Correlation of HbA1c levels in pregnancy with maternal and perinatal outcomes at Rahima Moosa Mother and Child Hospital

A thesis submitted in partial fulfilment for the degree Master of Medicine in Obstetrics and Gynaecology in the School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand.

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DECLARATON

I, Esrom Dimakatso Motjela, declare that this research report is my own original work and has not been submitted or published for any degree program or examination in any institution. I am submitting this research report in the submissible format with my protocol and extended literature review in the department of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. Any literature work done by others and cited in this research report has been given due acknowledgement and listed in the references section.

Esrom Dimakatso Motjela

Signature:

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ABSTRACT

Background: Limited data exists regarding the prognostic value of glycated haemoglobin A1c (HbA1c) levels during pregnancy in relation to perinatal and maternal outcomes. This study investigates the indications for HbA1c testing at Rahima Moosa Mother and Child Hospital (RMMCH), including its correlation with both perinatal and maternal outcomes.

Methods: A retrospective analysis of 298 antenatal patient records with HbA1c tests at RMMCH over 3 months (January to March 2020) was conducted. Data were retrieved from the National Health Laboratory Service (NHLS) database and managed using REDCap. Descriptive and analytical statistics were performed using Stata statistical software version 15 (Stata Corp, Texas, USA).

Results: The majority of the women were between the age of 18 to 34 (n=199, 66.8%), African ethnicity (n= 215, 72,2%), had multiparity and class I obesity (n=106, 43.1%). The commonest indication for HbA1c testing was body mass index at booking (BMI: n=135, 54.9%) , followed by gestational diabetes mellitus (GDM: n=96, 22.5%) and advanced maternal age (AMA: n=56, 13.1%). A significant relationship was noted between HbA1c ≥6.5% and maternal outcomes such as post-partum haemorrhage (PPH: p-value=0.0004) and diabetic ketoacidosis (p-value=0.0003). In terms of perinatal outcomes, a significant relationship was also noted between HbA1c ≥6.5% and APGAR score at 5 min (p-value=0.0050), birthweight (p-value=0.0500), and macrosomia (p-value=0.0161).

Conclusion: The commonest indications for HbA1c testing at the study site were monitoring of GDM, high BMI and AMA. The sensitivity of HbA1c to detect adverse outcome is higher at 6.5%, however a value of >7.0% would achieve higher sensitivity if used for screening for adverse outcomes. HbA1c is associated with maternal and perinatal adverse outcomes making it a useful tool in the management of GDM.

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ABBREVIATIONS

ADA	American Diabetes Association
AOL	Augmentation of Labour
AROM	Artificial Rupture of Membrane
BMI	Body Mass Index
CEO	Chief Executive Officer
CPAP	Continuous Positive Airway Pressure
CS	Caesarean Section
DM	Diabetes Mellitus
ENND	Early Neonatal Death
FPG	Fasting Plasma Glucose
FSB	Fresh Still Birth
GDM	Gestational diabetes Mellitus
GHPT	Gestational Hypertension
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome
HbA1C	Haemoglobin A1C
ICU	Intensive Care Unit
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IDF	International Diabetes Federation
IOL	Induction of Labour
LGA	Large for Gestational Age
MMR	Maternal Mortality Ratio
MSB	Macerated Still Birth
MSL	Meconium Stained Liquor

NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NVD	Normal Vaginal Delivery
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovarian Syndrome
PLWD	People Living With Diabetes
POH	Poor Obstetric History
PPH	Postpartum Haemorrhage
PNMR	Perinatal Mortality Rate
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory Distress Syndrome
REDCaP	Research Electronic Data Capture
RMMCH	Rahima Moosa Mother and Child Hospital
SASOG	South African Society of Obstetricians and Gynaecologists
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SROM	Spontaneous Rupture of Membranes
USA	United States of America
T1DM	Type 1 Diabetes Mellitus
T2 DM	Type 2 Diabetes Mellitus
TOP	Termination of Pregnancy
WHO	World Health Organisation

CHAPTER 1: SUBMISSIBLE ARTICLE TO JOURNAL OF ENDOCRINE, METABOLISM AND DIABETES OF SOUTH AFRICA

TITLE: Correlation of HbA1c levels in pregnancy with maternal and perinatal outcomes at Rahima Moosa Mother and Child Hospital

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ABSTRACT

Background: Limited data exists regarding the prognostic value of glycated haemoglobin A1C (HbA1c) levels during pregnancy. This study investigates the indications for HbA1c testing at Rahima Moosa Mother and Child Hospital (RMMCH), including its correlation with both perinatal and maternal outcomes.

Methods: A retrospective analysis of 298 antenatal patient records with HbA1c tests at Rahima Moosa Mother and Child Hospital over months (January to March 2020) was conducted. Data were retrieved from the National Health Laboratory Service (NHLS) database and managed using REDCap. Descriptive and analytical statistics were performed using Stata statistical software version 15 (Stata Corp, Texas, USA).

Results: The majority of the women were between the age of 18 to 34 (n=199, 66.8%), African ethnicity (n= 215, 72,1%), had multiparity and class I obesity at booking (n=106, 43.1%). The commonest indication for HbA1c testing was body mass index at booking (BMI: n=135, 54.9%) , followed by gestational diabetes mellitus (GDM: n=96, 22.5%) and advanced maternal age (AMA: n=56, 13.1%). A significant relationship was noted between HbA1c ≥6.5% and maternal outcomes such as post-partum haemorrhage (PPH: p-value=0.0004) and diabetic ketoacidosis (p-value=0.0003). In terms of perinatal outcomes, a significant relationship was also noted between HbA1c ≥6.5% and APGAR score at 5 min (p-value=0.0050), birthweight (p-value=0.0500), and macrosomia (p-value=0.0161).

Conclusion: The commonest indications for HbA1c testing at the study site were monitoring of GDM, high BMI and AMA. The sensitivity of HbA1c to detect adverse outcomes is higher at 6.5%, however, a value of >7.0% would achieve higher sensitivity if used for screening for adverse outcomes. HbA1c is associated with maternal and perinatal adverse outcomes making it a useful tool in the management of GDM.

INTRODUCTION

The prevalence of gestational diabetes mellitus (GDM) in South Africa (SA) is estimated at 1.6% to 8.8% based on limited data and selective risk-based screening. [1] It complicates about 10% of all pregnancies globally. [2] GDM has increasingly become a global burden alongside the obesity endemic . [3]The World Health Organisation (WHO) classifies pregestational diabetes mellitus (PDM) as type 1 (T1DM) or type 2 (T2DM), and gestational diabetes mellitus (GDM) as severe hyperglycaemia during pregnancy. GDM is defined gestational diabetes mellitus (GDM)) as carbohydrate intolerance resulting in hyperglycaemia of varying severity with onset or first recognition during pregnancy. [4]

"Allen first recognised HbA1c in 1958 as component of human haemoglobin (Hb), while 10 years later Rahbar demonstrated the presence of an 'abnormal' Hb in diabetic patients." "In 1970, the first application of HbA1c was made, followed by the appearance of the first available method to measure HbA1c levels." "In 1993, the importance of HbA1c in the prognosis of DM related complications was demonstrated, and in 2010 HbA1c ≥6.5% was established as a diagnostic criterion for DM by the American Diabetes Association (ADA)." [5]

"HbA1c is a fragment formed by the binding of glucose to the C chain or D chain of haemoglobin A (HbA) because of the non-enzymatic catalysis of mature haemoglobin (Hb) and glucose." [6] "The synthesis of HbA1c is very slow and relatively irreversible. HbA1c can be maintained in the whole lifespan (120 days) of red blood cells." "The synthesis rate of HbA1c is positively rated to the glucose concentration of red blood cells and HbA1c levels reflect the mean blood glucose level within the past 8 to 10 weeks." [6]

The use of HbA1c as a diagnostic test offers the following advantages: no fasting is required, it is low-cost, reflects chronic hyperglycaemia, and remains stable in blood samples, making it a reliable indicator of long-term blood glucose concentration over three months. Additionally, the measurement can be made regardless of the time of day. [7] However, there are limitations to using HbA1c as a diagnostic test, as it measures glycation rather than directly measuring blood glucose levels. HbA1c may vary with age and ethnicity. People of African ethnicity may have a higher HbA1c level than Caucasians. [8] Evidence indicates HbA1c levels correlate differently with plasma glucose amongst African Americans when

compared to Caucasians, and about 10% of African Americans have a haemoglobin C trait that could interfere with HbA1c assay. [9] This might necessitate ethnicity-specific thresholds.

