conditional length related associations

In Table 5.5, having three or more previous births was negatively associated with the infant conditional length (β = 0.34, 95% CI: -0.78; 0.10, p < 0.05). In addition, infant conditional length was negatively non-significantly associated with the following confounders: maternal age, GDM status, HIV status, previous pregnancies, previous baby ≥ 4 kg, secondary school education and neonatal sex.

5.3 Multiple linear regressions

Multiple linear regression analysis was performed and adjusted for maternal and infant variables. Variables of interest were as follows: birth weight, length, head circumference, fat mass index, fat free mass index, conditional weight, and conditional length.

5.3.1 Birth weight models and associations

A summary of all the Models related to birth weight is presented in Table 5.6. In Model 1, results show that a unit increase in gestational age (β = 150.06, 95% CI: 66.25; 233.87, p = 0.001) was positively significantly associated with birth weight. Results from Model 2, show an increase in maternal gestational age at delivery was significantly associated with an increase at birth weight (β = 142.50, 95% CI: 59.01; 225.98, p = 0.001). Infants born to obese women were likely to have significantly higher weight at birth (β = 375.69, 95% CI: 62.10; 689.27, p = 0.019) compared to mothers with a normal BMI.

After adjusting for neonatal sex, gestational age, maternal BMI, marital status and highest level of education in Model 3, the birth weight was significantly associated with maternal obesity (β = 371.51, 95% CI: 65.09, 677.93, p = 0.018) and gestational age (β = 161.79, 95% CI: 78.43, 245.15, p < 0.001) and women with secondary school education level (β = 633.94, 95% CI: -

187.03, 908.93, p = 0.016). Model 4 results show that maternal obesity (β = 358.57, 95% CI: 48.61; 668.53, p = 0.024) was significantly associated with birth weight compared to women with a normal BMI. Maternal education at secondary school level (β = 617.60, 95% CI: 99.24; 1135.97, p = 0.020) was significantly associated with infant birth weight.

5.3.2 Length models and associations

A summary of all models related to birth length is presented in Table 5.7. Model 1, results shows that gestational age (β =1.01, 95% CI: 0.56; 1.45, p < 0.001) was significantly associated with birth length and the neonatal sex did not have any effect on birth length.

In Model 2 gestational age, (β = 0.99, 95% CI: 0.53; 1.44, p = 0.001) was positively associated with birth length while these confounders (neonatal sex, maternal age and BMI) were non-significantly associated with birth length. In Model 3, infants born to obese women (β = 371.51, 95% CI: 69.05; 677.93, p = 0.018) who had secondary school education (β = 633.94, 95% CI: 119.07; 1148.82, p = 0.016) were more likely to have significantly greater head circumferences, compared to infants of women with a normal BMI, with no schooling or only primary school education respectively. In Model 4, length at birth was non-significantly associated with the following confounders: neonatal sex, gestational age, maternal BMI, marital status, highest level of education and previous baby ≥ 4 kg, previous births.

Table 5.6 Multiple linear regression models for associations between maternal and infant exposure variables and infant weight at birth

	Birth weight (kg)											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	64.60	-138.50; 267.71	0.530	69.39	-136.19; 274.96	0.505	14.86	-191.93; 221.65	0.887	-1.86	-210.20; 206.48	0.986
Gestational age at birth, weeks	150.06	66.25; 233.87	**0.001**	142.50	59.01; 225.98	**0.001**	161.79	78.43; 245.15	**<0.001**	159.82	75.36; 244.27	**<0.001**
Maternal age (years)				-4.22	-22.64; 14.19	0.651	-4.67	-22.66; 13.33	0.608	-5.68	-25.01; 13.65	0562
BMI at OGTT categories												
Normal (kg/m^2)				Ref			Ref			Ref		
Overweight (kg/m^2)				210.99	-119.58; 541.58	0.209	173.26	-155.86; 502.38	0.299	169.45	-162.75; 501.65	0.314
Obese (kg/m^2)				375.69	62.10; 689.27	**0.019**	371.51	65.09; 677.93	**0.018**	358.57	48.61; 668.53	**0.024**
Marital status												
Single							Ref			Ref		
Co-habiting/ married							40.81	-175.46; 257.08	0.299	32.87	-185.96; 251.71	0.767
Highest level of education												
No schooling/ primary school							Ref			Ref		
Secondary school							633.94	119.07; 1148.82	**0.016**	617.60	99.24; 1135.97	**0.020**
Tertiary education							360.95	-187.03; 908.93	0.195	360.89	-190.01; 911.79	0.197
Previous births												
None										Ref		
One or two										15.97	-255.62; 287.56	0.907
Three or more										142.41	-246.29; 531.11	0.469
Previous baby ≥4 kg												
No										Ref		
Yes										276.17	-113.71; 666.04	0.163
R-squared per model		0.097			0.142			0.208			0.227	

Model 1 examined the association of neonatal sex and gestational age to infant birth weight.
Model 2,3 and4 examines the stepwise addition of confounders (maternal BMI, marital status, highest level of education, previous births and previous baby ≥ 4kg) to Model 1.Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

Table 5.7 Multiple linear regression models for associations between maternal and infant exposure variables and infant length at birth

	Birth length (cm)											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	- 0.25	-1.33; 0.84	0.651	- 0.28	-1.40; 0.84	0.617	14.86	-191.93; 221.65	0.887	- 0.61	-1.76; 0.55	0.301
Gestational age at birth, weeks	1.01	0.56; 1.45	**<0.001**	0.99	0.53; 1.44	**<0.001**	161.79	78.43; 245.15	**<0.001**	1.08	0.62; 1.55	**<0.001**
Maternal age (years)				0.01	- 0.09; 0.11	0.876	- 4.67	-22.66; 13.32	0.608	- 0.00	- 0.11; 0.11	0.922
BMI at OGTT categories												
Normal (kg/m^2)				Ref			Ref			Ref		
Overweight (kg/m^2)				0.58	-1.22; 2.38	0.525	173.26	-155.86; 502.38	0.299	0.28	-1.57; 2.12	0.768
Obese (kg/m^2)				0.84	-0.87; 2.55	0.335	371.51	65.09; 677.93	**0.018**	0.85	-0.87; 2.57	0.331
Marital status												
Single							Ref			Ref		
Co-habiting/ married							40.81	-175.46; 257.08	0.709	0.40	- 0.82; 1.61	0.517
Highest level of education												
No schooling/ primary school							Ref			Ref		
Secondary school							633.94	119.07; 1148.82	**0.016**	2.65	- 0.22; 5.83	0.070
Tertiary education							360.95	-187.03; 908.93	0.195	1.20	-1.86; 4.25	0.439
Previous births												
None										Ref		
One or two										- 0.31	-1.82; 1.20	0.863
Three or more										0.87	-1.29; 3.02	0.428
Previous baby ≥4 kg												
No										Ref		
Yes										0.29	-1.88; 2.45	0.794
R-squared per model	0.141			0.149			0.208			0.207		

Model 1 examined the association of neonatal sex and gestational age to infant birth length.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal BMI, marital status, highest level of education, previous births and previous baby ≥ 4kg) to Model 1.Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

5.3.3 Head circumference models and associations

A summary of the multiple linear regression results for head circumference with multiple variables is presented in Table 5.8. In Model 1 after adjusting for neonatal sex and gestational age, there were no statistically significantly associations. In Models 2, infants born to obese women (β = 0.75, 95% CI: 0.02; 1.49, p = 0.045) were more likely to have significantly greater head circumferences, compared to infants of mothers with a normal BMI.

In Model 3 the main predictor of an infant's head circumference was the gestational age (p = 0.048) and being born to an obese mother (p = 0.045). The other confounders (neonatal sex, maternal age and highest level of education) were not statistically significantly associated with the infant's head circumference at birth. Model 4 show maternal obesity (β = 0.75, 95% CI: 0.01; 1.49, p = 0.047) had a positive significant effect on the infant's head circumference, compared to mothers with a normal BMI.

5.3.4 Fat mass index models and associations

Table 5.9 represents a summary of the linear regression models related to fat mass index. The results of Model 1 show that a unit increase in fat mass index was associated with a 0.95 week longer gestational age (95% CI: 0.05; 1.85, p = 0.039). In Model 2 there was no statistical significance in the associations of fat mass index with the other variables (neonatal sex, gestational age, and maternal BMI).

Model 3 show that an increase in infant fat mass index was significantly associated with a higher maternal education level, secondary and tertiary schooling (β = 2.37, 95% CI: 0.02; 4.72, p = 0.048 and β = 3.12, 95% CI: 0.62; 5.61, p = 0.015 respectively) compared to no schooling or primary school education .The results of Model 4 show that secondary school (β = 2.40, 95% CI: 0.02; 4.77, p = 0.048) and tertiary education (β = 3.20, 95% CI: 0.68; 5.72, p = 0.013) were significantly associated with the fat mass index. There was no significant difference in the other confounders (neonatal sex, maternal BMI, HIV status, marital status, previous births and previous baby ≥ 4 kg) in this Model.