Standardization of HbA1c measurement has been improved through the introduction of the National Glycohemoglobin Standardization Program (NGSP) protocols, however, not all countries have achieved this. [10] Plasma glucose concentration is also difficult to assay with consistent accuracy. It is estimated that up to 12% of patients can be misclassified in the diagnosis of diabetes due to laboratory instrument error in measuring glucose. [11]

The lifespan of erythrocytes is reduced during pregnancy by approximately 17 days and has been reported to be between 90 to 120 days. HbA1c levels are low in the second trimester, plateauing at 20–24 weeks, followed by an increase in the third trimester. [12] Some conditions cause falsely decreased levels of HbA1c such as anaemia due to blood loss, haemolytic anaemia (by shortening the lifespan of erythrocytes), and splenomegaly as it leads to increased red cell turnover. [13] Conversely, certain conditions prolong the lifespan of red blood cells such as iron deficiency anaemia, vitamin B_{12} and folic acid deficiency anaemia (due to reduced erythrocyte proliferation) or functional asplenia due to decreased destruction of blood cells. Both an increase and decrease in erythrocyte lifespan could affect HbA1c levels. Furthermore, several drugs and substances such as salicylates, opioids and lead poisoning, have been reported to interfere with HbA1c levels. [14] These must be taken into consideration when interpreting HbA1c values.

The American Diabetes Association (ADA) suggested that HbA1c values of 5.7%–6.4% established a diagnosis of pre-diabetes, while a value of ≥6.5% defines diabetes in the general population. [15] However, Oral Glucose Tolerance Test (OGTT) remains the "gold standard" for the diagnosis of gestational diabetes (GDM), it detects 90% of PLWDs. In contrast, HbA1c ≥6.5% identifies 30–40% of previously undiagnosed PLWDs. [16] Although OGTT performs better in the diagnosis of GDM, the test is time-consuming, requires the patient to be fasting and uses multiple samples. [17]

In response to an International Expert Committee's, recommendation that the HbA1c assay be used for diagnosing diabetes in non-pregnant individuals, the Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) issued a position statement on the use of HbA1c assays for diagnosing diabetes mellitus. The report highlighted the advantages and limitations of HbA1c as a measure of chronic glycaemic levels and recommended a diagnostic cut point of ≥6.5% for diabetes diagnosis. [18]

GDM is diagnosed mostly using OGTT. [16] HbA1c has attracted interest as a possible monitoring and diagnostic technique, HbA1c shows average blood glucose levels over the previous 8 to 12 weeks. [6]Recent research has looked at how useful HbA1c is in pregnancy and how it relates to outcomes. Higher HbA1c values at 18 weeks gestation were linked, large-for-gestational-age newborns, preterm delivery, and preeclampsia among women without documented diabetes. [19] Even with third-trimester HbA1c levels optimised, research shows that increased HbA1c in early pregnancy was linked with negative outcomes in women with type 1 diabetes. [20] In Chinese women with GDM, Muhuza et al. (2023) found notable correlations between HbA1c ≥5.5% at GDM diagnosis and macrosomia, pregnancy-induced hypertension, premature delivery, and primary caesarean section. [21]

Despite multimodal prenatal diabetic treatment, infants of diabetic mothers in Qatar still had higher birth weight and macrosomia, according to Bayoumi et al. (2021). [22] Gojnic et al. (2022) underlined variations in pregnancy problems and outcomes between women with several forms of diabetes in Serbia. [23] Research on the value of HbA1c in pregnancy in different populations and resource- constrained environments is especially needed. With a population of South Africa where the prevalence of GDM is estimated to be between 1.6% and 8.8%, this study intends to fill in these gaps by looking at the relationship between HbA1c levels at different times in pregnancy and a spectrum of mother and perinatal outcomes. By doing this, we want to help create more efficient approaches for GDM diagnosis and management in environments with limited resources, hence possibly enhancing the results for mothers and their children.

The objectives of the study is to describe the demographics of all pregnant women in whom an HbA1c was tested between 1 January 2020 and 31 March 2020. And also describe the relationship of the HbA1c level with maternal and perinatal outcomes (up to 30 days). Unlike other studies that sometimes emphasise single time points or specific patient groups, our study investigates HbA1c levels throughout pregnancy in a varied, resource-limited environment. Including women with and without diagnosed diabetes will help us to offer a more complex picture of how HbA1c levels relate to outcomes over the whole range of glycaemic management. Moreover, this study expands on already conducted research by investigating these links in a population with inadequate data on GDM and HbA1c use, so providing perhaps useful information for other low- and middle-income nations. Our ultimate aim is to help create more efficient, context-appropriate techniques for GDM diagnosis and

management in resource-limited environments, therefore enhancing the results for women and children both in South Africa and elsewhere.

Materials and methods

Study Design

Examining the clinical records of pregnant patients at Rahima Moosa Mother and Child Hospital (RMMCH), this study was carried out as a retrospective cohort study. The study design led to a thorough investigation of HbA1c levels and their relationship with different mothers and perinatal outcomes, so offering important new perspectives on the management of diabetes during pregnancy in our context.

Study setting

RMMCH, a 388-bed regional hospital, serves as one of the primary teaching hospitals for the University of the Witwatersrand in Johannesburg, South Africa. Managing a volume of between 10,000 and 16,000 deliveries yearly, RMMCH is the only specialised mother and child institution in the area and among the busiest maternity departments in Gauteng. This great patient volume gave our study a large dataset that would enable a strong investigation of HbA1c levels and their effect on pregnancy outcomes over a heterogeneous patient population.

Study Sample and Sample Size

We investigated all pregnant women who had HbA1c tests at RMMCH between January 1 2020 and March 31 2020. This particular period of time was selected since it predates the start of the COVID-19 pandemic, thus reducing any possible confusing elements regarding changes in healthcare services and results brought about by the pandemic. The study included patients with pre-existing diabetes, GDM, and those under GDM screening among other backgrounds. We sought to portray a whole picture of HbA1c testing and its consequences in pregnancy treatment at our institution by encompassing this wide spectrum of patients.

Data Collection Tools

We used a multi-step technique to guarantee a methodical and exhaustive data-collecting procedure. First, we searched the National Health Laboratory Service (NHLS) database to get all HbA1c test findings recorded at RMMCH for the designated study period. This

comprehensive search allows us to identify all potential subjects, regardless of their diagnosis or the reasons for testing. We then accessed the medical records from the Medical Records Department of RMMCH using these hospital numbers. Every file was examined to verify the patient's pregnancy status at the time of the HbA1c test, a vital step that let us rule out non-pregnant women who might have received the test for another medical condition.

This screening approach guaranteed that our target group of expectant mothers was reflected in our study sample. We compiled the data including mother's age, parity, gestational age at delivery, body mass index (BMI) at booking, all HbA1c readings done throughout the antenatal period, risk factors for diabetes, and other pregnancy outcomes for all confirmed pregnant women. Based on the criterion given by the American College of Obstetricians and Gynaecologists (ACOG) in their Practice Bulletin Number 216, published in January 2020, we defined macrosomia in our analysis as a birth weight greater than or equal to 4000 grams. [24] This uniform definition guarantees comparison with other investigations and conforms with present clinical practice recommendations.

Description of analysis

Macrosomia was defined as a birth weight of 4000g grams or more. [24] Descriptive analysis was conducted for categorical variables by computing frequencies and percentages. Continuous data was assessed for normality using the Shapiro-Wilk test. Subsequently, normally distributed continuous variables were summarised with means and standard deviations. Non-normally distributed variables were presented as medians and interquartile ranges. The participants were divided into HbA1c (i.e., < 6.5%) and HbA1c (i.e., ≥6.5%).

Association between abnormal HbA1c, maternal and perinatal outcome categorical variables were assessed using the Fischers exact test as the small cell sizes precluded the use of the Chi-square test. The Mann-Whitney U (Rank sum) test was used to evaluate the association between abnormal HbA1c, and maternal and fetal outcomes for continuous variables. The performance of HbA1C in predicting adverse maternal and neonatal outcomes was assessed by Receiver Operating Curve (ROC) analysis. A p-value < 0.05 was statistically significant. Stata statistical software version 15 (Stata Corp, Texas USA) was used for all analyses.

Ethical consideration

Permission to conduct this study was obtained from the Chief Executive Officer (CEO) of RMMCH, the Academic Head of the Department of Paediatrics as well as the Academic

Head of the Department of Obstetrics and Gynaecology at the institution. Ethical approval for the study was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Approval number: M220275). The study was registered with the National Health Laboratory Service Academic Division and registered with the National Health Research Database (NHRD number:202201_007).

Results

There were 376 HbA1c samples tested during the study period, however, only 298 were included in this analysis. Sixty-two samples were excluded because they belonged to non-pregnant women and 16 files could not be found (Fig 1). Table I is a summary of the demographic characteristics of the study population. The majority of the women were between the age of 18 to 34 (n=199, 66.8%), African ethnicity (n=215, 72.1%) and had class I obesity at booking (n=106, 43.1%). The majority of women were multiparous. Almost all. women were booked (n=271, 91.0%) with a mean gestational age of 17 weeks. Just below one-fourth (n=71, 23.8%) tested Human Immunodeficiency Virus (HIV) positive. The majority of those (n=69, 97.2%) were on Antiretrovirals (ARVs) and most of them (n=62, 89.9%) were on Tenofovir, Emtricitabine and Efavirenz (TEE).

In this cohort of 298 patients, multiple indications prompted HbA1c testing (n=424). Notably, some patients had more than one risk factor for testing, however, the commonest indication for HbA1c testing was body mass index at booking (BMI: n=135, 54.9%) , followed by gestational diabetes mellitus (GDM: n=96, 22.5%) and advanced maternal age (AMA: n=56, 13.1%: Table II). A significant relationship was noted between HbA1c levels and diabetic ketoacidosis (p-value=0.0003) and PPH (p-value=0.0004). However, there was no significant association between HbA1c levels and maternal adverse outcomes such as caesarean section (p-value=0. 1578), perineal trauma (p-value=0. 0608) and hysterectomy (p-value=1.0000: Table III).

BMI was calculated for all participants using weight and height measurements taken at the first antenatal booking visit. Given weight varies greatly during pregnancy, this method was selected to give a consistent baseline measurement across all individuals. Since it reflects the pre-pregnancy or early pregnancy BMI, which is most pertinent for evaluating diabetes risk and possible pregnancy outcomes, the booking visit BMI was utilised for all further analyses in this study. We note that women who booked late in pregnancy may not fairly represent their pre-pregnancy BMI, so restricting our study's accuracy.

In terms of perinatal outcomes, there was a significant relationship between HbA1c and APGAR score at 5 min (p-value=0.0050), birthweight (p-value=0.0500) and macrosomia (p-value=0.0161) was noted. However, there was no significant relationship between HbA1c levels and perinatal outcomes such as neonatal respiratory distress syndrome (p-value=0.2337) and congenital anomalies (p-value=1.0000: Table IV). However, ROC curve analysis suggests that a cut-off of HbA1c 7% (Area under the Curve (AUC)=0.69) would perform better than 6.5% (AUC=0.62) if used as a screening test for poor outcomes in this cohort. Indeed, a 7% cut-off has the best balance between sensitivity (45.5%) and specificity (95.5%) and has the highest correct classification (74.5%) as shown in Figure 3 a-c.

Table I: Baseline characteristics of women in the study (n=298)

Description	Value
Age (years), median (IQR, range)	33.5 (30-37, 21-44)
Age categories, n (%)	
18 - 34	199 (66.8)
≥35	99 (33.2)
Race, n (%)	
African	215 (72.1)
Indian	25 (8.4)
White	9 (3.0)
Coloured	49 (16.5)
Parity, median (IQR, range)	2 (1-3, 0-5)
Parity categories, n (%)	
Parity 0	8 (2.7)
Parity 1	95 (31.9)
Multipara (2 to 4)	186 (62.4)
Grande-multipara ≥5	9 (3.0)
Gravidity, median (IQR, range)	3 (3-4, 1-8)
Gravidity categories, n (%)	
Gravida 1	5 (1.7)
Gravidity (2 - 4)	255 (85.6)
Gravidity ≥5	38 (12.7)
BMI (kg/m^2) at booking (n=246), median (IQR, range)	30.4 (28.2-33.2, 20.1-38.6)
BMI categories at booking, n (%)	
Underweight (<18.5)	1 (0.4)
Normal (18.5-24.9)	12 (4.9)
Overweight (25-29.9)	98 (39.8)
Class I obesity (30-34.9)	106 (43.1)
Class 2 obesity (35-39.9)	28 (11.4)
Class 3 obesity (≥40)	1 (0.4)
Not done	52 (17.4)

Booking status, n (%)	
Booked	271 (91.0)
Unbooked	27 (9.0)
HIV positive, n (%)	71 (23.8)
Last recorded CD4+ count (cells/µL) (n=71), median (%)	515 (189)
Last recorded Undetectable HIV-VL (copies/mL) (n=69), n (%)	59 (85.5)
ART regimen (n=69), n (%)	
TLD	7 (10.1)
TEE	62 (89.9)
EGA at booking (weeks), median (IQR, range)	17 (14-20, 8-41)
Gestation at first sonar, n (%)	
EUS (<21 weeks)	207 (69.5)
LUS (≥21 weeks)	55 (18.5)
Not done	36 (12.0)

n (Number), SD (Standard Deviation), IQR (Interquartile Range), BMI (Body Mass Index), VL (Viral Load), ART (Antiretroviral Therapy), TLD (Tenofovir, Lamivudine, Dolutegravir), TEE (Tenofovir, Emtricitabine, Efavirenz), EGA (Estimated Gestational Age), EUS (Early Ultrasound), LUS (Late Ultrasound).

Table II: HbA1c (n=298) testing

Description	**n (%) or mean (SD) or median (IQR, range)**
Indication for HbA1c tests(N=424)	
BMI at booking	135(54.9)
GDM screening	96 (22.6)
AMA	56 (13.2)
Previous Macrosomia	47 (11.1)
POH	33 (7.8)
Type 2 DM	32 (7.5)
Type 1 DM	19 (4.5)
Family history	19 (4.5)
Miscarriage	18 (4.2)
Stillbirth	13 (3.1)
Glucosuria	13 (3.1)
Polyhydramnios	10 (2.4)
Previous GDM	9 (2.1)
Thyroid diseases	9 (2.1)
Multiple pregnancies	4 (0.9)
SLE	3 (1.2)
Collapse in pregnancy	3 (1.2)
PCOS	2 (0.5)
Abruptio placenta	1 (0.2)
GHPT	1 (0.2)

n (Number), SD (Standard Deviation), IQR (Interquartile Range), OGTT (Oral Glucose Tolerance Test), HbA1C (Haemoglobin A1c), AMA (Advance Maternal Age), BMI (Body Mass Index), POH (Poor Obstetric History), GDM (Gestational Diabetes Mellitus), SLE (Systemic Lupus Erythematous) PCOS (Polycystic Ovarian Syndrome), GHPT (Gestational Hypertension).

Table III: Relationship of the HbA1c level with maternal outcomes

Description	n	HbA1c <6.5% n=133 n (%)	HbA1c ≥6.5% n=165 n (%)	P-value (Fisher's exact test)
Spontaneous labour	119	57 (42.9)	62 (37.6)	0.3771
IOL	125	55 (41.4)	70 (42.4)	0.9031
IOL method: Oral misoprostol	121	52 (39.1)	69 (41.8)	0.1989
IOL method: PV misoprostol (TOP)	9	2 (1.5)	7 (4.2)	0.1989
Poor progress of labour	16	4 (3.0)	12 (7.3)	0.1317
Placenta praevia	5	2 (1.5)	3 (1.8)	1.0000
Abruptio placenta	6	2 (1.5)	4 (2.4)	0.6927
Mode of delivery: CS	103	40 (30.1)	63 (38.2)	0.1578
Mode of delivery: NVD	195	93 (69.9)	102 (61.8)	0.1578
Perineal trauma	32	9 (6.8)	23 (13.9)	0.0608
PPH	77	21 (15.8)	56 (33.9)	0.0004
Hysterectomy	1	0 (0)	1 (0.6)	1.0000
Sepsis	3	2 (1.5)	1 (0.6)	0.5925
DKA	14	0 (0.0)	14 (8.5)	0.0003

n (Number), HbA1c (Haemoglobin A1C), IOL (Induction of Labour), PV (Per Vaginal), TOP (Termination of Pregnancy), CS (Caesarean Section), NVD (Normal Vaginal Delivery), PPH (Postpartum Haemorrhage), DKA (Diabetic Ketoacidosis).

Table IV Relationship of the HbA1c level with fetal and perinatal outcomes

Continuous Variables

Description	Total Median (IQR)	HbA1c <6.5% Median (IQR)	HbA1c ≥6.5% Median (IQR)	P-value*
Apgar at 5 mins	8 (7-9)	8 (8-9)	7 (6-8)	**0.0050**
Birthweight (g)	3500 (3200-3800)	3500 (3200-3700)	3600 (3200-3800)	**0.0500**
EGA at delivery by ACOG (weeks)	38 (37-39)	38 (37-39)	38 (37-39)	0.5900

Description	Total n	HbA1c <6.5% n (row %)	HbA1c ≥6.5% n (row %)	P-value*
Fetal outcome status	290			0.3319
- FSB	3	1 (0.8)	2 (1.8)	
- MSB	12	4 (3.0)	8 (4.9)	
- Born alive	275	127 (95.5)	148 (89.7)	
- Early pregnancy loss	8	1 (0.7)	7 (3.6)	
Admission to monitor for hypoglycaemia	92	36 (27.1)	56 (33.9)	0.2481
Respiratory distress	108	43 (32.3)	65 (39.4)	0.2337
Infection or sepsis	13	6 (4.5)	7 (4.2)	1.0000
Hyperbilirubinemia	21	13 (9.7)	8 (4.9)	0.1551
NICU admission	40	14 (10.5)	26 (15.7)	0.2546

Transitional care unit**	127	52 (39.1)	75 (45.5)	0.3541
Outcome	298			0.2047
- Death	18	5 (3.8)	13 (7.8)	
- Discharge	280	128 (96.2)	152 (92.2)	
Congenital anomalies diagnosed at birth	9	4 (3.0)	5 (3.0)	1.0000
Shoulder dystocia	2	0 (0.0)	2 (1.21)	0.5025
Anomalies diagnosed antenatally on scan	9	4 (3.0)	5 (3.0)	1.0000
Macrosomia	15	2 (1.5)	13 (7.9)	**0.0161**
Malpresentation	9	3 (2.3)	6 (3.6)	1.0000

P-values for categorical variables were calculated using Fisher's exact test. For continuous variables, the Mann-Whitney U test was used.