Table 5.8 Multiple linear regression models for associations between maternal and infant exposure variables and infant head circumference at birth

	Birth head circumference (cm)											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male		Ref		Ref			Ref			Ref		
Female	-0.11	- 0.59; 0.37	0.641	- 0.08	- 0.57; 0.41	0.744	-0.15	- 0.64; 0.34	0.540	- 0.15	- 0.65; 0.34	0.539
Gestational age at birth, weeks	0.19	- 0.01; 0.38	0.063	0.17	- 0.03; 0.36	0.095	0.20	0.00; 0.40	**0.048**	0.20	- 0.00; 0.40	0.050
Maternal age (years)				-0.02	- 0.06; 0.03	0.429	-0.02	- 0.06; 0.03	0.421	- 0.02	- 0.06; 0.03	0.429
BMI at OGTT categories												
Normal (kg/m^2)				Ref			Ref			Ref		
Overweight (kg/m^2)				0.16	- 0.62; 0.94	0.679	0.13	- 0.66; 0.91	0.752	0.13	- 0.67; 0.92	0.751
Obese (kg/m^2)				0.75	0.01; 1.49	**0.048**	0.75	0.02; 1.49	**0.045**	0.75	0.01; 1.49	**0.047**
Highest level of education												
No schooling/ primary school							Ref			Ref		
Secondary school							1.05	- 0.19; 2.28	0.725	1.04	- 0.20; 2.19	0.100
Tertiary education							0.67	- 0.64; 1.99	0.312	0.67	- 0.65; 1.99	0.315
Previous births												
No										Ref		
Yes										0.04	- 0.89; 0.97	0.930
R-squared per model		0.030			0.080			0.111			0.110	

Model 1 examined the association of neonatal sex and gestational age to infant birth head circumference.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal BMI, highest level of education and previous births) to Model 1.
Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

Table 5.9 Multiple linear regression models for associations between maternal and infant exposure variables and infant fat mass at birth

	Birth fat mass index (kg/cm^2)											
	Model 1			**Model 2**			**Model 3**			**Model 4**		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	0.95	0.05; 1.85	**0.039**	0.87	- 0.38; 1.78	0.060	0.87	- 0.06; 1.80	0.067	0.78	- 0.16; 1.73	0.103
Gestational age at birth, weeks	0.28	- 0.09; 0.65	0.139	0.29	- 0.09; 0.66	0.134	0.37	- 0.01; 0.75	0.057	0.36	- 0.02; 0.75	0.065
BMI at OGTT categories												
Normal (kg/m^2)				Ref			Ref			Ref		
Overweight (kg/m^2)				0.81	- 0.67; 2.29	0.281	1.13	- 0.36; 1.62	0.136	1.01	- 0.52; 2.53	0.193
Obese (kg/m^2)				0.56	- 0.80; 1.93	0.417	0.70	- 0.66; 2.01	0.311	0.60	- 0.79; 1.99	0.393
Maternal HIV status				0.56	- 0.43; 1.55	0.268	0.63	- 0.36; 1.62	0.211			
Negative										Ref		
Positive										0.56	- 0.45; 1.57	0.275
Marital status												
Single							Ref			Ref		
Co-habiting/ married							0.18	- 0.81; 1.16	0.725	0.09	- 0.92; 1.09	0.866
Highest level of education												
No schooling/ primary school							Ref			Ref		
Secondary school							2.37	0.02; 4.72	**0.048**	2.40	0.02; 4.77	**0.048**
Tertiary education							3.12	0.62; 5.61	**0.015**	3.20	0.68; 5.72	**0.013**
Previous births												
None										Ref		
One or two										0.25	- 0.97; 1.46	0.689
Three or more										1.09	- 0.59; 2.77	0.201
Previous baby ≥4 kg												
No										Ref		
Yes										0.38	-1.39; 2.15	0.670
R-squared per model					0.070			0.119			0.134	

Model 1 examined the association of neonatal sex and gestational age to infant birth fat mass.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal BMI, HIV status, marital status, highest level of education, previous births and previous baby ≥ 4kg) to Model 1. Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

5.3.5 Fat free mass index models and associations

All Models related to infant fat free mass index are summarised in Table 5.10. Model 1 show that neonatal sex and gestational age were not predictors of fat free mass index. Model 2 show a negative association between neonatal sex, gestational age, maternal BMI and maternal HIV status after adjusting for the infant fat free mass index however none of these associations were significant.

Results from Model 3 show that infants born to women with tertiary education ($\beta = 4.24$, 95% CI: 0.18; 8.30, $p = 0.041$) had statistically significantly greater fat free mass index compared to infants born to women with no schooling or primary school education. Model 4 show tertiary education to be a significant determinant of fat free mass index ($\beta = 4.45$, 95% CI: 0.36; 8.55, $p = 0.033$). Model 4 show a negative association with fat free mass index and maternal confounders, but all the findings were non-significant, even after additional adjusting for neonatal sex, gestational age, HIV status, highest level of education, maternal BMI, previous births and previous baby ≥ 4 kg.

5.3.6 Conditional weight models and associations

All the Models associated with conditional weight are summarised in Table 5.11. Model 1 show that neonatal sex was a determinate of conditional weight. Furthermore Model 2 show that neonatal sex and maternal GDM status were significantly associated with conditional weight from birth until 54 days during early infant growth. After adjusting for neonatal sex, gestational age and maternal GDM status, results show that obese women had infants with significantly greater conditional weights compared to women with a normal BMI.

5.3.7 Conditional length models and associations

Table 5.12 represents a summary of linear regression results related to conditional length, Model 1 show significant findings of neonatal sex and the conditional weight. After controlling for neonatal sex, gestational age and maternal educational level in Model 4, the conditional weight was significantly associated with neonatal sex, maternal GDM status and maternal obesity.

Table 5.10 Multiple linear regression models for associations between maternal and infant exposure variables and infant fat free mass at birth

	Birth fat free mass index (kg/cm^2)											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	0.57	- 0.90; 2.04	0.444	0.39	-1.08; 0.87	0.601	0.48	-1.00; 1.95	0.525	0.29	-1.21; 1.80	0.700
Gestational age at birth, weeks	- 0.04	- 0.65; 0.56	0.892	- 0.02	- 0.63; 0.59	0.952	0.09	- 0.52; 0.71	0.767	0.08	- 0.54; 0.70	0.808
BMI at OGTT categories												
Normal (kg/m^2)				Ref			Ref			Ref		
Overweight (kg/m^2)				1.38	-1.02; 3.77	0.258	1.90	-0.53; 4.33	0.124	1.61	- 0.86; 4.09	0.199
Obese (kg/m^2)				0.76	-1.46; 2.97	0.500	0.98	-1.22; 317	0.381	0.77	-1.48; 3.02	0.500
Maternal HIV status												
Negative				Ref			Ref			Ref		
Positive				1.37	- 0.23; 2.98	0.093	1.50	- 0.11; 3.10	0.068	1.38	-0.26; 3.01	0.098
Highest level of education												
No schooling/ primary school							Ref			Ref		
Secondary school							2.91	- 0.91; 6.73	0.134	3.01	- 0.84; 6.86	0.124
Tertiary education							4.24	0.18; 8.30	**0.041**	4.45	0.36; 8.55	**0.033**
Previous births												
None										Ref		
One or two										0.64	-1.31; 2.59	0.519
Three or more										2.06	- 0.64; 4.75	0.134
Previous baby ≥4 kg												
No										Ref		
Yes										0.00	-2.88; 2.88	1.000
R-squared per model		0.005			0.037			0.075			0.094	

Model 1 examined the association of neonatal sex and gestational age to infant birth fat free mass.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal BMI, HIV status, highest level of education, previous births and previous baby ≥ 4kg) to Model 1.
Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

Table 5.11 Multiple linear regression models for associations between maternal and infant exposure variables and infant conditional weight

	Conditional weight											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	- 0.27	-0.43; -0.12	**<0.001**	- 0.28	-0.44; - 0.13	**<0.001**	-0.30	-0.44; -0.15	**<0.001**	-0.27	-0.43; -0.12	**0.001**
Gestational age at birth, weeks	0.04	-0.02; 0.10	0.224	0.01	-0.05; 0.08	0.683	0.03	-0.04; 0.10	0.400	0.02	-0.04; 0.09	0.485
GDM status												
Negative				Ref			Ref			Ref		
Positive				-0.27	-0.47; -0.07	**0.008**	-0.25	-0.46; 0.10	**0.014**	-0.29	-0.49; -0.08	**0.006**
BMI at OGTT categories												
Normal (kg/m^2)							Ref			Ref		
Overweight (kg/m^2)							0.02	-0.23; 0.28	0.863	0.08	-0.18; 0.34	0.557
Obese (kg/m^2)							-0.27	-0.50; -0.03	**0.027**	-0.24	-0.48; -0.01	0.045
Highest level of education												
No schooling/ primary school										Ref		
Secondary school										0.20	-0.30; 0.70	0.430
Tertiary education										0.39	-0.13; 0.91	0.145
R-squared per model	0.020			0.030			0.049			0.056		

Model 1 examined the association of neonatal sex and gestational age to infant conditional weight between birth and 54 days.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal GDM status, BMI, and highest level of education) to Model 1.
Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

Table 5.12 Multiple linear regression models for associations between maternal and infant exposure variables and infant conditional length

	Conditional length											
	Model 1			Model 2			Model 3			Model 4		
Exposure variables	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Neonatal sex												
Male	Ref			Ref			Ref			Ref		
Female	- 0.47	-0.62; -0.32	**<0.001**	- 0.48	-0.63;- 0.34	**<0.001**	-0.47	-0.62; -0.33	**<0.001**	-0.46	-0.61; -0.32	**<0.001**
Gestational age at birth, weeks	0.06	-0.00; 0.12	0.052	0.04	-0.03; 0.01	0.261	0.02	-0.04; 0.85	0.502	0.02	-0.04; 0.08	0.531
GDM status												
Negative				Ref			Ref			Ref		
Positive				-0.25	-0.44; -0.06	**0.009**	-0.27	-0.46; -0.08	**0.005**	-0.28	-0.48; -0.09	**0.004**
BMI at OGTT categories												
Normal (kg/m^2)							Ref			Ref		
Overweight (kg/m^2)							0.02	-0.22; 0.26	0.871	0.04	-0.21; 0.28	0.753
Obese (kg/m^2)							0.28	0.05; 0.50	**0.015**	-0.29	0.06; 0.51	**0.012**
Highest level of education												
No schooling/ primary school										Ref		
Secondary school										0.10	-0.38; 0.57	0.684
Tertiary education										0.16	-0.33; 0.65	0.525
R-squared per model	0.061			0.070			0.088			0.089		

Model 1 examined the association of neonatal sex and gestational age to infant conditional length between birth and 54 days.
Model 2, 3 and 4 examines the stepwise addition of confounders (maternal GDM status, BMI and highest level of education) to Model 1.
Significant results are presented in bold, $p < 0.05$. (Ref) is the reference category.