Transitional care unit is a neonatal high care.

n (Number), SD (Standard Deviation), IGR (Interquartile Range), FSB (Fresh Still Birth), MSB (Macerated Stillbirth), G (Grams), EGA (Estimated Gestational Age), ACOG (American College of Obstetrics and Gynaecology), NICU (Neonatal Intensive Care Unit).

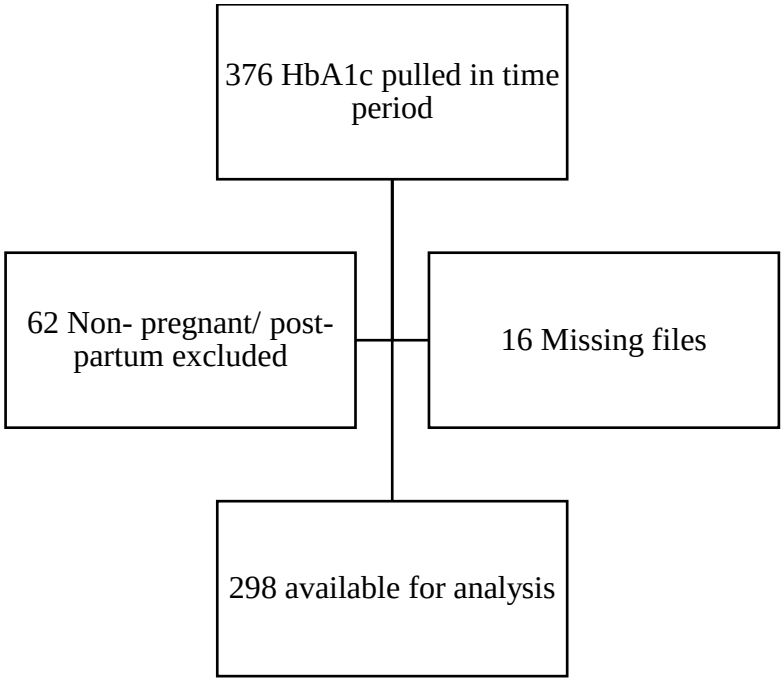

Figure 1: Depicts the flow chart outlining the study population

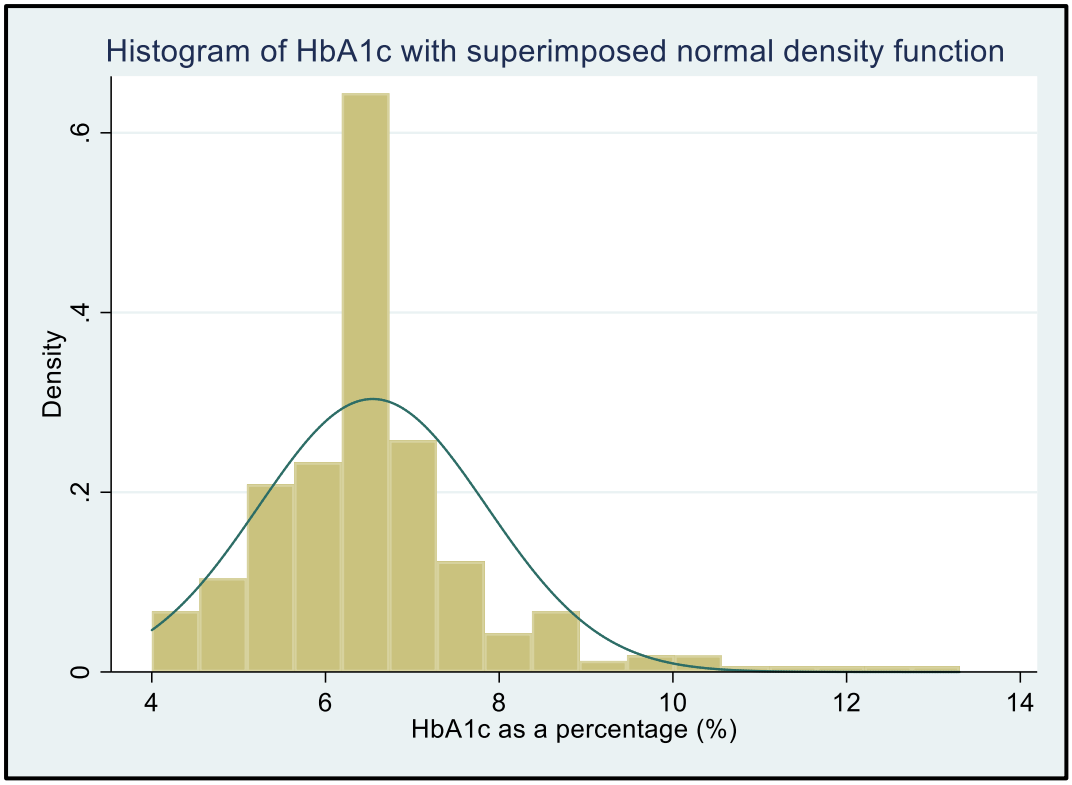

Figure 2: Histogram of HbA1c with superimposed normal density function

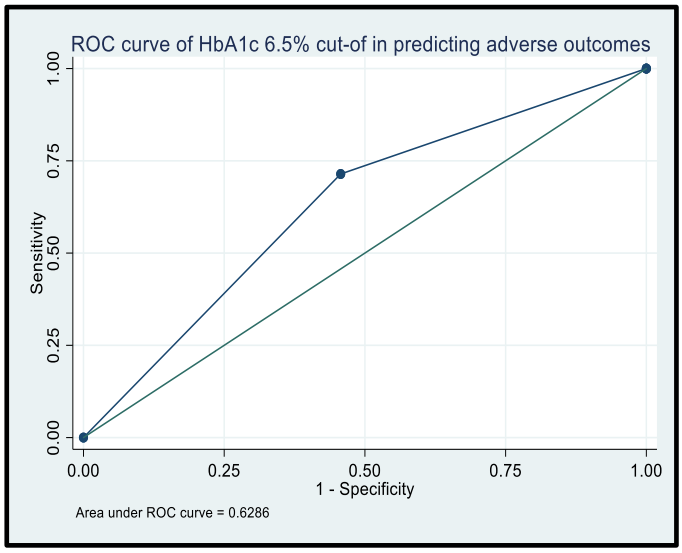

Fig 3a: ROC curve of HbA1c 6.5% cut-off in predicting adverse outcomes

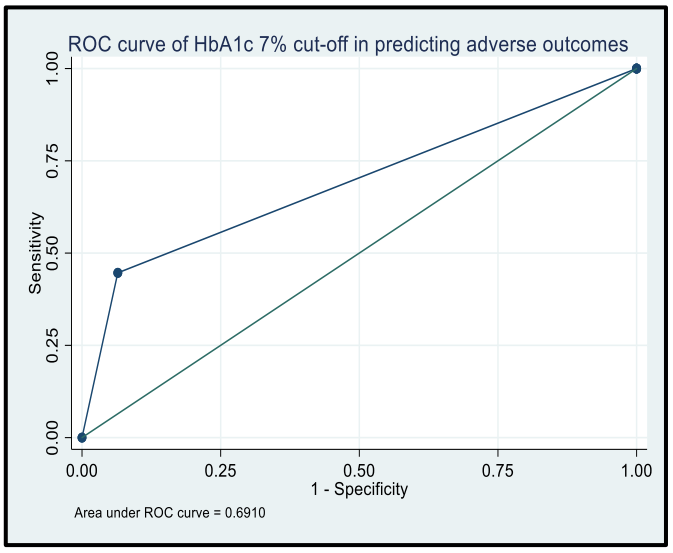

Figure 3 b: ROC curve showing HbA1c 7% cut-off in predicting adverse outcomes

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 4)	100.00%	0.00%	37.58%	1.0000	
(>= 5)	91.07%	9.68%	40.27%	1.0083	0.9226
(>= 6)	81.25%	33.87%	51.68%	1.2287	0.5536
(>= 7)	44.64%	94.62%	75.84%	8.3036	0.5850
(>= 8)	23.21%	100.00%	71.14%		0.7679
(>= 9)	11.61%	100.00%	66.78%		0.8839
(>= 10)	7.14%	100.00%	65.10%		0.9286
(>= 11)	4.46%	100.00%	64.09%		0.9554
(>= 12)	2.68%	100.00%	63.42%		0.9732
(>= 13)	0.89%	100.00%	62.75%		0.9911
(> 13)	0.00%	100.00%	62.42%		1.0000

Fig 3 c: Variation between sensitivity and specificity as the HbA1c cut-off point is increased from 4 to 13%

Figure 3a-c: Comparison of the performance of HbA1c 6.5% vs 7.0% cut-off in predicting adverse outcome

Discussion

This study investigated the utilization of HbA1c at RMMCH, including the rationale for testing and its correlation with perinatal and maternal outcomes. GDM has increasingly become a global burden alongside the obesity epidemic. [25] GDM has rapidly increased in SA, with the prevalence ranging from 1.6% to 25.8% between 1969 and 2018. [1] Risk factors related to developing diabetes such as economic development and increased urbanization associated with unhealthy diet and physical inactivity could have contributed to the above. [26]

Despite the democratic transition, RMMCH continues to cater primarily to the Coloured community. The majority of the patients in this study were from the African ethnicity (n=215, 72.1%). This is despite the hospital being situated in a historically Coloured-dominated area. We suspect that this finding has to do with the referral system because of the large number of African patients that are referred to this institution from the west of Johannesburg. The age of the study population is similar to that of Abeokuta and Port Harcourt Nigeria, in terms of the high number of younger women. [27] These results are also similar to national trends as per statistics S.A 2022 report stating that "Nearly 70% percent of all births in 2022 were from mothers aged 20–34 years. [28]

The commonest indication for doing an HbA1c in this study was for monitoring of GDM (n=96, 22.6%) and only a small proportion (n=43, 6.9%) for screening for GDM in women who had missed screening due to various factors. These were women with risk factors who presented either early in pregnancy with a miscarriage or presented at RMMCH after 28 weeks. The NICE guidelines propose using fasting plasma glucose and 2-hour plasma glucose for diagnosing GDM. [29] There are different opinions regarding the use of HbA1c for GDM screening. The NICE guideline believes that the sensitivity of HbA1c is too poor to replace OGTT. [29] On the contrary, the Royal College of Obstetricians and Gynaecologists (RCOG) encourages the utilisation of HbA1c as a complementary diagnostic tool to OGTT. [30] It acknowledges that the test is limited in terms of its sensitivity but highlights the advantages this method offers. Particularly, HbA1c provides a unique retrospective measurement of glucose control over the preceding weeks, unlike the point-in-time snapshot given by OGTT. This adds a layer of information and can help tailor treatments better. We

postulate that HbA1c is likely to perform better as a screening tool in women with undiagnosed pre-existing diabetes instead of GDM.

The results mirror the present clinical practice at RMMCH, which follows the South African Society of Obstetricians and Gynaecologists (SASOG) standards. [31] Using HbA1c in the study population especially for high-risk patients fits SASOG's recommendations for early diagnosis of overt diabetes or established GDM. When diabetes is discovered early in pregnancy, this strategy which entails checking fasting blood glucose and HbA1c at the first prenatal visit allows for timely intervention.

The study's findings highlight the challenges of screening for GDM in South Africa. Despite the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) advocating for universal screening, [32] these study captures the reality of limited resources in our environment. As advised for settings with limited resources, instead of universal screening we used a risk factor-based screening strategy. [33]Emphasising those most likely to develop GDM, this focused strategy enables more effective use of limited resources. But it also raises issues of possibly missing instances among women without clear risk indicators, so stressing the need for continuous assessment of our screening techniques.

Risk-based screening is advantageous due to its efficiency and specificity. By targeting those identified as high-risk, this screening approach makes effective use of medical resources, and can potentially reduce the risk of overdiagnosis and unnecessary treatment. [34] Conversely, the disadvantage of a risk-based screening lies primarily in its potential for missing those who have GDM who have not been screened because they did not have risk factors. [35]

Indeed, the large number of HbA1c tests carried out in the study cohort, including for illnesses not usually associated with regular HbA1c testing in pregnancy, is a remarkable result that calls for attention. This approach combines elements specific to the research environment with others. First, the frequency of obesity and other GDM risk factors in the population could have resulted in a lower HbA1c testing threshold for doctors. Secondly, even in cases when national or international recommendations do not usually indicate it, the limited resources in the environment may ironically result in the more frequent use of HbA1c as a reasonably affordable and accessible screening tool. For example, in cases of systemic lupus erythematosus (SLE), recurrent miscarriage, or unexplained collapse, doctors may have

employed HbA1c as a general metabolic screen, presumably in view of the limited availability of more specific assays.

Moreover, since some antiretroviral drugs can affect glucose metabolism, the high HIV prevalence in the community (23.8%) might help explain this pattern. Still, this approach raises serious issues concerning the distribution of resources and the possibility of overdiagnosis. Although in some cases HbA1c testing in these situations reveals undiscovered diabetes or prediabetes, the clinical value and cost-effectiveness of this method remain unknown. This finding highlights the necessity for further research on the significance of HbA1c in various obstetric situations outside its conventional usage in diabetes screening and monitoring as well as clearer local policies on HbA1c testing in pregnancy.

Universal screening ensures that no pregnant woman, regardless of her risk status, remains undiagnosed with GDM. Early detection ensures timely treatment, potentially abating the risk of adverse maternal and neonatal outcomes such as macrosomia and pre-eclampsia. [36] The disadvantages of universal screening include exerting a strain on the limited healthcare resources, particularly in low-income countries lacking robust healthcare infrastructures. Furthermore, universal screening may result in overdiagnosis, thereby leading to unwarranted interventions, causing unnecessary anxiety and possible iatrogenic harm. [37]

Over the last few decades, the prevalence of pregnancies in women of AMA has significantly increased worldwide. [38] This demographic shift has deep-seated ramifications on maternal and neonatal outcomes and raises the need to prioritise the timely diagnosis and management of GDM through equitable, evidence-based screening measures; like the OGTT. A study from Morocco found a correlation between AMA and the risk of developing GDM, fundamentally citing age as a significant risk factor. [39] It is important to note the causes of GDM are multifactorial, hence in this study we found that one patient had more than one risk factor for conducting OGTT.

SA is now regarded as one of the world's most obese nations. [3] Obesity is one of the major risk factors for the development of GDM, with a resulting increase in the risk of caesarean section, pre-eclampsia, and hypertension. [40] A majority of women (n=135, 54.9%) had an elevated BMI, a common indication for evaluating HbA1c levels during pregnancy. Additionally, we observed a higher prevalence of class 1 obesity among women (n=106, 43.1%) who underwent HbA1c testing. These findings align with previous studies that have also reported a significant association between BMI and abnormal levels of HbA1c levels. [41]

In 2023, a Korean study identified a significant correlation between obesity and elevated HbA1c levels, which significantly impacted pregnancy outcomes. [42] Weight gain is a crucial modifiable risk factor for GDM. Therefore, preventing weight gain prior to pregnancy appears to be a possible strategy for reducing the incidence of GDM.

There is no consensus on the cut-off levels of normal HbA1c values during pregnancy that is associated with adverse maternal and fetal outcomes. [43] Furthermore, different studies have used different cut-off values to predict adverse pregnancy outcomes. However, Versantvoort et al studied HbA1c levels in healthy pregnant women and concluded that the cut-off levels of HbA1c in the first, second and third trimesters were 5.4%, 5.5% and 5.8% respectively for predicting feto-maternal outcomes. [44] These variations in cut-off levels reflect the differences in study populations and the specific outcomes being investigated. It is crucial to consider these variations and limitations when interpreting the findings of studies that correlate HbA1c levels with maternal and fetal outcomes.

We suggest a cut of 7.0% for predicting adverse pregnancy outcomes. This finding highlights the importance of early intervention strategies for women in South Asia and Sub-Saharan Africa. This is in keeping with existing data which shows that below HbA1c of 7.0%, there is minimal risk of adverse outcomes, but the risk increases exponentially when HbA1c is above 7.0%. For instance, an HbA1c of 7-10% is associated with a 7.0% risk of adverse outcomes, whilst an HbA1c of 11.0% is associated with a 15.0% risk of adverse outcomes. [45] However, we cannot conclude that the best cut-off of HbA1c is 7.0% based on a single study. More studies are needed to determine the best cut-off levels of HbA1c in predicting poor pregnancy outcomes.

This study revealed a trend towards an association between HbA1c levels ≥6.5% and perineal trauma (13.9% vs 6.8%, p-value=0.0608), though it did not reach statistical significance at the conventional 0.05 level. This association could be attributed to factors such as an increased incidence of macrosomic babies or suboptimal birthing techniques, both of which contribute to this complication. Interestingly, a similar pattern was observed in a study conducted in Saudi Arabia. [46] In that study, a direct relationship was identified between macrosomia (≥4000g) and perineal trauma when HbA1c levels >6.1%. However, it's worth noting that our study utilized a higher threshold for HbA1c ≥6.5% compared to the Saudi study.

There is a significant association between HbA1c levels ≥6.5% and postpartum haemorrhage (PPH). Women with HbA1c levels ≥6.5% experienced a higher incidence of PPH compared to those with levels <6.5% (33.9% vs 15.8%, p-value=0.0004). This observation is consistent with Zhang et al.'s study, which found that women with GDM had an increased risk of PPH, supporting the concern that HbA1c levels above 6% pose a significant risk for PPH. [47]However, Zhang et al. only observed an increase in PPH with excessive gestational weight gain. The comparison between these studies is limited as only BMI at booking was used in our analysis.