5.4 Conditional weight and length associations with maternal GDM status

Table 5.13 show that infant weight gain during one, three, four and six months of age was significantly associated with maternal GDM status. Infants born to women with GDM grew significantly taller in the second and the fifth month of life compared to infants born to women without GDM.

Table 5.13 Associations related to conditional weight and length gain during the first six months of life.

Infants conditionals	**GDM status**		
	B	**95% CI**	**P-value**
Conditional weight 0 - 54 days	-0.27	-0.46; -0.08	**0.005**
Conditional weight 54 - 73 days	-0.02	-0.22; 0.19	0.862
Conditional weight 73 - 111 days	0.58	0.38; 0.79	**<0.001**
Conditional weight 111 - 138 days	-0.26	-0.48; -0.03	**0.026**
Conditional weight 138 - 164 days	0.01	-0.14; 0.32	0.450
Conditional weight 164 - ≥ 165 days	-0.46	-0.69; -0.23	**<0.001**
Conditional length 0 - 54 days	-0.27	-0.45; -0.09	**0.004**
Conditional length 54 -73 days	-0.35	-0.56; -0.15	**0.001**
Conditional length 73 -111 days	0.03	-0.18; 0.24	0.788
Conditional length 111 - 138 days	0.14	-0.09; 0.37	0.223
Conditional length 138 - 164 days	-0.22	-0.44; -0.00	**0.049**
Conditional length 164 - ≥165 days	0.10	-0.13; 0.34	0.383

Significant results are presented in bold, $p < 0.05$, Reference group is the women who were not exposed to GDM during pregnancy.

CHAPTER SIX: Discussion and Conclusion

Introduction

This chapter provides an overview and discussion of the key findings of the study in relation to the objectives. The study's strengths and limitations and future recommendations are also included.

6. 1 Summary of findings

A summary of the research findings is shown in Table 6.1. There are two main themes that emerge from these findings: (1) the uptake of universal screening and the effectiveness of selective screening for GDM; and (2) the growth and body composition parameters together with the related associations.

Table 6.1 Summary of the research findings

Study objective	Key findings
1. To determine the uptake of universal screening and the effectiveness of selective screening for GDM	• The uptake of universal screening for GDM of pregnant women was 57%. • Reported barriers to GDM screening were as follows: not interested in being tested, difficulty in getting time off from work and school, relocating to another province, previously tested at CHBAH and kept rescheduling but failed to attend. • Selective screening for GDM applied at CHBAH may have missed 51% of women who then tested positive for GDM in this study.
2. To compare anthropometric parameters (weight, length and head circumference) and body composition (fat mass and fat free mass) at birth until six months of life between infants born to mothers with, and those without, GDM	• The longitudinal case control study included 22 infants born to mothers with GDM and 110 infants born to mothers without GDM. • The median (interquartile ranges) gestational age was 38 (37.00 - 39.00) weeks for women with GDM and 39 (38.00-40.00) weeks for women without GDM ($p = 0.002$). • There was no significant difference in weight, length and head circumference from birth until six months of age between infants born to mothers with GDM and those born to mothers without GDM. • Infants born to mothers with GDM had no significant differences in body composition (fat mass and fat free mass) in the first six months of life compared to infants born to mothers without GDM. • None of the infants exposed and unexposed to GDM were overweight or obese at any point according to the zBMI in the first six months of life. • Infants exposed to GDM had significantly higher conditional weight gain at one ($p = 0.005$), three ($p < 0.001$), four ($p = 0.026$) and six months ($p < 0.001$) of age compared to unexposed infants. • The conditional length gain was significantly higher at birth ($p = 0.004$), two ($p = 0.001$) and five months ($p = 0.049$) in infants exposed to GDM compared to those unexposed.
3. To determine the association between maternal obstetric history (number of previous pregnancies and previous births), maternal demographics (marital status, total number of years of formal education), HIV status, and BMI and infant birth outcomes (birth weight, length, head circumference, fat mass and fat free mass	• Infant birth weight was significantly associated with gestational age ($p < 0.001$), maternal obesity ($p = 0.024$) and maternal education ($p = 0.020$). Higher infant birth weight was associated with more advanced gestational age, increased maternal obesity and higher maternal educational level. • Gestational age ($p < 0.001$) was a determinant of birth length. • Gestational age ($p = 0.048$) and obese women ($p = 0.045$) were predictors of the infants head circumference. Infants born to mothers who were obese were more likely to have a bigger head circumference compared to infants born to mothers with a normal BMI.

	• Neonatal sex (p = 0.039), secondary schooling (p = 0.048) and tertiary education (p = 0.015) were significantly associated with the fat mass index. Female babies born to mothers who were more educated had significantly more fat mass compared to male babies born to mothers with a primary education level or no schooling. • Tertiary education (p = 0.033) was a predictor of the fat free mass index. The more educated the mother was the more likely that the baby had greater fat free mass.

6.2 The uptake of universal screening and the effectiveness of selective screening for GDM

6.2.1 The identification approach and uptake of screening for GDM

In my study, even though an infographic pamphlet on GDM was given to all women at recruitment only, 57% of the women took up the offer and underwent universal screening for GDM. For all the women, the initial visit to the ANC clinic occurred before 20 weeks of gestation. My study shows that the understanding of the benefits of screening for GDM was poor amongst the group of pregnant women in CHBAH. In this study, screening was offered at no cost and travelling expenses were covered. Different from my study, cost has previously been reported to be a potential hindrance to access of healthcare services (141). It is possible that the women in my study did not prioritise their health as other social demands may have influenced their decision making and prioritised others health above their own wellbeing.

Obstetricians in an attempt to limit foetal size in women with GDM, often induce delivery or perform an elective caesarean section at 37 and 38 weeks of gestation (142). In the current study the infants born to mothers with GDM were delivered at 38 weeks compared to 39 weeks of infants born to mothers without GDM. The obstetrician intervention of inducing mothers with GDM may be the reason for the normal birth weight. The caesarean section rate in my study was the same in mother with and those without GDM. Which was different to what others found, the authors reported 86% of the women with GDM had a caesarean section (3). The main reason for the caesarean section in women with GDM is attributed the women giving birth to macrosomic baby (3, 101, 116) but these finding were not seen in my study.

Ina publication in 2018, Macaulay et al., reported that 56.9% of the women were treated using diet therapy alone and 48% required medication (46). My study proposed that GDM treatment was effective since there were no macrosomic babies at delivery, and there were no differences in anthropometric parameters of babies born to mothers exposed and not exposed to GDM. The ultimate outcome for GDM treatment is to prevent complications at delivery and promote healthy maternal and foetal care (66). The first approach to managing GDM is using lifestyle interventions (for example dietary changes and physical activity) (65). If glucose levels are not controlled after making dietary or physical changes, pharmacological treatment is implemented by prescribing either insulin or metformin (67, 68). The key aim of the treatment of GDM is to attain good glycaemic control and avoid excessive foetal growth to get normal birth weight at delivery (73, 74).

6.2.2 Barriers to the uptake of universal screening for GDM

It is of concern that 43% of women did not take up the offer to be tested for GDM. Dissemination of information about the importance of screening for GDM testing was possibly insufficient in my study. The uptake of GDM testing is reliant on pregnant women understanding the medical condition, diagnostic criteria and the test (38). A study about native African women with GDM but residing in Sweden reported that the lack of knowledge about GDM might be related to socio-demographic influences such as educational background, traditional beliefs, attitudes towards diabetes or they previously had experience with a diabetic relative (65). In my study among the women screened 25% reported on family history of diabetes that is they were living with or caring for a diabetic family member. Other societal barriers that women in the study encountered were difficulty in getting time off work and relocation to another province for family support. Approximately 70% of the women in the study were single a representation of the demographics of women living in Soweto (46). They may also have been breadwinners in their households making it essential for them to not miss work at all. The assumption of the study is that participants answered truthfully.

Although in my study we offered a stipend for transport, this may have not been an adequate incentive for women to come for the test. A previous study mentioned societal barriers related to GDM screening in eight LMICs. The authors found that the expectations of women in society (for example childbearing, childcaring and household duties) resulted in them neglecting their own health. Women are often too busy or do not have the time to travel long distances to get to the ANC (75). A systematic review reported that women complained about the travelling distance to various GDM testing centres, the use of public transport which was unfavourable, the overnight fasting period and the two hours it takes to undergo the OGTT is a challenge for women and is therefore a reason why they decline to be tested (2). Some women in general suffer from nausea.

6.2.3 Effectiveness of selective screening for GDM

My study shows that 51% of women with GDM would have been overlooked based on the identification of risk factors alone. Different from my study results, Cosson *et al*., (143)

reported about 34.7% of GDM women were missed by selective screening for GDM which could have resulted in pregnancy complications had they not being diagnosed and untreated. Selective screening is based on the presence of risk factors, meaning a portion of women who develop GDM will experience complication including an oversize foetus which may lead to a macrosomic baby or still birth and possibly a caesarean section at delivery.

In addition, selective screening will not be a true representation of the GDM cases in a population. It is known that the high costs of GDM testing limits many health facilities from diagnosing GDM (144). In South Africa pregnant women are referred from district hospitals and local clinics to a central hospital where screening for GDM is performed and may be the hospital has insufficient capacity to screen a great number of pregnant women with GDM. The cost of universal screening is expensive, but one needs to think about the benefits.

6.3 Infant growth and body composition parameters together with related associations

6.3.1 Birth weight

The anthropometric birth outcomes which included weight, length and head circumference were similar between infants born to mothers with and without GDM. These findings are similar with those of other studies (93, 102, 103) that reported similar birth weight amongst infants of mothers with and those without GDM. This may be attributed to the mothers having good glycaemic control which leads to normal foetal growth and a normal weight baby (1). Also, maternal glucose levels during pregnancy may have been mildly elevated in the women with GDM and therefore did not significantly influence the infants' birth weight. Shang *et al*.,(64), however, found that women with mildly increased glucose levels can still give birth to big babies therefore glucose levels need to be closely checked during pregnancy. Other studies (100, 116) have found that infants born to mothers with GDM had higher birth weight compared to infants born to mothers without GDM which may be a consequence of uncontrollable maternal glucose levels leads to macrosomia (92) but this did not occur in my study. In my study I found that there was a significant time difference between when the mothers with GDM and those without GDM underwent the OGTT. The mothers without GDM were tested significantly earlier in pregnancy therefore GDM may have still developed and affected the birth weight.