Babies born to mothers with HbA1c ≥6.5% had notably lower Apgar scores at 5 minutes (p-value=0.0050). This corresponds with the results of an Italian study showing a direct association between Apgar scores <9 at five minutes and high HbA1c >7.0% during pregnancy. [48] Though statistically significant, the clinical relevance of this variation could vary as well. Though they may indicate some degree of difficulties in immediate postnatal adaption, Apgar scores between 6 and 8 are usually seen as reassuring. Either increased rates of caesarean birth in women with poorly controlled GDM or foetal hyperinsulinemia resulting in newborn hypoglycemia could moderate the connection between mother hyperglycaemia and worse Apgar scores. Future research should seek to clarify these processes and investigate treatments to enhance newborn outcomes in pregnancies affected by raised HbA1c. These results underline the requirement of ideal glycaemic management throughout pregnancy as well as the need for a whole approach to treat GDM including gestational weight increase. Future studies should try to separate the effects of hyperglycaemia and excessive weight gain on pregnancy outcomes, maybe by means of rigorous control of confusing variables in prospective trials.

This retrospective cohort study found that the likelihood of an adverse Apgar score increased with higher HbA1c levels. This association between elevated HbA1c and poor Apgar scores can be explained by the effects of maternal hyperglycaemia. Hyperglycaemia during pregnancy can lead to fetal hyperinsulinemia, resulting in macrosomia, which can complicate delivery and potentially lead to birth asphyxia, as reflected in a low Apgar score. We observed a strong link between elevated HbA1c levels (≥6.5%) and an increased occurrence of macrosomic babies, supported by consistent findings from prior studies. [49] In this study, elevated HbA1c levels >7.0% were a significant risk factor for macrosomia. However, our

study diverged from previous studies due to differences in demographics (specifically, the Indian population with a higher prevalence of overweight individuals, AMA, ethnicity association with diabetes and poor socioeconomic status) and a larger sample size.

Limitations

1. The short duration of three months might limit the generalizability of the findings to the entire population. A longer study duration would provide a more comprehensive understanding of the relationship between HbA1c levels and maternal and perinatal outcomes.

2. The retrospective nature resulted in missing files and incomplete medical records which can introduce bias and reduce the reliability of the data.

3. It is important to note that the study was conducted at a single centre. This raises the possibility of centre-specific factors influencing the results.

Conclusion

This study offers an insightful analysis of the use of HbA1c testing and its relationship with mothers and perinatal outcomes in South Africa. Our results show that adverse events especially postpartum haemorrhage, reduced Apgar scores, and macrosomia particularly postpartum haemorrhage, are much linked with HbA1c levels ≥6.5%. Particularly in resource-limited environments where more complicated testing may not be readily available, these relationships highlight the possible relevance of HbA1c as a tool for risk assessment and management in pregnancy.

At Rahima Moosa Mother and Child Hospital, the commonest indicators for HbA1c testing were monitoring GDM, BMI, and AMA. This is in line with advice from the SASOG and reflects the present clinical approach in our institution. On the other hand, the great number of HbA1c tests conducted for conditions not usually connected with normal HbA1c testing in pregnancy points to a need for more research on the value of HbA1c in different obstetric situations and clearer local guidelines.

Fascinatingly, our ROC curve study indicates that in our sample, a cut-off of 7.0% for HbA1c could outperform the standard 6.5% in terms of unfavourable outcomes prediction. Should this result be validated in more extensive prospective investigations, healthcare practice in related environments may be greatly impacted. It emphasises the possible requirement of

population-specific thresholds and the need to consider local settings while implementing international rules.

Although this study offers significant information on the use of HbA1c in pregnancy in a South African population, it also points out various areas of future research need. These include the need for prospective studies to confirm our conclusions, research on the long-term consequences of raised HbA1c in pregnancy, and evaluation of techniques for applying HbA1c testing in antenatal care protocols in resource-limited environments. Furthermore studies looking at the cost-effectiveness of several screening and monitoring techniques for GDM in the South African setting would be beneficial.

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Appendix A: Protocol.

2.1. Introduction

Gestational diabetes (GDM) is a metabolic disorder characterised by carbohydrate intolerance with onset or first recognised during pregnancy. It is due to inadequate insulin secretion or decreased insulin action (1). Pregnancy normally increases insulin resistance and leads to an increase in the pancreatic B-cell response to meet the increasing demands during pregnancy. When the B-cells fail to meet the demand it leads to (GDM) (2).

Diabetes mellitus (DM) is a common medical complication of pregnancy and it is associated with adverse maternal and perinatal outcomes. The prevalence of diabetes worldwide doubled since 1980 and the rate in the general population paralleled the rate in pregnancy (3). It complicates about 10% of all pregnancies globally (4). Gestational diabetes (GDM) is a metabolic disorder characterised by carbohydrate intolerance with onset or first recognised during pregnancy. It is due to inadequate insulin secretion or decreased insulin action (1). Pregnancy normally increases insulin resistance and leads to an increase in the pancreatic B-cell response to meet the increasing demands during pregnancy. When the B-cells fail to meet the demand it leads to GDM (2).

DM is a common medical complication of pregnancy and it is associated with adverse maternal and perinatal outcomes. The prevalence of diabetes worldwide doubled since 1980 and the rate in the general population paralleled the rate in pregnancy (3). It complicates about 10% of all pregnancies globally (4).

2.2. Prevalence

The pervasiveness of GDM in South Africa is assessed to be 1.6 - 8.8% dependent on particular risk factor-based screening (4). The prevalence varies depending on the population and diagnostic criteria used. The 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)guidelines recommends universal screening, according to which all pregnant women will be screened for GDM with the IADPSG criteria (4). However, South Africa is a low-middle income country. The increased cost of universal screening for GDM may not be affordable.

Diabetes during pregnancy can be divided into two subtypes: pre-gestational diabetes mellitus type 1 (T1DM) or type 2 (T2DM), and GDM (7). GDM usually constitutes around 90% of all pregnancies complicated by diabetes, while pre-existing diabetes accounts for the remaining 10%(8).

GDM is usually the result of β-cell dysfunction on a background of chronic insulin resistance during pregnancy and thus both β-cell impairment and tissue insulin resistance represent critical components of the pathophysiology of GDM. β-cell dysfunction is thought to be the result of prolonged, excessive insulin production in response to chronic fuel excess. β-cell dysfunction is exacerbated by insulin resistance. Reduced insulin-stimulated glucose uptake further contributes to hyperglycaemia, overburdening the β-cells, which have to produce additional insulin in response (5). Chronic insulin resistance occurs when cells no longer adequately respond to insulin. The rate of insulin-stimulated glucose uptake is reduced by 54% in GDM when compared with normal pregnancy (6).

The placenta also secretes leptin during human pregnancy, it primarily acts on neurons within the arcuate nucleus of the hypothalamus to decrease appetite and increase energy expenditure. Specifically, leptin inhibits appetite-stimulators neuropeptide Y and agouti-related peptide, and it activates the anorexigenic polypeptide pro-opiomelanocortin. In fact, the placenta is responsible for the majority of plasma leptin during pregnancy. Placental leptin production is increased in GDM, probably as a result of placental insulin resistance, and this further contributes to hyperleptinemia. This is also thought to facilitate amino acid transport across the placenta, contributing to fetal macrosomia (6). The placenta contributes to insulin resistance during pregnancy via its secretion of hormones and cytokines. As the barrier between the maternal and fetal environments, the placenta itself is also exposed to hyperglycaemia and its consequences during GDM. This can impact transport of glucose, amino acids, and lipids across the placenta. The receptiveness of the placenta to glucose uptake means that it is particularly sensitive to maternal hyperglycaemia, and this directly contributes to increased fetal growth and macrosomia (6).

GDM is associated with upregulated hepatic glucose production (gluconeogenesis). Gluconeogenesis is increased in the fasted state, and not adequately suppressed in the fed state. This is not believed to be entirely the result of inaccurate glucose sensing due to insulin resistance, as the majority of glucose uptake by the liver (~70%) is not insulin dependent. Increased protein intake and muscle breakdown may also stimulate the process by providing excess gluconeogenesis substrate. Despite this, the liver does not seem to be a primary pathogenic driver of type 2 diabetes mellitus(T2DM) or GDM (6).

2.4. Diagnosis of gestational diabetes

2.4.1. South African guidelines for diagnosis of gestational diabetes.

The 2013 diagnostic criteria for gestational diabetes in adult population.

Formal systematic testing for GDM is usually done between 24 and 28 weeks of gestation. To determine if GDM is present in pregnant women, a standard OGTT should be performed after overnight fasting (8–14 hours) by giving 75 g anhydrous glucose in 250–300 ml water (9). Plasma glucose is measured fasting and after 2 hours.

The diagnosis of GDM at any time during pregnancy should be based on any one of the following values: The criteria says one value is sufficient to make a diagnosis

- Fasting plasma glucose = 5.1-6.9 mmol/l.
- 1-h post 75g oral glucose load >=10.0 mmol/l.
- 2-h post 75g oral glucose load 8.5 – 11.0 mmol/l.

In 2017, the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) recommended risk factor-based selective screening at 24 - 28 weeks' gestation using the IADPSG criteria (10). Risk factors include advanced maternal age, obesity, a family history of DM, previous adverse pregnancy outcome, congenital abnormality, recurrent miscarriages, delivery of a stillborn child, delivery of a macrosomic baby in a previous pregnancy, certain ethnic backgrounds, or significant or persistent glycosuria (10). The diagnostic criteria are as follows:

- Fasting plasma glucose (FPG) ≥ 5.1- 6.9 mmol/l.
- One-hour post-glucose load (75 g) plasma glucose ≥ 10.0 mmol/l.
- Two hours' post-glucose load (75 g) plasma glucose ≥ 8.5-11 mmol/l.

One or more of these criteria must be satisfied for the diagnosis of GDM to be made (10).

Criteria for the diagnosis of diabetes from the American Diabetes Association in the adult population.

- Fasting plasma glucose of >7.0 mmol/L.
- OR 2-h Plasma glucose of >11.1 mmol/L during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

or HbA1c ≥ 6.5%.

or in a patient with classic symptoms of hyperglycemia or hyperglycaemic crisis, a random plasma glucose of>11.1 mmol/L (11).

2.5. The role of hemoglobin A1c (HbA1c) in pregnancy

2.5.1. Levels in pregnancy:

HbA1c is a special fragment formed by the binding of glucose to the C or D chain of haemoglobin A and as a result of non-enzymatic catalysis of mature haemoglobin (H and glucose. HbA1c can reflect the mean blood glucose level within past 8 to 10 weeks and is not affected by daily fluctuations in the blood glucose concentration (12).

It is lower in all three trimesters of normal pregnancy, although no consensus on the reference range of HbA1c in pregnant women at different period of gestation have been reached till now. To improve the adverse pregnancy outcomes in pregnant women with GDM, strict euglycaemic control of the blood glucose with treatment is needed (13).

2.5.2. HbA1c for diagnosis in pregnancy:

HbA1c has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress, changes in diet, or illness(14).However, these advantages may be offset by the lower sensitivity of HbA1c at the designated cut point, greater cost, limited availability of HbA1cesting in certain regions of the developing world, and the imperfect correlation between HbA1c and average glucose in certain individuals. The HbA1c test, with a diagnostic threshold of 6.5 %, diagnoses only 30 % of the diabetes cases identified collectively using HbA1c, FPG (patient fasted overnight from 22h00 and blood is taken in the morning before breakfast), or 2 hour plasma glucose(14).

2.5.3. HbA1c for monitoring in pregnancy:

Daily self-monitoring of blood glucose is recommended in all patients with diabetes in pregnancy and GDM for euglycaemic control. Measurement of blood glucose (fasting and post prandial) may not actually reflect the mean blood glucose levels. Thus, HbA1c may serve as an adjunctive parameter reflecting the mean blood glucose in pregnancy over last 3 months (15). The role of HbA1c in pregnancy with pre-gestational diabetes is well documented. In 2015 NICE guidelines recommend to measure HbA1c levels in all pregnant women with pre-existing diabetes at the first visit and also to consider measuring it in the second and third trimesters to assess the level of risk for the pregnancy (16). A recent study by Hughes et al, conducted in New Zealand among 16,122 pregnant women found an early pregnancy HbA1c 5.9% to be a clinically relevant marker for major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death, although the results could not be adjusted for potential confounding factors (17).

2.6. Effects of Gestational diabetes on the mother and the fetus:

During pregnancy placental hormones play a major role in developing insulin resistance, normal glucose metabolism after the removal of placenta post- delivery

(18). Most of the studies have focussed on HbA1c level at the time of screening for GDM in second trimester and the literature regarding HbA1c levels in third trimester with outcomes is very sparse (18).

GDM is associated with adverse pregnancy outcomes in the fetus like macrosomia, stillbirth and metabolic complications, maternal complications include lifetime risk of obesity and developing diabetes (19). Infants born to diabetic mothers are at risk for developing obesity, diabetes and metabolic syndrome in later years of life (20). Pregnancies complicated by diabetes are associated with significantly increased risks for both mother and child (21). Concerning mothers with type 1 diabetes the risks of pre-eclampsia (12.7%), caesarean section (CS) (44.3%) and maternal mortality (0.6%) are significantly higher than in mothers

without diabetes (20). Fetuses of women with diabetes in pregnancy have an increased risk for malformations, especially congenital heart disease and anomalies of the nervous system (22). This is due to poor glycaemic control during the period of organogenesis which occurs in the first trimester of pregnancy (23). Long term sequelae in offspring with in utero exposure to maternal hyperglycaemia include higher risks of obesity, impaired glucose metabolism and diabetes in later life (23).

As the role of HbA1c in GDM patients for prediction of maternal and fetal outcome has not been proven due to scarcity of data. The detection of gestational diabetes in pregnancy enables the identification of short term and long-term maternal complications. Use of appropriate diagnostic criteria to screen women for GDM will enable treatment and prevention of fetal and maternal complications and to improve pregnancy outcome.

2.7. Justification for research:

The prevalence of GDM, has increased by more than 30% within one or two decades in a number of countries, forming an emerging world- wide epidemic. HbA1c is done routinely in patients with diabetes and thus offers a useful marker to judge pregnancy outcomes with.

2.8. Aim:

The aim of the study is to describe the correlation of HbA1c levels in pregnancy with maternal and fetal outcome at RMMCH. The study will include all women who had HbA1c drawn from 1 January 2020 to 31March 2020.

2.9. Objectives:

2.9.1. Primary objectives:

1.To describe the relationship of the HbA1c level with maternal outcome.

2.To describe the relationship of the HbA1c level with fetal and neonatal outcome (upto 30 days).

2.9.2. Secondary objectives:

1.To describe the demographics of all pregnant women in whom an HbA1c was tested between 1 January 2020 and 31 March 2020.

2.10. Methods:

2.10.1. Study design:

This is a retrospective study in which the outcomes of a cohort of pregnant women with DM from RMMCH will be reviewed.

2.10.2. Study Setting:

This study will be conducted in the Obstetrics Department at RMMCH. RMMCH is a Regional hospital that serves as a referral centre for Region B and C Johannesburg. Surrounding facilities refer high risk cases to RMMCH.

2.10.3. Study sample, sampling and size:

This is a retrospective study of all diabetic pregnant women in whom an HbA1c was tested between 1 January 2020 and 31 March 2020. The study will involve about +/-150 patients

who had HbA1c taken during the study period. The maternal and fetal outcome of the pregnancy will be documented.

2.10.4. Data Collection:

The hospital numbers of the eligible women during the study period will be retrieved from the NHLS after searching for all HbA1c's in the time period. Then, the case notes will be retrieved from the Medical Records Departments of the hospital using the hospital numbers. A proforma containing information on the maternal age, parity, gestational age at delivery, Body mass index (BMI), and HbA1cmeasurements during prenatal period will be used to extract information from the case notes. Data regarding risk factors for diabetes and pregnancy outcomes will also be noted. The perinatal and pregnancy outcomes will be compared between pregnant women with normal HbA1c and abnormal HbA1c at RMMCH under the University of the Witwatersrand circuit in Johannesburg.

2.10.5. Inclusion Criteria:

HbA1c results available from the National health laboratory (NHLS) database during our study period.

2.10.6. Exclusion criteria

Patients without HbA1c taken during our study period in pregnancy.

2.10.7. Data analysis:

Data from case notes will be captured onto REDCaP (Research Electronic Data Capture) over a period of 3 months. Statistical analysis will be conducted in consultation with a

biostatistician. Categorical variables will be described using frequencies and percentages. Parametric data if normally distributed will be described using mean and standard deviation. Non-parametric data or data that are not normally distributed will be described using median, interquartile range. Chi-squared or Fisher's Exact tests will be used to compare categorical variables'. Numerical data will be compared using either an unpaired t-test or a Mann-Whitney as appropriate. A p-value of <0.05 will be considered significant. Data analysis will be done over a period of 3 months with the help of the statistician from university of Witwatersrand.

2.11. Ethics.

Permission to perform this study will be obtained from the CEO of RMMCH, the Academic Head of the Department of paediatrics as well as the Academic Head of the Department of Obstetrics and Gynaecology at RMMCH.

Approval will also be sought from the University of the Witwatersrand Human

Research Ethics Committee before the data collection commences. Register with

National health laboratory service academic division.

2.12. Funding.

Any funding will be financed by the primary investigator.

To attend conferences	R5 000
Printing	R5 000
Publications	R 5 000
Total	R 15 000

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Appendix B: Data collection sheet.