6.3.2 Infant weight gain

Interestingly in my study I showed significant increased conditional weight gain at one, three and four months amongst infants born to women with GDM compared to infants born to women without GDM. This is different to what the Cambridge Baby Growth Study (93) who reported an increase in weight gain from birth until three month of age which was followed by a deceleration weight gain from three months until 12 months in infants born to mothers with GDM compared to infants born to mothers without GDM. Dode *et al*., (77) found a deceleration in growth for the first three months of life in infants born to mothers with GDM. Furthermore a slower weight gain was reported by Parker *et al*., (105) from birth until six months using weight-for-length z-scores amongst infants born to mothers with GDM. The difference in these studies may be attributed to the *in utero* genetic modification of pancreatic cells in response to maternal hyperglycaemia may influence later growth in infants exposed to GDM (1).

6.3.3 Infant body composition

The ADP was used to report on the body composition of infants in the first six months of life. Different from my results other studies (99, 101, 115, 116) that reported high body fat of infants exposed to GDM compared to unexposed infants. Catalono *et al*., (116) suggested the findings of high body fat in infants of mothers with GDM may be due to the mother had one or more previous pregnancies. The results in my study may be due to good control of maternal glucose that has been shown to yield the same adiposity in infants exposed and unexposed to GDM.

6.3.4 Association related to infant's anthropometry and body composition

6.3.4.1 Maternal obesity

With the consideration that 42% of city dwelling women are obese in South African (145), it is not a surprise that 47% of mothers were obese in the study. The large numbers of obese women may be related to the availability and intake of foods that are high in sugar, salt, and saturated fats together with a slight physical activity, which is related with pregnancy (124-126). Mothers who were obese were likely to give birth to bigger babies (weight) compared to mothers with a normal BMI. These finding were supported by Prentice *et al*., (93) which found that infants born to obese mothers tended to be larger babies but it contradicts those of Uebel *et al*., (106) who reported similar birth weights amongst in infants born to obese and non-obese mothers. This findings may be due to obese mothers are more likely to have high glucose levels, which cross the placenta to the growing foetus and lead to higher infant birth weight (94).

Maternal obesity, just like GDM, is a determinant of birth weight which results in adverse health consequences for the infant and the mother (91, 104, 123, 146).

In my study babies born to obese mothers were taller at birth compared to babies born to mothers with a normal BMI. Infant birth length has been suggested to be an indicator of maternal nutritional status during pregnancy and also genetic factors like the modification of pancreatic cells in response to maternal high glucose (147).

It has been previously reported that the head circumference is a cursor of the brain growth (148) and in my study to some extent maternal obesity was associated with the head circumference at birth. Different to my study, other studies found that maternal pelvic bone (149), maternal height (150) and around 50% of genetic factors determines the size of the neonatal head circumference at birth (151).

6.3.4.2 Gestational age

In my study gestational age was a predictor of infant adiposity. Similarly to my study results, Durnwald *et al*., (101) observed an association between maternal gestational age and infant body fat and body fat % measured using total body electrical conductivity estimates of body composition. This association may be attributed to fat deposition during foetal growth. In contrast Catalano *et al.,* (104) who used the total body electrical conductivity and Au *et al*., (102) who used the ADP reported that gestational age was not associated with infant body composition (fat mass and body fat percentage) between mothers with GDM and mothers with controlled glucose levels.The different methodology may account for the different findings. Aris *et al*., (110) interestingly used skinfold thickness equations to estimate the body composition and found gestational age to be a determinant of fat mass in the GUSTO birth cohort in Singapore. The use of the skinfold thickness equation showed results equivalent to those obtained using the ADP in the current study.

6.3.4.3 Maternal education

The effect of maternal education on birth outcomes was significant in this study. Obese mothers with a secondary schooling education level were more likely to give birth to taller babies, compared to mothers with a normal BMI with no schooling or primary school education. In the study a higher maternal education was associated with greater likelihood of the offspring

having higher fat free mass index. Although the pathway is not completely understood the association maybe attributed to maternal education being a representation of higher socio-economic status therefore access to food or the benefit of being educated and having greater awareness of infant care and access to health services (152).

6.4 Study strengths and limitations

The first strength of the study was the prospective study design used to collect the data, from as early as before 20 weeks of pregnancy. The data collection included maternal demographics and medical history which allowed for the adjustment of potential confounders. The second strength was the longitudinal follow-up of GDM exposed versus unexposed infants' study, from birth until six months of age. To my knowledge, this has not previously been conducted in South Africa. Lastly, infant body composition was determined using ADP which is currently the ideal method to determine fat mass and fat free mass (135).

There are some limitations to this study. Firstly, self-selection bias occurred owing to the missing data and loss to follow-up of the women who were GDM positive. By the time the infancy follow-up study had started, some of the GDM positive women had already delivered their babies well before and could not be included in the infancy project. Secondly, although sample size was determined prior to undertaking the study, therefore the results of this study should be further validated using a larger sample. Thirdly, infant abdominal circumference was not measured, and this may have yielded significant findings in anthropometric measurements in infants exposed and unexposed to GDM. Fourthly, infant feeding practices for the interpretation of infant weight gain. Lastly assessment of infant growth was done from birth until six months of age only, thus the long-term consequences of GDM on the children's growth and body composition could not be established.

6.5 Recommendations for future studies

Future studies should consider more interactive awareness campaigns to educate communities about screening for GDM. Prospective qualitative studies may give further insight into the barriers encountered in the uptake of GDM screening. The clinical staff (nurses, doctors and researchers) should work closely together to promote the screening of GDM and propose realistic methods to increase the detection of affected women.

A more extensive longitudinal study following the infants born to women with GDM into childhood and early adulthood could lend some insight into how infant outcomes impacts on later growth and development.

Due to obesity and GDM following a vicious intergenerational cycle, health sectors should implement interventional studies such as sustainable health programs to address overweight and obesity in women of childbearing age. Public health campaigns should focus on maternal and infant nutrition and promote physical exercise. These interventional programs should be community orientated and affordable.

6.6 Conclusion

There is little research on GDM in South Africa. This study was one of the first in South Africa to follow up infants born to women with GDM and those without GDM. The findings of the study show no significant differences in the first six months of life in the growth and body composition of infants born to women with and without GDM.

It is of concern that 51% of mothers with GDM would have been undiagnosed and untreated. Therefore, universal screening for GDM offered on a research basis emerged to be beneficial compared to the selective screening applied at CHBAH. It is mandatory to establish policies aimed at improving GDM screening in our hospitals.

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APPENDICES

Appendix A: Mothers information and consent sheet



MRC/WITS DEVELOPMENTAL PATHWAYS FOR HEALTH RESEARCH UNIT

Department of Paediatrics, School of Clinical Medicine
University of the Witwatersrand
Johannesburg



GESTATIONAL DIABETES STUDY
INFORMATION SHEET

Hello, I Martha Ngobeni with Shane Norris and Aryeh Stein are researchers for the Department of Paediatrics at the University of Witwatersrand and Emory University. The South African Medical Council, World Diabetes Foundation and Emory Global Health Institute fund this study. We are conducting a research study to investigate the prevalence of gestational diabetes in Soweto. Before you decide to participate, we would like you to understand why the research is being done, and what it would involve for you and your baby.

What is involved in the sub-study?

This study will be conducted at the MRC/Wits Developmental Pathways for Health Research Unit based at Chris Hani Baragwanath Academic Hospital (CHBAH). There are certain investigations that we will be performing at our offices, but you still need to go for your regular public clinic and doctor checkups.

If you agree to participant on the study we will collect the following data:

- Blood samples for insulin and glucose metabolism.

- Ask you a series of questions related to yourself and your pregnancy.

- Collect placenta and the cord blood at delivery for women diagnosed with gestational diabetes mellitus (GDM).

A research nurse will be present to advise or assist you during your pregnancy. You will be requested to contact the nurse when you go into labour so she can arrange to be present at the delivery of your baby to collect the placenta and cord blood.

Below are detailed procedures of what the study involves:

Interviewer-completed questionnaire

At your visits we will fill in a questionnaire with your help about your education, household circumstances, employment, events that have recently taken place and your health during your pregnancy and after you deliver your baby. If you are uncomfortable about answering any of the questions you need not answer them. If you refuse to answer a question, you will not be penalised or lose any benefits to which you are entitled to in the study.

Blood taking

A nurse will collect blood from you (from a vein in your arm) at these visits:

Visit 1: (± 25 ml total; 5 teaspoons) for glucose and insulin

You may feel a prick, discomfort, bleeding or bruising when blood is taken where the needle enters your body. Sterile, disposable syringes will be used once only so there is no chance of infection. This procedure is safe and there will be no charge for these blood tests. The results from the test will be absolutely confidential; meaning a code will be used instead of your name. We will tell you the results of your blood tests and explain them in detail so that you can understand what they mean. If the results indicate there is a health concern we will assist in referring you to the appropriate doctors.

Haemoglobin

A nurse will perform s finger prick test on you to check your haemoglobin levels. Haemoglobin is a protein that carries oxygen in your blood.

Urine dipstick test

As part of your follow-up visit, we will collect a urine sample from you to perform a urine dipstick test, which can indicate if there is protein, blood, and sugar in your urine. The nurse will explain the test to you and provide you with the results immediately and counsel you on what the results mean.

Measurements

We would like to measure your weight, height and blood pressure at each visit.

The Oral Glucose Tolerance Test

When we eat certain foods our bodies break the food down into sugar (glucose) which provides us with energy. When our blood sugar levels rise our bodies produce a hormone called insulin to control the sugar levels. However, sometimes there can be too much sugar in our blood stream which can cause problems. One of the most common problems resulting from too much sugar is a condition called diabetes. Some women can develop diabetes during pregnancy without ever having had it before (this is called gestational diabetes). Developing diabetes during pregnancy can impact the mother's and baby's health. Therefore, we want to determine your glucose and insulin levels.