Last Normal Menstrual Period	Sure
	Unsure
Booking status	Booked
	Unbooked
	Gestational Age at first booking
First Ultrasound Date	Early Scan
	Late Scan
Gestational age at booking by ACOG	
Estimated date of delivery	
Any Anomalies	Yes
	No

Birth weight (intergrowth 21)	
Age	
Race	
Gravidity	
Parity	
BMI	
Date of test (HBA1C)	
Values of HbA1c	First reading
	Last reading
OGTT	Reading
	Trimester
	Risk factor for conducting OGTT
Pre-eclampsia	
Covid status	
Steroid use	
Thyroid disease	
Asthma	
Dietician consult	Yes
	No
Diabetic diet	Yes
	No
	Controlled or Uncontrolled
Glucophage	Date started

	Final dose recorded
	Controlled or uncontrolled
Insulin	Date started
	Final dose recorded Controlled or uncontrolled
HIV Status	Reactive
	Non-reactive
Last CD4 count recorded	
Viral load last recorded	
ARV regimen	TLD
	TEE
	Other

Progress of labour	
Spontaneous labour	Yes
	No
Induction of labour	Method used
	Bishop score
Shoulder dystocia	Yes
	No
Cephalo-pelvic disproportion	Yes

	No
No progress	Yes
	No
Malpresentation	Yes
	No
Macrosomia	Yes
	No
Placenta praevia	Yes
	No
Abruptio placenta	Yes
	No
Polyhydramnios	Yes
	No
Spontaneous rupture of Membranes	Yes
	No
Modes of delivery	
C/section: Indication	Fetal distress
	Or other indications
Vaginal	Normal
	Vacuum
	Forceps
Perineal trauma	Yes
	No

Maternal outcome of the pregnancy	
Acute complications	
Post-partum haemorrhage	Yes
	No
Uterine rupture	Yes
	No
Hysterectomy	Yes
	No
Diabetic ketoacidosis	Yes
	No
Intermediate complications	
Infections/ Sepsis	Yes
	No
Late Complications	
Death	Yes
	No
Critical care needed	
High care	Yes
	No
ICU	Yes
	No

Fetal Outcome	
Alive	Yes
	FSB
	MSB
Birth Weight	
Date of delivery	
Apgar at 5 min	
Gestational age using ACOG	
Any admission for Hypoglycaemia	
Respiratory distress syndrome	Surfactant
	Nasal prongs
	Intubation
	CPAP
Hyperbilirubinemia	Yes
	No
	Light therapy
	Exchange transfusion
Abnormalities diagnosed post-delivery	
NICU admission	
High care admission	
Transitional care unit	

Date of discharge	
Date of death	

Appendix C: Hospital Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Rahima Moosa Mother and Child Hospital
Enquiries: Adjunct Professor Ashraf Coovadia
Tel: 011 470 9284/9100
Email: Karen.Marshall@wits.ac.za

TITLE OF RESEARCH PROJECT:

"CORRELATION OF HBA 1c IN PREGNANCY WITH MATERNAL AND PERINATAL OUTCOME AT RAHIMA MOOSA MOTHER AND CHILD HOSPITAL"

NAME OF SUPERVISOR:
Dr Amy Wise

NAME OF RESEARCHER:
Dr Esrom Motjela

NHRD REF NO: GP_202201_007

Dear Dr Motjela,

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail. Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form to ensure that the terms of this agreement are always complied with.

Yours sincerely,

DR FREW BENSON
Acting Chief Executive Officer
Rahima Moosa Mother and Child Hospital
Date: 2022/01/28

Appendix D: Ethics Approval

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE

NO. M220275

NAME: (Principal Investigator)	Dr ED Motiela
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	Correlation of HbA1c levels in pregnancy with the maternal and perinatal outcome at Rahima Moosa Mother and Child Hospital
DATE CONSIDERED:	2022/02/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs A Wise, R Dawa and Z Bayat

Dr CB Penny, Chairperson, HREC (Medical)

APPROVED BY:

DATE OF APPROVAL: 2022/04/08

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

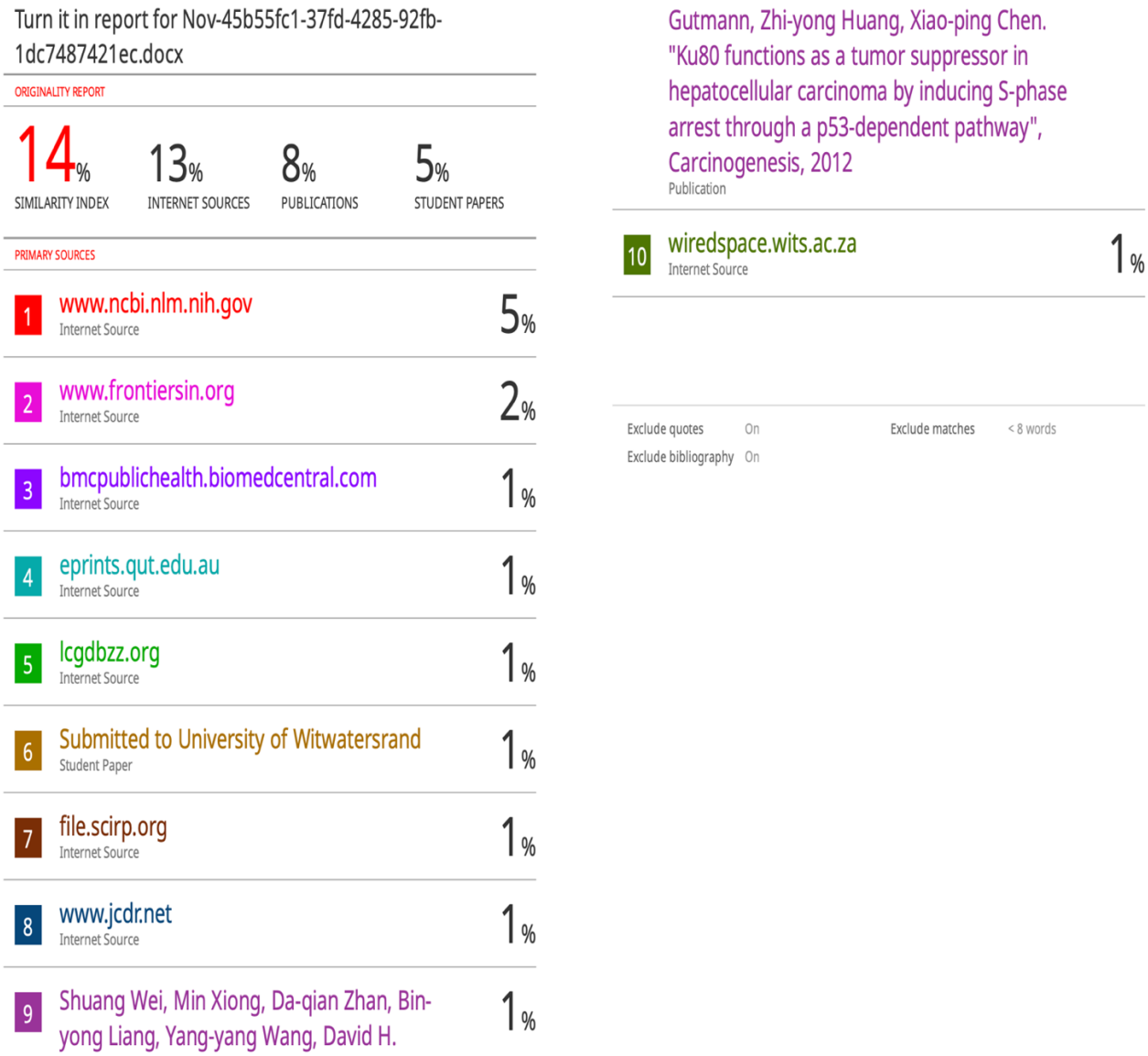
To be completed in duplicate and ONE COPY returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in February and therefore reports and re-certification will be due in the month of February each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

10/04/2022

Signature of Principal Investigator Date

Appendix E: Turnitin plagiarism report.



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Appendix F: Guidelines for Journal of Endocrine, Metabolism and Diabetes of South

Africa.

Guidelines for manuscript preparation.

1. Please consult the "Uniform requirements for manuscripts submitted to biomedical journals" at www.icmje.org
2. The submission must be in UK English, typed in Microsoft Word with no double spaces after the full stops, double paragraph spacing, font size 12 and font type Times New Roman
3. All author details (full names, qualifications and affiliation) must be provided.
4. The full contact details of corresponding author (tel, fax, e-mail, postal address) must be on the manuscript.
5. There must be an abstract and five keywords.
6. References must be strictly in Vancouver format. (Reference numbers in the text must be strictly numerical and be typed in superscript, not in brackets and must be placed AFTER the full stop or comma.)
7. Please consult the guide on Vancouver referencing methods at:http://www.nlm.nih.gov/bsd/uniform_requirements.html
8. It must be clear where every figure and table should be placed in the text. If possible, tables and figures must be placed in the text where appropriate. If too large or impractical, they may be featured at the end of the manuscript or uploaded as separate supplementary files.
9. All photographs must be at 300 dpi and clearly marked according to the figure numbers in the text. (Figure 1, Table II, etc.)
10. Scientific measurements: These should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above.
11. All numbers below ten, without percentages or units, must be written in words.
12. Figure numbers: Arabic; Table numbers: Roman,
13. Abbreviations: These should be spelt out when first used in the text and thereafter used consistently.
14. The submission must be reviewed by a language expert proficient in UK English.

Appendix G: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

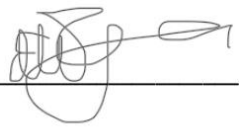
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Esrom Dimakatso Motjela (Student number: 0705057X) am a student registered for the degree of Masters in Obstetrics and Gynaecology in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 19/09/2024