When you are around 24-28 weeks (6-7 months) pregnant an oral glucose tolerance test (OGTT) will be performed on you. You will have to have fasted from 10pm the night before you come for this visit. You may drink water but must not eat any food or drink anything else. The test will involve you drinking approximately 1 cup of a sweet sugary drink. Before you drink the liquid a nurse will prick your finger to check your fasting blood sugar level and she will take two blood samples from a vein in your arm (one for glucose and one for insulin testing). You will then be given the sugary liquid to drink. This has to be drunk within 5 minutes. Thereafter, two blood samples will be taken from you at 30 minutes, 1 hour and 2 hours after you have swallowed the drink.

As soon as this test is completed we will offer you a sandwich and a drink.

If the results of the OGGT come back normal, there will no need for us to contact you.

If your OGGT results suggest that you may have gestational diabetes, you will be telephonically contacted and asked to come in to our Unit to get a referral letter to the Diabetic Clinic at CHBAH.

Delivery Process

You need to be booked into CHBH Antenatal Clinic for regular antenatal care and management. You will have a research nurse available to you throughout your pregnancy. Once you are ready to be admitted to hospital/clinic, you will need to contact the research nurse who

will be present at your delivery to collect the placenta and cord. After you deliver your baby we will collect some biological samples; placenta, cord and the cord blood, will also like to measure your babies weight, length and head circumference. We would also like to contact you after you deliver your baby to obtain information regarding the delivery.

We might also contact you to invite you to participant in another study after you deliver your baby.

Possible risks

Sample of blood: You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint.

What to do if you have problems: If it is discovered that you may have a health problem when your blood results or other results are received, you will be notified and the right health care practitioner to help you with your problem and treatment will be recommended.

Possible benefits:

If we find any problems during your visit or the baby's we will refer you to Chris Hani Baragwanath Academic Hospital for management.

Costs to you:

Participation in the research will involve no cost to you. You will be given a sandwich and fruit juice once your measurements and assessments have been completed. You will also be given R100 for transport costs.

Voluntary participation in research:

You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to stop at any time. Your refusal to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

Records of your participation in this research:

You have the right to privacy. The principal investigators will keep information about your participation in locked files. Your data collected will be labelled with a code to ensure privacy. The Emory Institutional Review Board and Emory Office of Research Compliance as offices would also have access to anonymous study records if warranted.

Ethical approval: The Gestational Diabetes study, will submit a protocol to the University of Witwatersrand's, Human Research Ethics Committee (HREC)

Publication of the results of the research: The results of this research may appear in scientific publications without identifying you in any way.

Your questions:

The investigator listed on the first page of this form is available to answer your questions about this research. You may contact the investigator at any time on the following number (011)933-1122. If you require any further information or have any questions/complaints about the study please contact the Human Research Ethics Committee of the University of the Witwatersrand: Chairperson Prof P Cleaton-Jones, Chairperson Tel 011-7172301. Secretariat: Zanele Ndlovu and Langutani Masingi 011-7171252/1234 zanele.ndlovu@wits.ac.za or langutani.masingi@wits.ac.za

YOU WILL HAVE A COPY OF THIS INFORMATION SHEET TO KEEP

If you are happy to take part in the study please read and sign the attached consent form and contact us to confirm your participation.

Your signature on the consent form certifies the following:

· You have read the information provided in this consent form.
· You have received answers to all of your questions.
· You have freely decided to participate in this research.
· You understand that you are not giving up any of your legal rights.

MRC/WITS DEVELOPMENTAL PATHWAYS FOR HEALTH RESEARCH UNIT

Department of Paediatrics, School of Clinical Medicine
University of the Witwatersrand, Johannesburg

GESTATIONAL DIABETES STUDY
CONSENT SHEET

I agree to myself being a participant in the study. The goals and methods of the study are clear to me. I understand that the study will involve follow up visits which will include an interview, collection of biological samples, blood taking and glucose tolerance test. All the details and purposes of this study have been explained to me. I understand that I have the right to refuse to participate in the study.

I agree to participation in the study on the condition that:

1. I can withdraw voluntarily from the study at any time and that no adverse consequences will follow on withdrawal from the study.

2. I have the right not to answer any or all questions posed in the interviews and not to participate in any or all of the procedures / assessments.

3. The University of the Witwatersrand's Human Research Ethics committee has approved the study protocol and procedures.

4. All results will be treated with the strictest confidentiality.

5. Only group results, and not my individual results, will be published in scientific journals and in the media.

6. The study scientific team are committed to treating participants with respect and privacy through interviews conducted in private and follow-up counselling available on request.

7. I will receive a referral note to a health service if any result is out of the normal range or a problem is detected during the course of the study.

PARTICIPANT

_____

Printed Name Signature / Mark or Thumbprint Date and Time

RESEARCH ASSISTANT

_____

Printed Name Signature Date and Time

Appendix B: Pamphlet given to mothers at recruitment



DEFINITION

Diabetes occurs when there is a higher level of glucose in the blood than is normal. Glucose is when food is broken down into glucose in the blood. It travels through your body in the blood. A hormone called insulin then helps glucose move from your blood to your cells. Once glucose is in your cells, it can be used for energy.

A problem making or using insulin means glucose cannot move into your cells. Instead, the glucose builds up in your blood. The build-up is called hyperglycaemia (meaning to much sugar).

The extra glucose can affect the mother (increase her risk for diabetes after the pregnancy) and may result in an oversized fetus (baby).

CAUSES

It is caused by reduced sensitivity to insulin during pregnancy.

RISK FACTORS

- Obesity or being overweight – This can affect the body's ability to use insulin.
- Gestational diabetes in a previous pregnancy
- Family history of type 2 diabetes
- Previous delivery of a large baby, specifically 4kg or more
- Sleep-disordered breathing – abnormal breathing during sleep ranging from snoring to sleep apnea
- History of polycystic ovary syndrome
- Previous stillbirth or too much amniotic fluid surrounding a baby during pregnancy
- Multiple pregnancy – carrying two or more babies

Also, hormones that help the baby's growth may interfere with insulin.

SYMPTOMS

Screening women does not remove symptoms. Early detection and management may prevent later symptoms. If symptoms do occur, they may include:

- Increased urination
- Thirst
- Hunger
- Weakness
- Vaginal or urinary tract infections

DIAGNOSIS

If you don't have a history of diabetes, you can have an Oral Glucose Tolerance Test at 24-28 weeks of gestation. You will be given a drink that has a special glucose solution in it. The level of glucose in your blood will be measured.

IT IS EXPECTED THAT MORE THAN 10% OF WOMEN IN SOWETO MAY DEVELOP DGM

TREATMENT

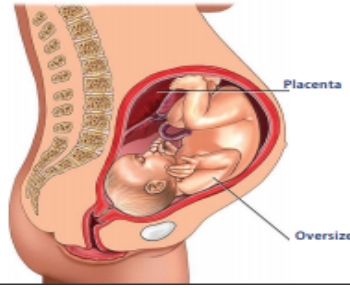
The goal of treatment is to return blood glucose levels to normal. Treatment may include:

DIET

A dietitian can help you develop a healthy meal plan. Guidelines include:

- Eat a balanced diet. Do not skip meals.
- Eat plenty of fruits, vegetables, and high fiber foods.
- Limit the amount of fat you eat.
- Avoid foods high in sugar such as fizzy drink, sweets, and cookies.
- Manage your portion sizes at each meal.
- Plan a bedtime snack each night. It should include protein and complex carbohydrates such as beans, potatoes, corn, or rice.
- Keep a record of your food intake. Share this information with your doctor.

Do not gain more weight during pregnancy than your doctor advises. Excess weight can increase complications in your pregnancy. It will also make it more difficult to control your diabetes.



EXERCISE

Physical activity can make it easier for your body to use glucose. There are some precautions you may need to take or certain exercises you may need to avoid. Ask your doctor about an exercise plan.

BLOOD SUGAR TESTING

A blood glucose monitor will help you check your glucose levels throughout the day. Knowing your glucose level will help you plan your meals, activities, and medication. Keep a record of your results. Discuss them with your doctor at your visits.

MEDICATION

You may need to give yourself insulin injections to control diabetes. For some pregnant women, oral medication is recommended.

After delivery, glucose levels usually return to normal. Your glucose levels will be checked at about 6 weeks post-partum check-up. This is when most women are tested to make sure that you no longer have diabetes.

PREVENTION

The following may help prevent gestational diabetes:

- Do not gain more weight than recommended during pregnancy.
- Eat a healthy diet.
- Exercise regularly. Talk to your doctor before starting an exercise program.
- If you smoke, talk to your doctor about ways to quit.

Appendix C: Clinical questionnaire

MRC/Wits Developmental Pathways for Health

Research Unit

University of the Witwatersrand

Gestational Diabetes Mellitus Study

MATERNAL CLINICAL QUESTIONNAIRE

GDM Study number: _____

Interviewer's name: _____

Interview date:_____

Section 1: Gestational age

Has she had an ultrasound scan? If yes, on what date was the scan done?	Yes/No
Where was the scan done?	
Based on the ultrasound findings, how far pregnant was she when she was scanned?	
How far pregnant is she today (weeks)? Please use the pregnancy wheel to work out her gestation age	

Section 2: Measurements

Weight (kg) ☐☐☐ . ☐

Height (cm) ☐☐☐ . ☐

BMI (kg/m^2) ☐☐ . ☐

Section 3: Blood pressure

Pulse ☐☐☐

Systolic bp ☐☐☐

Diastolic bp ☐☐☐

Pulse ☐☐☐

Systolic bp ☐☐☐

Diastolic bp ☐☐☐

Pulse ☐☐☐

Systolic bp ☐☐☐

Diastolic bp ☐☐☐

Section 4: Medical History

Please tick on the correct box below

During this pregnancy, have you been diagnosed with, or taking any treatment for the following conditions?	Yes	No
Diabetes		
Thyroid disease		
Any type of malignancy/cancer (including leukaemia or lymphoma)		
Cardiac disease		
Epilepsy		
Mental illness e.g. Clinical depression		
Hypertension / chronic hypertension		
Chronic respiratory disease (including chronic asthma)		
Hepatitis B or C		
Malaria- within past 5 years		
Tuberculosis		
Any other clinical relevant condition		
HIV or AIDS?		

Please complete the following questions for HIV positive woman ONLY

Date tested HIV positive?	
CD 4 count: pre-pregnancy (include the date) Pregnancy (include the date)	
Viral load : pre-pregnancy (include the date) Pregnancy (include the date)	
WHO Stage of disease currently, circle the correct option	Clinical stage 1 Clinical stage 2 Clinical stage 3

	Clinical stage 4 (AIDS) Not available
Which treatment is she receiving (e.g. FDC) if other, please specify When was the treatment started?	
During this pregnancy has she received any different ART treatment prior to the above mentioned treatment regimen IF yes, on which date?	
Why was the treatment changed?	

Section 5: Obstetric History

Number of previous pregnancies	
Date of last delivery, miscarriage or termination	
Number of extrauterine or ectopic pregnancies	
Number of molar pregnancies or choriocarcinoma	
Number of miscarriages	
Number of stillbirths	
Number of terminations	
Number of previous births	
Number of any previous neonatal deaths	
History of pregnancy induced hypertension	
History of pre-eclampsia eclampsia	

Appendix D: Demographics and socio-economic status questionnaire

MRC/Wits Developmental Pathways for Health Research Unit

University of the Witwatersrand

Gestational Diabetes Mellitus Study

DEMOGRAPHICS AND SOCIO-ECONOMIC STATUS QUESTIONNAIRE

GDM Study number:_____

Interviewer's name:

_____

Interview date:

_____

Section 1: Demographics

Marital status:

Single	☐	Widowed	☐
Married/cohabiting	☐	Separated/divorced	☐

Total number of formal education ☐☐

Highest level of education

No school attended	☐	Professional/technical training	☐
Primary school	☐	University	☐
Secondary	☐		

Which of the following best describes your occupation

Housework	☐	Skilled manual work	☐
Student	☐	Unskilled manual work	☐
Professional/technical	☐	Other	☐

Administrative support, services or sales ☐

Section2: SOCIO-ECONOMIC STATUS

Does the mother's home have or own any of the following

Electricity	☐	Cell phone	☐	Bicycle	☐
Radio	☐	personal computer	☐	Motorcycle/bike	☐
Television	☐	Farm animals	☐	Car/truck/tractor	☐
Refrigerator	☐	Agricultural land	☐		

Total number of people living in your home ☐☐

Total number of sleeping rooms in your home ☐☐

Main fuel of cooking in the home

Gas	☐	Electricity	☐	Straw/shrubs/grass	☐
Oil	☐	Charcoal	☐	Animal dung	☐
Kerosene	☐	Wood	☐	No cooking	☐

Main source of drinking water

Piped water into dwelling	☐	Tanker truck/cart with small tank	☐
Protected dung well	☐	Unprotected dung	☐
Protected spring	☐	Unprotected spring	☐
Rain water	☐	Surface water	☐
Public tap/standpipe	☐	Other	☐

Type of toilet facility

Flush to pipe sewer system	☐	Ventilated improved pit (latrine)	☐
Flush to septic tank	☐	No facility or bush or field	☐
Traditional pit toilet	☐	Other	☐

Toilet shared with other households ☐ N

Main flooring material

Earth/sand/mud	☐	Vinyl/linoleum	☐	Carpet	☐
Wood planks	☐	Ceramic tiles	☐	Other	☐
Parquet or finished wood	☐	Cement	☐		

Main wall material in the house

No walls	☐	Prefab	☐	Bare brick/cement block	☐
Plastic/cardboard	☐	Corrugated iron/zinc	☐	Plaster/finished	☐
Mud	☐	Mud or cement	☐	Other	☐

Appendix E: Delivery and birth outcomes questionnaire

MRC/Wits Developmental Pathways for Health Research Unit

Gestational Diabetes Mellitus Study

DELIVERY AND BIRTH OUTCOME QUESTIONNAIRE

GDM study number:_____

Interviewer's name:_____

Interview date: _____

Section 1: Delivery and birth outcome information

Date of delivery_____

Time of delivery_____

Gestational Age at delivery_____

Apgar scores_____

Sex of the baby_____

Discharge date of the mother_____

Discharge date of the baby_____

Newborn status at birth: Alive ☐ Intrapartum death ☐ Antepartum death ☐

Comments:_____

_

Fetal presentation at delivery: Cephalic ☐ Breech ☐ Other ☐

Comments:_____

_ ☐ ☐ ☐

Onset of Labour: Spontaneous induced No labour

Comments_____

Premature rupture of membranes: Yes ☐ No ☐

Comments:_____

Mode of delivery: Vaginal spontaneous ☐ Caesarean Section ☐

Comments: _____

Delivery mode: Non-assisted ☐ Assisted ☐ Forceps/Vacuum ☐

Comments:_____

Baby Admitted: Yes ☐ No ☐ If YES ward #:_____

Comments and diagnosis:_____

During this pregnancy were you diagnosed with, or treated for, any of the following conditions?

Chronic hypertension Yes ☐ No ☐

Pregnancy-induced hypertension
(Blood pressure > 140/90, no proteinuria) Yes ☐ No ☐

Pre-eclampsia Yes ☐ No ☐
(Blood pressure > 140/90 and proteinuria)

Severe pre-eclampsia / eclampsia / HELLP syndrome Yes ☐ No ☐

Other pregnancy complications, please specify _____

Did you have any problems after delivery?

Postpartum hemorrhage (> 500 ml blood) Yes ☐ No ☐

Postpartum high blood presssure Yes ☐ No ☐

Other post-partum complications, please specify _____

Please note: ONLY collect samples from women who were diagnosed with Gestational Diabetes Mellitus during pregnancy.

Placenta collected: Yes ☐ No ☐

Cord blood collected? Yes ☐ No ☐

Section 2: Birth outcomes

Date:_____

Time:_____

How old is the baby today? _____

Infant's weight: ☐☐☐☐ g

Infant's length: ☐☐☐ ☐ cm

Infant head circumference: ☐☐ .☐ cm

Anthropometrist1:_____

Infant's weight: ☐☐☐☐

Infant's length: ☐☐☐ ☐ cm

Infant head circumference: ☐☐. ☐cm

Anthropometrist2:_____

Has the PEAPOD assessment been done? (Please attach report) Yes ☐ No ☐

Appendix F: Laboratory sheet for the OGGT blood collection



Gestational Diabetes Mellitus Study

Biochemical Investigations Checklist

Patients Label

VISIT 1: Glucose Testing

GDM Study number:

Date:

D	D		M	M		Y	Y

Fasting:

Y	N

Finger prick	Hb meter	Hb	

Urine dipstick results:

Glucose	Neg	±	+	++	+++	
Ketones	Neg	±	+	++	+++	
Blood	Neg	Hemolysis +	++	+++	Non Hemolysis +	++
Protein	Neg	Trace	+	++	+++	++++
Leukocytes	Neg	+	++	+++		

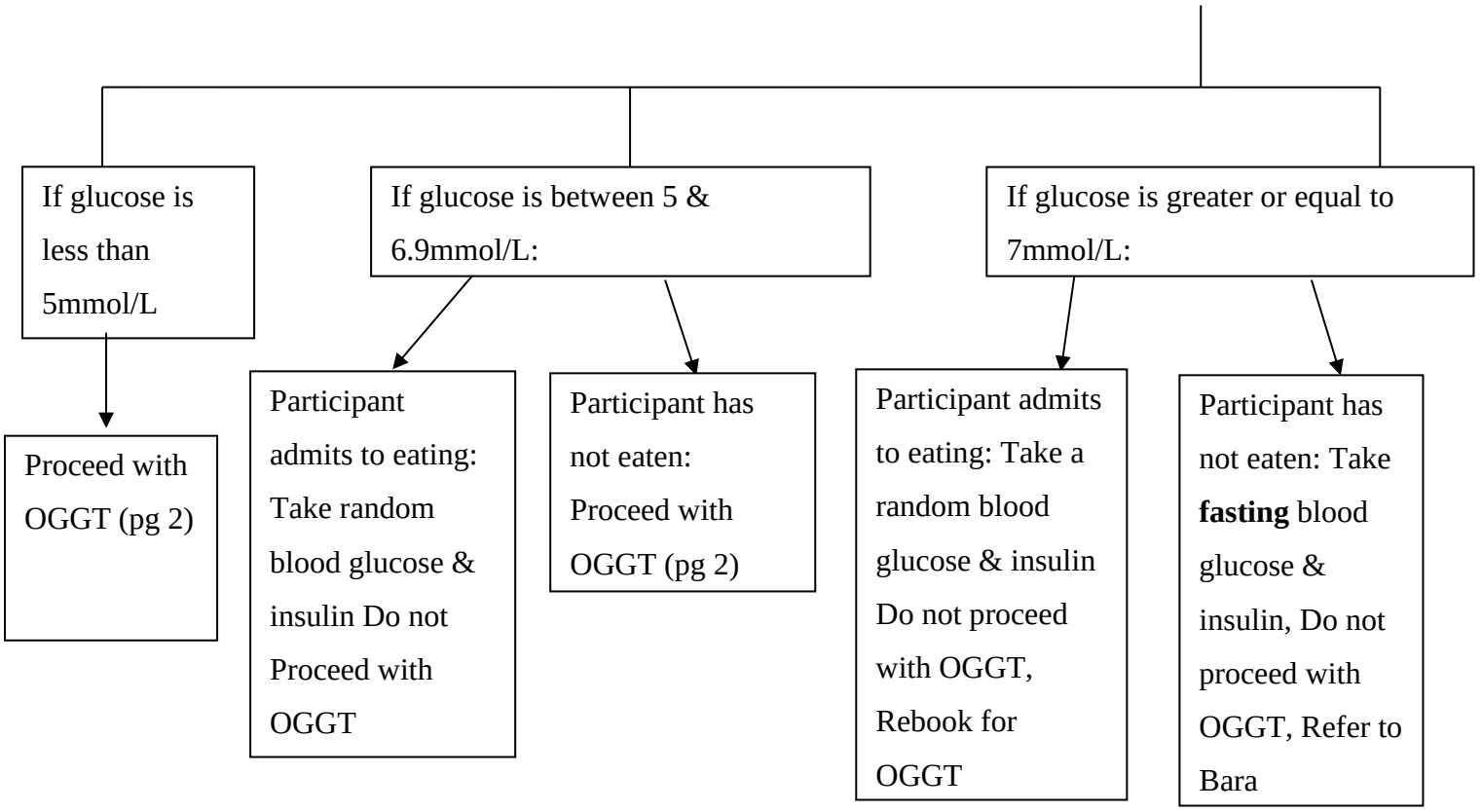
Blood	Red top	5ml Micronutrient analysis x2
	Purple top	4ml HBA1C x1

Time of blood taking:

		H		

Gestational Diabetes Mellitus Study

Finger Prick	Glucometer	Accu-check	_____ mmol/L



Time of blood taking: | | | H | | |

Gestational Diabetes Mellitus Study

VISIT 4: OGGT

0 Minutes		
	Red Top	Insulin X1
	Grey Top	Glucose

Time of blood taking: | | | H | | |

30 Minutes		
	Red Top	Insulin X1
	Grey Top	Glucose

Time of blood taking: | | | H | | |

60 Minutes		
	Red Top	Insulin X1
	Grey Top	Glucose

Time of blood taking: | | | H | | |

120 Minutes		
	Red Top	Insulin X1
	Grey Top	Glucose

Time of blood taking: | | | H | | |

Completed by: _____ Bloods processed by: _____

Appendix G: Case group information and consent sheet

MRC/WITS DEVELOPMENTAL PATHWAYS FOR HEALTH RESEARCH UNIT

Department of Paediatrics, School of Clinical Medicine
University of the Witwatersrand, Johannesburg

GESTATIONAL DIABETES AND BABY GROWTH/ BODY COMPOSITION STUDY

Case Group

INFORMATION SHEET

Hello, I Martha Ngobeni with Shane Norris and Aryeh Stein are researchers for the Department of Paediatrics at the University of Witwatersrand and Emory University. The South African Medical Council, World Diabetes Foundation and Emory Global Health Institute fund this study. We are conducting a research study to investigate the effect of gestational diabetes on birth outcome, as well as how gestational diabetes affects the growth and body composition of babies over the first six months after birth. Before you decide to participate, we would like you to understand why the research is being done, and what it would involve for you and your baby.

What is involved in the sub-study?

This study will be conducted at the MRC/Wits Developmental Pathways for Health Research Unit based at Chris Hani Baragwanath Academic Hospital. There are certain investigations that we will be performing at our offices, but your baby will still need to go for his/her regular public clinic and doctor checkups.

If you agree to take part in the sub-study, we will collect the following research data:

At delivery: biological samples (placenta & cord blood), measure the baby's weight, length, head circumference and air-displacement plethysmograpgy (PEAPOD)
6 weeks visit: measure the baby's weight, length, head circumference and PEAPOD. Collect ± 5 ml of maternal blood for glucose.
8 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
12 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
16 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
20 weeks visit: measure the baby's weight, length, head circumference and PEAPOD

24 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
Ask you a series of questions related to your delivery and the baby

Each visit will take approximately 30-60 minutes

Below are detailed procedures of what the study involves:

Interviewer-completed questionnaire

At your first visit we will fill in a questionnaire with your help about your baby's delivery. If you are uncomfortable about answering any of the questions you need not answer them. If you refuse to answer a question, you will not be penalised or lose any benefits to which you are entitled to in the study.

Measurements

We would like to do a follow-up on your baby's growth for a period of 6 months. We will request you to bring the baby to the unit for body measurements (weight, height and head circumference). The baby will visit us in the first 48 hours after delivery, 6, 8, 12, 16, 20, 24 weeks.

PEAPOD

The PEAPOD is a machine that determines infant body composition. The machine is safe and non-invasive. The process entails the baby being placed into a warmed test chamber where body mass and body volume is measured. The baby will lie inside the chamber for a few minutes and you will be able to see him/her through a glass lid. PEAPOD assessment will be done immediately after delivery and when the baby comes for her/his follow up visits at 6, 8, 12, 16, 20, 24 weeks.

Possible risks

Sample of blood: You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint. What to do if you have problems: If it is discovered that you or your baby may have a health problem when your blood results or other results are received concerning your baby, you will be notified and the right health care practitioner to help you with your problem and treatment will be recommended.

Possible benefits:

If we find any problems during your visit or the baby's we will refer you to Chris Hani Baragwanath Academic Hospital for management. Although you may not benefit directly from this study, results from this study will improve understanding on how babies grow and may benefit babies born in the future.

Costs to you:

Participation in the research will involve no cost to you. You will be given a sandwich and fruit juice once your measurements and assessments have been completed. You will also be given R100 for transport costs.

Voluntary participation in research:

You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to stop at any time. Your refusal to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

Records of your participation in this research:

You have the right to privacy. The principal investigator will keep information about your participation in locked files. Your babies data collected will be labelled with a code to ensure privacy. The Emory Institutional Review Board and Emory Office of Research Compliance as offices would also have access to anonymous study records if warranted.

Ethical approval: The Gestational Diabetes and Infancy study, will submit a protocol to the University of Witwatersrand's, Human Research Ethics Committee (HREC)

Publication of the results of the research: The results of this research may appear in scientific publications without identifying you in any way.

Your questions:

The investigator listed on the first page of this form is available to answer your questions about this research. You may contact the investigator at any time on the following number (011)933-1122. If you require any further information or have any questions/complaints about the study

please contact the Human Research Ethics Committee of the University of the Witwatersrand: Chairperson Prof P Cleaton-Jones, Chairperson Tel 011 717 2301. Secretariat: ZaneleNdlovu and LangutaniMasingi 011 717 1252/1234 zanele.ndlovu@wits.ac.za or langutani.masingi@wits.ac.za

YOU WILL HAVE A COPY OF THIS INFORMATION SHEETTO KEEP

If you are happy to take part in the study please read and sign the attached consent form and contact us to confirm your participation.

Your signature on the consent form certifies the following:

· You have read the information provided in this consent form

· You have received answers to all of your questions.

· You have freely decided to participate in this research.

· You understand that you are not giving up any of your legal rights.

GESTATONAL DIABETES AND BABY GROWTH/BODY COMPOSITION STUDY

CONSENT SHEET

I agree to myself being a participant in the study. The goals and methods of the study are clear to me. I understand that the study will involve follow up visits which will include an interview, measurements and a body composition scans. All the details and purposes of this study have been explained to me. I understand that I have the right to refuse to participate in the study.

I agree to participation in the study on the condition that:

1. I can withdraw voluntarily from the study at any time and that no adverse consequences will follow on withdrawal from the study.

2. I have the right not to answer any or all questions posed in the interviews and not to participate in any or all of the procedures / assessments.

3. The University of the Witwatersrand's Human Research Ethics committee has approved the study protocol and procedures.

4. All results will be treated with the strictest confidentiality.

5. Only group results, and not my individual results, will be published in scientific journals and in the media.

6. The study scientific team are committed to treating participants with respect and privacy through interviews conducted in private and follow-up counselling available on request.

7. I will receive a referral note to a health service if any result is out of the normal range or a problem is detected during the course of the study.

PARTICIPANT

_____

Printed Name Signature / Mark or Thumbprint Date and Time

RESEARCH ASSISTANT

_____

Printed Name Signature Date and Time

Appendix H: Control group information and consent sheet

MRC/WITS DEVELOPMENTAL PATHWAYS FOR HEALTH RESEARCH UNIT

Department of Paediatrics, School of Clinical Medicine
University of the Witwatersrand, Johannesburg

BABY GROWTH AND BODY COMPOSITION STUDY

Control Group

INFORMATION SHEET

Hello, I Martha Ngobeni with Shane Norris and Aryeh Stein are researchers for the Department of Paediatrics at the University of Witwatersrand and Emory University. The South African Medical Council, World Diabetes Foundation and Emory Global Health Institute fund this study. We are conducting a research study to investigate the growth and body composition of babies over the first six months after birth. Before you decide to participate, we would like you to understand why the research is being done, and what it would involve for you and your baby.

What is involved in the sub-study?

This study will be conducted at the MRC/Wits Developmental Pathways for Health Research Unit based at Chris Hani Baragwanath Academic Hospital. There are certain investigations that we will be performing at our offices, but your baby will still need to go for his/her regular public clinic and doctor checkups.

If you agree to take part in the sub-study, we will collect the following research data:

At delivery: biological samples (placenta & cord blood), measure the baby's weight, length, head circumference and PEAPOD
6 weeks visit: measure the baby's weight, length, head circumference and PEAPOD.
8 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
12 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
16 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
20 weeks visit: : measure the baby's weight, length, head circumference and PEAPOD

24 weeks visit: measure the baby's weight, length, head circumference and PEAPOD
Ask you a series of questions related to your delivery and the baby

Each visit will take approximately 30-60 minutes

Below are detailed procedures of what the study involves:

Interviewer-completed questionnaire

At your first visit we will fill in a questionnaire with your help about your baby's delivery. If you are uncomfortable about answering any of the questions you need not answer them. If you refuse to answer a question, you will not be penalised or lose any benefits to which you are entitled to in the study.

Measurements

We would like to do a follow-up on your baby's growth for a period of 6 months. We will request you to bring the baby to the unit for body measurements (weight, height and head circumference). The baby will visit us in the first 48 hours after delivery; 6, 8, 12, 16, 20 and 24 weeks.

PEAPOD

The PEAPOD is a machine that determines infant body composition. The machine is safe and non-invasive. The process entails the baby being placed into a warmed test chamber where body mass and body volume is measured. The baby will lie inside the chamber for a few minutes and you will be able to see him/her through a glass lid. PEAPOD assessment will be done immediately after delivery and when the baby comes for her/his follow up visits at 6, 8, 12, 16, 20 and 24 weeks.

What to do if you have problems: If it is discovered that your baby may have a health problem when the results are received, you will be notified and the right health care practitioner to help you with your problem and treatment will be recommended.

Possible benefits:

If we find any problems during your visit or the baby's we will refer you to Chris Hani Baragwanath Academic Hospital for management. Although you may not benefit directly from

this study, results from this study will improve understanding on how babies grow and may benefit babies born in the future.

Costs to you:

Participation in the research will involve no cost to you. You will be given a sandwich and fruit juice once your measurements and assessments have been completed. You will also be given R100 for transport costs.

Voluntary participation in research:

You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to stop at any time. Your refusal to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

Records of your participation in this research:

You have the right to privacy. The principal investigator will keep information about your participation in locked files. Your babies data collected will be labelled with a code to ensure privacy. The Emory Institutional Review Board and Emory Office of Research Compliance as offices would also have access to anonymous study records if warranted.

Ethical approval: The Gestational Diabetes and Infancy study, will submit a protocol to the University of Witwatersrand's, Human Research Ethics Committee (HREC)

Publication of the results of the research: The results of this research may appear in scientific publications without identifying you in any way.

Your questions:

The investigator listed on the first page of this form is available to answer your questions about this research. You may contact the investigator at any time on the following number (011)933-1122. If you require any further information or have any questions/complaints about the study please contact the Human Research Ethics Committee of the University of the Witwatersrand: Chairperson Prof P Cleaton-Jones, Chairperson Tel 011 717 2301. Secretariat: ZaneleNdlovu and LangutaniMasingi 011 717 1252/1234 zanele.ndlovu@wits.ac.za or langutani.masingi@wits.ac.za

YOU WILL HAVE A COPY OF THIS INFORMATION SHEETTO KEEP

If you are happy to take part in the study please read and sign the attached consent form and contact us to confirm your participation.

Your signature on the consent form certifies the following:

· You have read the information provided in this consent form

· You have received answers to all of your questions.

· You have freely decided to participate in this research.

· You understand that you are not giving up any of your legal rights.

GESTATONAL DIABETES AND BABY GROWTH/BODY COMPOSITION STUDY

CONSENT SHEET

I agree to myself being a participant in the study. The goals and methods of the study are clear to me. I understand that the study will involve follow up visits which will include an interview, measurements and a body composition examanation. All the details and purposes of this study have been explained to me. I understand that I have the right to refuse to participate in the study.

I agree to participation in the study on the condition that:

1. I can withdraw voluntarily from the study at any time and that no adverse consequences will follow on withdrawal from the study.

2. I have the right not to answer any or all questions posed in the interviews and not to participate in any or all of the procedures / assessments.

3. The University of the Witwatersrand's Human Research Ethics committee has approved the study protocol and procedures.

4. All results will be treated with the strictest confidentiality.

5. Only group results, and not my individual results, will be published in scientific journals and in the media.

6. The study scientific team are committed to treating participants with respect and privacy through interviews conducted in private and follow-up counselling available on request.

7. I will receive a referral note to a health service if any result is out of the normal range or a problem is detected during the course of the study.

PARTICIPANT

Printed Name	Signature / Mark or Thumbprint	Date and Time

RESEARCH ASSISTANT

Printed Name	Signature	Date and Time

Appendix I: Infant anthropometry and peapod measures



Gestational Diabetes Mellitus Study

ANTHROPOMETRIC MEASUREMENTS AND PEAPOD

Infant's study number: ☐☐☐☐☐☐☐

Mother's GDM Study number: ☐☐☐☐☐☐☐

Infant's Age: ☐☐ weeks ☐☐ days

Infant's Weight: ☐☐☐☐ g

Infant's Length: ☐☐☐ ☐ cm

Infant Head circumference: ☐☐ ☐ cm

Anthropometrist 1: _____

Infant's Weight: ☐☐☐.☐ g

Infant's Length: ☐☐☐ ☐ cm

Infant Head circumference: ☐☐.☐ cm

Anthropometrist2:_____

Infant's Weight: ☐☐☐.☐ g

Infant's Length: ☐☐☐ ☐ cm

Infant Head circumference: ☐☐ ☐ cm

Has the PEAPOD assessment been done? (Please attach report) ☐ ☐

Road to Health Card (Please attach a copy)

Appendix J: Calculation of z-scores, using Stata 14

	Conditional weight 2	**Conditional weight 3**	**Conditional weight 4**	**Conditional weight 5**	**Conditional weight 6**	**Conditional weight 7**
Weight 1	0.67 (0.48-0.86) **0.000**	0.00 (0.16-0.15) 0.963	0.04 (0.12-0.20) 0.639	0.06 (0.21-0.10) 0.449	0.14(0.01-0.29) 0.068	0.00 (0.17-0.17) 0.086
Weight 2		1.05 (0.91-1.19) **0.000**	0.32 (0.03-0.60) **0.032**	0.43(0.71-0.16) **0.002**	0.25 (0.52-0.02) 0.066	0.10(0.41-0.21) 0.516
Weight 3			0.72 (0.49-0.96) **0.000**	0.41 (0.14-0.68) **0.003**	0.12 (0.39-0.14) 0.361	0.07 (0.38-0.23) 0.628
Weight 4				0.96 (0.74-1.19) **0.000**	0.01 (0.28-0.31) 0.931	0.08 (0.42-0.26) 0.641
Weight 5					1.18 (0.95-1.41) **0.000**	0.03 (0.39-0.46) 0.873
Weight 6						1.18 (0.89-1.47) **0.000**
Weight 7						
Length 1	16.11 (48.87-16.65) 0.332	2.42 (21.72-26.55)	27.08 (54.55-0.40) **0.053**	14.02 (39.90-11.86) 0.283	22.09 (45.28-1.09) 0.061	30.26 (3.27-57.25) **0.029**
Length 2	61.57 (25.24-97.90) **0.001**	21.79 (5.62-10.05)	21.71 (1.24-56.65) 0.220	48.52 (9.97-87.08) **0.014**	0.76 (41.36-39.83) 0.970	39.26 (84.14-5.63) 0.085
Length 3		5.90(27.87-39.67) 0.729	19.85 (59.81-20.12)	20.73 (15.24-56.70) 0.254	3.21 (29.57-35.99) 0.845	17.66 (53.72-18.41) 0.331
Length 4			12.44 (17.30-42.17)	15.09 (43.84-13.66) 0.299	4.90 (20.23-30.04) 0.698	20.71 (7.81-49.23)0.151
Length 5				24.71 (7.77-57.18) 0.134	4.13 (33.35-25.08) 0.778	15. 61 (20.95-52.17) 0.396
Length 6					15.46 (2.27-33.19) 0.086	8.75 (28.71-11.21) 0.384
Length 7						1.76 (49.69-53.21) 0.946
	Conditional length 2	**Conditional length 3**	**Conditional length 4**	**Conditional length 5**	**Conditional length 6**	**Conditional length 7**
Length 1	0.19 (0.03-0.35) 0.020	0.26 (0.11-0.40) **0.000**	0.07 (0.28-0.15) 0.539	0.13 (0.06- 0.31) 0.189	0.30 (0.04-0.63) 0.079	0.12 (0.02-0.26) 0.100
Length 2		0.24 (0.04-0.43) **0.018**	0.27 (0.01-0.53)**0.040**	0.12(0.16-0.42) 0.384	0.07 (0.66-0.51) 0.799	0.03 (0.27-0.21) 0.819
Length 3			0.57 (0.30-0.84) **0.000**	0.00 (0.27-0.27) 0.996	0.11 (0.36-0.58) 0.645	0.03 (0.16-0.22) 0.734
Length 4				0.29 (0.09- 0.49) **0.006**	0.11 (0.24-0.47) 0.527	0.13 (0.02-0.28) 0.078
Length 5					0.36 (0.05-0.77) 0.086	0.34 (0.17-0.51) **0.000**
Length 6						0.01 (0.11-0.10) 0.907
	Conditional weight 2	**Conditional weight 3**	**Conditional weight 4**	**Conditional weight 5**	**Conditional weight 6**	**Conditional weight 7**
Length 7						
Weight 1	0.00 (0.00-0.00) 0.402	0.00 (0.00-0.00) 0.874	0.00 (0.00-0.00) 0.684	0.00 (0.00-0.00) 0.595	0.00 (0.00-0.00) 0.221	0.00 (0.00-0.00) 0.291
Weight 2	0.00 (0.00-0.00) **0.001**	0.00 (0.00-0.00) 0.365	0.00 (0.00-0.00) 0.590	0.00 (0.00-0.00) 0.797	0.00 (0.00-0.00) 0.670	0.00 (0.00-0.00) 0.110
Weight 3		0.00 (0.04-0.43) 0.729	0.00 (0.00-0.00) 0.577	0.00 (0.00-0.00) 0.709	0.00 (0.01-0.00) 0.516	0.00 (0.00-0.00) 0.085
Weight 4			0.00 (0.00-0.00) 0.408	0.00 (0.00-0.00) 0.673	0.00 (0.00-0.01) 0.271	0.00 (0.00-0.00) **0.048**
Weight 5				0.00 (0.00-0.00) 0.134	0.00 (0.00-0.00) 0.227	0.00 (0.00-0.00) 0.244
Weight 6					0.00 (0.00-0.00) 0.086	0.00 (0.00-0.00) 0.325
Weight 7						0.00 (0.00-0.00) 0.946

Appendix K: Maters ethics certificate

R14/49 Martha Ngobeni

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150461

NAME: (Principal Investigator)	Martha Ngobeni
DEPARTMENT:	Paediatrics MRC/Wits Development Pathways for Health Research Unit Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Growth and Body Composition of Infants Born to Mothers with, and those without, Gestatinal Diabetes Mellitus
DATE CONSIDERED:	24/04/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Shane Norris and Shelley Macaulay
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/06/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned

contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES