Comparing Screening Strategies for Gestational Diabetes in a South African Population

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By

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Lastly, but most importantly I would like to thank my husband Zubair for his unwavering support, without whom I would not have achieved this.

Dedication

This work is dedicated to those who believed in me even when I stopped believing in myself.

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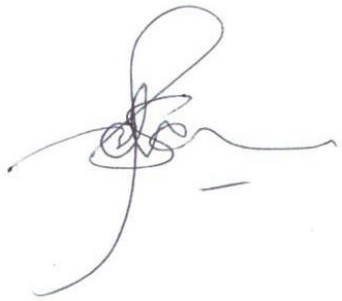
List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ANOVA	Analysis of Variance
AUROC	Area Under the Receiver Operating Curve
BAP	Bland-Altman Plot
BMI	Body Mass Index
CI	Confidence Interval
CRH	Corticotrophin Releasing Hormone
CRP	C-Reactive Protein
CV	Co-efficient of Variance
DM	Diabetes Mellitus
FIGO	International Federation of Gynecology and Obstetrics
FPG	Fasting Plasma Glucose
FPR	False Positive Rate
GDM	Gestational Diabetes Mellitus
GH	Growth Hormone
HAART	Highly Active Anti-Retroviral Therapy
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes
HbA1c	Glycated Haemoglobin
HIV	Human Immunodeficiency Virus
HOMA-IR	Insulin Sensitivity Index
hPL	Human Placental Lactogen
IADPSG	International Association of Diabetes in Pregnancy Study Groups
IDF	International Diabetes Federation

IDI	Integrated Discrimination Improvement
IR	Interquartile Range
ISO	International Organisation of Standards
MUAC	Mid-upper Arm Circumference
NICE	National Institute of Care Excellence
NRI	Net Reclassification Index
OGTT	75g-2-Hour-Oral Glucose Tolerance Test
OR	Odds Ratio
POC	Point-of-Care
QUICKI	Quantitative Insulin Sensitivity Check Index
RBG	Random Blood Glucose
ROC	Receiver Operating Characteristic
SA	South Africa
SANAS	South African National Accreditation System
SE	Standard Error
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organisation

Declaration

I, Sumaiya Adam, hereby declare that the work on which this thesis is based is original and my own work (except where acknowledgements indicate otherwise), and that neither the whole work or any part of it has been, is being, or shall be submitted for another degree at this or any other institution.



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Sumaiya Adam

On 30th day of November 2017

Executive Summary

Globally, there is an alarming increase in the incidence of Type II diabetes mellitus (T2DM). It is well recognized that women who develop gestational diabetes (GDM) in their pregnancies are at increased risk of T2DM in later life. In addition, poor glycaemic control in pregnancy impacts adversely on the neonatal outcome, as well as the long term disease risks of that child. The risk of these outcomes increases continuously as maternal fasting plasma glucose levels increases. Several adverse outcomes have been associated with DM during pregnancy. These include pre-eclampsia, polyhydramnios, fetal macrosomia, fetal hepatomegaly and cardiomegaly, birth trauma, operative delivery, perinatal mortality and neonatal respiratory problems and metabolic complications such as hypoglycaemia, hyperbilirubinaemia, hypocalcaemia and polycythaemia.

Despite five decades of research there is little consensus regarding the optimal approach to screening for GDM. Recently most international organisations have recommended that all women should be screened for GDM. South Africa is a diverse multi-racial society with an increasing burden of non-communicable diseases. The health system is already overburdened, and the optimal approach to screening for GDM remains unclear.

A **prospective cohort observational study** was conducted at the Eyethu Yarona clinic (Lion Park Clinic), in Johannesburg, South Africa (SA). One thousand (1000) consecutive non-diabetic women who were less than 26 weeks pregnant were recruited. At recruitment the women completed a demographic questionnaire, and had a random glucose and glycated haemoglobin (HbA1c) drawn. A fasting blood glucose

was assessed within 2 weeks, and a serum specimen was frozen at -40°C for further testing at a later stage.

Patients had a 75 g 2-hour oral glucose tolerance test (OGTT) and HbA1c between 24 – 28 weeks gestation. All glucose measurements were done at the laboratory using standardized tests (venous blood) and on a Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) (capillary blood). GDM was diagnosed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria, i.e. any one abnormal reading was diagnostic of GDM: 0-hour ≥5.1 mmol/l, 1-hour ≥10 mmol/l, or 2-hour ≥8.5 mmol/l.

Thereafter a **nested cohort study** of HIV negative patients was conducted to investigate the association between the concentrations of biomarkers associated with glucose homeostasis and GDM in a South African population. C-reactive protein (CRP), adiponectin, and fasting insulin were measured on the stored serum samples. The Insulin Sensitivity Index (HOMA-IR = fasting insulin (microU/L) x fasting glucose (mmol/L) / 22.5), and Quantitative Insulin Sensitivity Check Index (QUICKI = 1 / [log (I_0) + log (G_0)]) were calculated for further evaluation of markers of insulin sensitivity.

The significance of this research was to assess the burden of disease of GDM in a South African population. The different diagnostic criteria were also compared, as well as the universal versus the traditional risk-factor based screening approach to GDM. Screening methods were compared so as to propose a simple, effective, cost efficient screening and diagnostic tool that may be implemented at primary health care level, which will in turn identify those pregnant women who warrant referral to a high care obstetric unit, thus improving both maternal and neonatal outcomes in our population.

Keywords

- gestational diabetes
- selective screening
- prediction model
- nomogram
- glucometer
- accuracy
- point-of-care testing
- biomarkers
- adiponectin
- insulin

Chapter 1

Introduction

Literature Overview:

Pregnancy is characterized by insulin resistance and hyperinsulinemia. Thus, it may predispose some women to develop gestational diabetes mellitus (GDM). Placental secretion of diabetogenic hormones such as growth hormone (GH), corticotrophin releasing hormone (CRH), human placental lactogen (hPL), and progesterone may predispose the pregnant women to insulin resistance. In addition, increased maternal adipose deposition, decreased exercise, and increased caloric intake may contribute to the problem. These metabolic changes ensure that the fetus has an ample supply of fuel and nutrients. GDM occurs when pancreatic function is insufficient to overcome the insulin resistance created by changes in diabetogenic hormones during pregnancy. [1] Diabetes mellitus (DM) diagnosed for the first time during pregnancy may be further categorized as gestational or overt.

Globally, there is an alarming increase in the incidence of Type II DM and DM is rapidly emerging as a major public health problem. DM and less serious forms of glucose intolerance are widespread in almost every population in the world. In 2000 about 17 million people worldwide had some form of DM. By 2030 an estimated 361 million people will be affected by this condition. [2] Data from South Africa on the prevalence of Type 2 DM varies from 3 – 28%. [3]

The incidence of GDM ranges from 14 - 35% when the International Federation of Gynecology and Obstetrics (FIGO)/World Health Organisation (WHO) criteria is applied. [4] The exact incidence of GDM in a South African population is as yet unknown. Incidence of GDM varies with the prevalence of Type 2 DM. Estimates of GDM vary between 7.3- 8.8%. [5]

During the last decade there has been increasing evidence suggesting that women with GDM are at increased risk of developing DM and the metabolic syndrome later in life. DM and its complications are largely preventable through relatively simple lifestyle interventions. In addition, poor glycaemic control in pregnancy impacts adversely on the neonatal outcome, as well as the long term disease risks of that child. The risk of these outcomes increases continuously as maternal fasting plasma glucose levels increases. Several adverse outcomes have been associated with GDM. These include pre-eclampsia, polyhydramnios, fetal macrosomia, fetal hepatomegaly and cardiomegaly, birth trauma, operative delivery, perinatal mortality and neonatal respiratory problems and metabolic complications such as hypoglycaemia, hyperbilirubinaemia, hypocalcaemia and polycythaemia. [6]

A diagnosis of GDM identifies a mother at high risk for the future development of Type 2 DM. The effects of maternal hyperglycaemia are associated with the development of metabolic problems including Type 2 DM in the offspring. [7] It has been shown that the treatment of GDM improves pregnancy outcomes. In the ACHOIS [8] trial the incidence of serious perinatal complications was 4% among women randomized to routine care compared to 1% in the intervention group. The number of GDM cases that needed to be treated to prevent one serious complication was 34. Failure to identify the women with GDM denies her the opportunity to have treatment for potentially preventable, serious fetal complications.

Historically, the screening of GDM has been shrouded in controversy. No simple, effective, universally-accepted screening method currently exists. Fifty years ago Mahan and O' Sullivan proposed the 1-hour 50 g oral glucose tolerance test. [9] Traditionally diagnostic criteria for GDM were based on long term risk of development

of diabetes mellitus after pregnancy, rather than the risk of adverse perinatal outcomes. Whilst there is consensus that overt diabetes in pregnancy is associated with adverse outcomes, the risk of lesser degrees of hyperglycaemia remains controversial.

Despite five decades of research there is little consensus regarding the optimal approach to screening for GDM. The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) [10], a large multi-center study, established a relationship between maternal hyperglycaemia and adverse outcomes. However, as associations with adverse outcomes were continuous with no obvious glucose thresholds at which risk increased, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) worked with the HAPO outcomes to translate the results of the HAPO study into clinical practice, and recommend new GDM diagnostic thresholds. [11] HAPO data showed a strong linear relationship with birth weight >90th percentile, cord C-peptide, and percent body fat. These outcomes were used to determine potential glucose levels as diagnostic thresholds. [10, 11] Following stepwise considerations the IADPSG recommended the diagnostic thresholds of 5.1 mmol/l, 10 mmol/l, and 8.5 mmol/l at 0-hour, 1-hour, and 2-hour respectively, for the diagnosis of GDM. [11] These thresholds represent glucose values at which the odds of adverse outcomes are 1.75 times the estimated odds of adverse perinatal outcomes at similar mean glucose values. [11]

Most recently the World Health Organisation (WHO) as well as most prominent international organisations (including FIGO), with notable exceptions being American College of Obstetricians and Gynecologists (ACOG) and National Institute of Care

Excellence (NICE), endorsed universal screening for GDM. [12] The WHO/FIGO supports the criteria recommended by the IADPSG.

They further suggest that the decision as to whether universal or selective screening be employed should be based on local circumstances and disease patterns. [12] Some low-income countries like India, that face similar heath challenges as SA have investigated the use of random or fasting glucose levels, the role of HbA1c in screening, and the use of scoring systems. [12] Furthermore, FIGO advises that point-of-care devices can be used if laboratories are not readily available. [12] However, the use of glucometers has varying efficacy. [13-15]

Identification of markers that will allow early diagnosis of women at increased risk of GDM early in pregnancy is desirable, as it will allow for interventions such as diet and exercise to be implemented, thus reducing the negative impact on the mother and the fetus. [12] Current diagnosis of GDM is based on a 75 g 2-hour oral glucose tolerance test (OGTT) performed between 24 and 28 weeks gestation, which is an expensive, invasive, time-consuming test that requires an overnight fast and involves multiple hospital visits. In addition, GDM is diagnosed in the late second trimester by when damage to the mother and fetus may have already occurred.

Improved methods and new markers for screening for GDM are required to increase the diagnosis rates and prevent maternal and neonatal morbidity. Endocrine/metabolic, pro-inflammatory mediators, markers of oxidative stress and epigenetic markers are strongly associated with abnormal lipid and carbohydrate metabolism, obesity and cardiovascular disease. [1, 16-19]

The primary difference in protein levels in plasma is due to disease. Specifically regulated proteins in plasma can be used for the diagnosis of GDM. GDM and DM

are potentially linked to inflammatory and prothrombotic activity. Lower adiponectin and greater C-reactive protein (CRP) levels have been associated with incident DM and GDM. [20] Pregnancy is a state of insulin resistance. Increased insulin levels are seen in patients with GDM.

South Africa is a diverse multi-racial society with an increasing burden of non-communicable diseases. The health system is already overburdened, and the optimal approach to screening remains unclear. Furthermore, the standard for screening and diagnosis of GDM remains the cumbersome and time-consuming 75 g 2-hour oral glucose tolerance test (OGTT), which at present is not done at the primary health care centers. In addition, there is no consensus regarding the optimal screening strategy for GDM in our population.

Therefore, if we accept that GDM is a diagnosis worthy of consideration, then as many women as possible should be tested for this problem. Adequate diagnosis of GDM can only be achieved through universal screening. The prevalence of risk factors has increased in the last decade. GDM has been increasingly diagnosed in women without risk factors who still remain at risk of adverse outcomes. [21] However, it is well known that women with GDM have certain definable risk factors. The main concern with selective screening based on historical and clinical risk factors is that most studies have found that if such a system were used, a significant proportion of GDM cases would be missed. [22-24] Additional data demonstrates that women without risk factors are no less prone to the complications of GDM. Weeks et al. [25] have found that the rates of macrosomia, caesarean section and shoulder dystocia are similar to those in women with GDM who have risk factors.

Current screening tests for GDM are inconvenient. Therefore, alternate screening tests for GDM are desirable. The use of glycated haemoglobin A1C (HbA1C) in screening for GDM remains controversial. Recent studies addressing the use of HbA1c in the diagnosis of GDM report discrepant conclusions regarding specificity and sensitivity of HbA1C as a screening tool. [26-27] Thus, current recommendations suggest that HbA1C be used as an adjunct in the screening of GDM.

Screening for GDM is contentious. There is little consensus and a single universally accepted guideline does not yet exist. South Africa has a multi-racial population with an increasing incidence of Type 2 DM. Data regarding GDM in the South African population is sparse. Thus it is necessary to investigate GDM in our population and develop guidelines outlining the most cost-effective and efficient screening strategy for our population.

Rationale for this Study:

DM and its complications are largely preventable through relatively simple interventions. The goals of diabetes prevention include delaying the onset of DM, preserving pancreatic β-cell function, preventing microvascular complications and preventing the associated increased risk of cardiovascular disease. There are low cost interventions with proven effectiveness, such as random glucose, fasting glucose and the use of scoring systems [12], that can reduce the impact of diabetes, whilst simultaneously addressing risk in other disease areas. The cost of intervening will be cheaper than not intervening and an investment in diabetes brings health gains in other areas.

Gestational diabetes mellitus (GDM) is carbohydrate intolerance of variable severity, which is first diagnosed during pregnancy. It occurs in about 3% of pregnancies. [27] Untreated or poorly controlled GDM can result in increased perinatal morbidity and mortality, and maternal complications at birth. While the GDM usually "goes away" after birth, it is an independent risk factor for Type 2 DM in later life. Further, infants of GDM pregnancies carry a higher risk of obesity and diabetes in later life. [29]

Historically, the screening of GDM has been shrouded in controversy. As yet there is insufficient evidence for or against universal screening. Available screening methods are time consuming and costly to the patient and the health system. Markedly elevated maternal glucose levels most often occur in women with pre-gestational DM. The additional risk for adverse health outcomes attributable to the milder degrees of maternal hyperglycaemia associated with GDM and the magnitude of the benefit of treating that risk are less certain.

SA is faced with a dual burden of disease with very little available information regarding GDM. However, with an increase in the sedentary lifestyle, obesity, and delayed childbearing the prevalence of GDM is on the increase. Thus there is a need to establish the burden of GDM, as women with GDM are at increased risk of adverse perinatal outcomes, as well as long-term risk of developing type 2 diabetes mellitus. Without an effective screening strategy, we will face an increase in maternal and perinatal adverse outcomes associated with undiagnosed and poorly controlled GDM.

However, South Africa is a low-middle income country. The increased cost of universal screening for GDM may not be affordable. In addition, women book late and often do not attend their antenatal visits as recommended. Thus there is need to identify women at risk of GDM as early in the pregnancy as possible. Alternatives to universal screening to identify women at high risk of developing GDM, such as the use of random or fasting glucose, the role of HbA1c, the applicability of point-of-care devices for the diagnosis of GDM, as well as novel screening tools such as scoring systems and biomarkers need to be explored in a South African population.

Aims:

[1] To determine the prevalence of GDM in a South African population. The prevalence of GDM was compared using the various diagnostic criteria. The risk factors associated with GDM were also compared.

[2] To develop a clinical prediction model for GDM in a South African population, and to evaluate the performance of the published prediction tools on our study population. The introduction of such a prediction tool would reduce the number of OGTTs, hence decreasing the workload and financial burden on an overburdened healthcare system.

[3] To investigate the performance of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany), which is the most commonly available point-of care-device in our setting, in the diagnosis of GDM.

[4] To investigate the association between the concentrations of biomarkers associated with glucose homeostasis and GDM in a South African population.

Methods:

A prospective cohort observational study was conducted at the Eyethu Yarona clinic (Lion Park Clinic), in Johannesburg, South Africa (SA). One thousand (1000) consecutive Black African women who were less than 26 weeks pregnant were recruited. Gestational age was determined by last normal menstrual period, early ultrasound performed before 24 weeks gestation, or an early symphysis fundal height measurement. Women known with overt diabetes mellitus (Type I or Type II) were excluded.

The research method is illustrated in Figure 1.

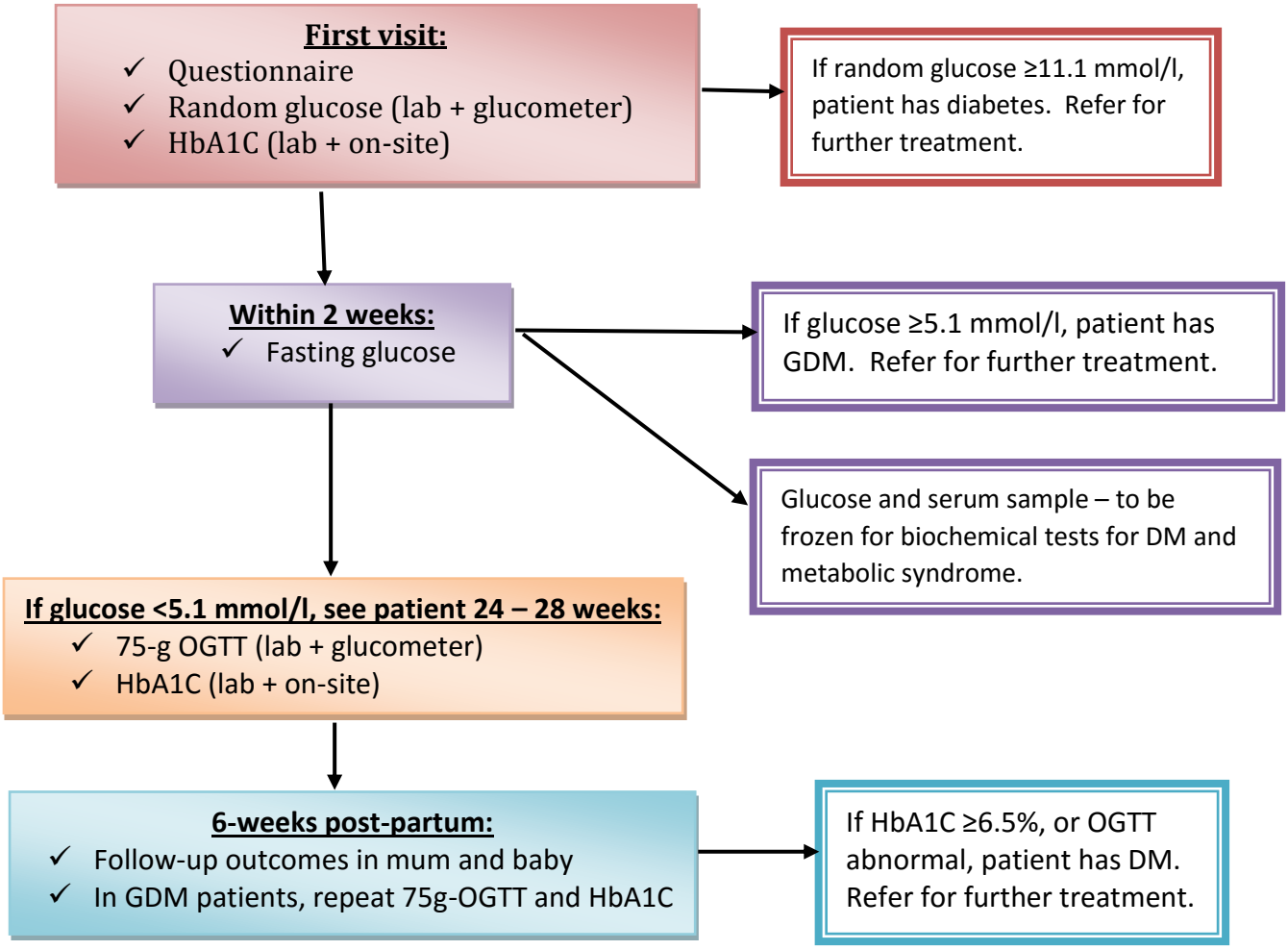

Figure 1: Research Method

At recruitment the women completed a questionnaire that assessed their demographics, historical risk factors for GDM, and physical characteristics. A random glucose and HbA1C were also drawn. If the random glucose was ≥11.1, she was diagnosed as an overt diabetic patient and was referred for appropriate management. The patients were followed up within a fortnight and had fasting glucose measured.

At the second visit a blood and a serum sample was obtained from the patients and was stored at -40°C. The stored serum specimens were tested to measure insulin, C-reactive protein (CRP), and adiponectin concentrations. The HOMA-IR and QUICKI were calculated with the fasting insulin and fasting glucose values. For the analysis of biomarkers, a nested case-cohort study was conducted, for which only the HIV negative patients were included.

Patients had a 75 g 2-hour OGTT and HbA1c between 24 – 28 weeks gestation. All glucose measurements were done at the laboratory using standardized tests (venous blood) and on a Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) (capillary blood). GDM was diagnosed according to the FIGO criteria, i.e. any one abnormal reading was diagnostic of GDM: 0-hour ≥5.1 mmol/l, 1-hour ≥10 mmol/l, or 2-hour ≥8.5 mmol/l. [12]

The patients were counseled and informed consent obtained prior to enrolment in the study. The protocol of this study was approved by the University of Pretoria Ethics committee (180/2012).

Figure 2 illustrates the patient flow through the study.

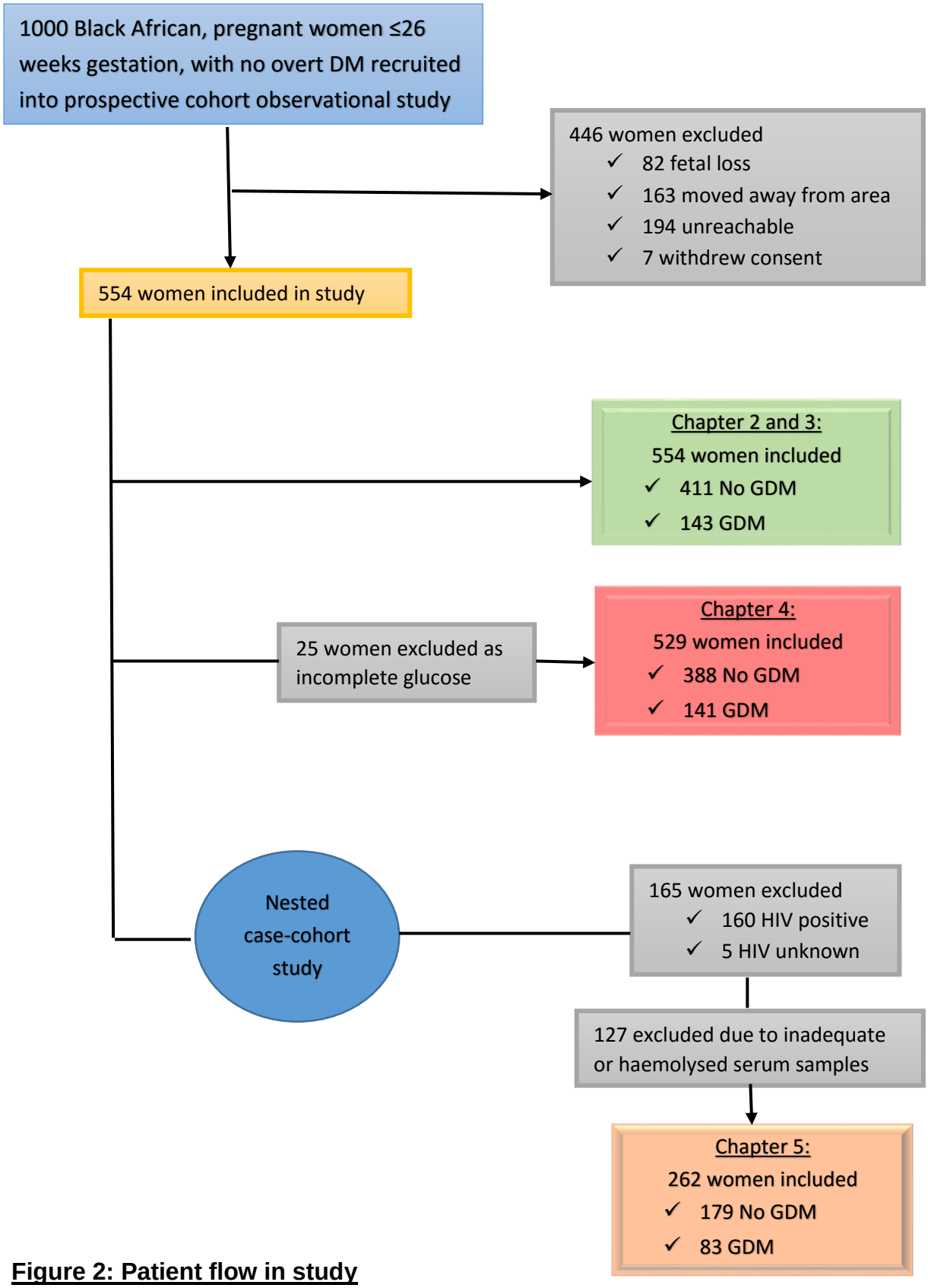

Figure 2: Patient flow in study

Unfortunately, due to the differing diagnostic criteria employed at different institutions in South Africa, all women diagnosed as having GDM according to the IADPSG criteria were not managed as high risk patients with GDM. Furthermore, due to the migrant nature of women in the informal settlements inadequate information regarding pregnancy outcomes was available for analysis.

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Chapter 2

Screening for gestational diabetes in a South African population: prevalence, comparison of diagnostic criteria and the role of risk factors

Adapted from:

Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. S Afr Med J (2017); 107(6):523-527. doi:10.7196/SAMJ.2017.v107i6.12043

Abstract

Background:

The prevalence of gestational diabetes (GDM) is increasing. Most major world organisations now recommend universal screening for GDM based on the IADPSG criteria. Currently there is a lack of consensus on the diagnostic criteria for GDM used in South Africa. SEMDSA's revised guidelines recommend the use of the IADPSG criteria for the diagnosis of GDM.

Objectives:

This study aimed to determine the prevalence of GDM in a South African population. The prevalence of GDM was compared using the various diagnostic criteria and evaluated the risk factors associated with GDM.

Methods:

This was a prospective cohort observational study carried out at a level 1 clinic in Johannesburg. All pregnant women at less than 26 weeks gestation were recruited. Patients known with diabetes mellitus were excluded. At recruitment a data questionnaire was completed and bloods were drawn for a random glucose and glycated haemoglobin (HbA1c). A 75g-2-hour oral glucose tolerance test was scheduled before 28 weeks gestation.

Results:

Five hundred and fifty-four (55.4%) patients completed the oral glucose tolerance test. The prevalence of gestational diabetes was 25.8% if universal screening and the IADPSG criteria were used. If universal screening and the NICE criteria were used the prevalence was 17%. If selective risk-factor based screening was used only 254

(45.8%) of women would have had an oral glucose tolerance test; that is the prevalence of gestational diabetes would have been 15.2% with the IADPSG criteria and 3.6% with the NICE criteria. Two hundred and fifty-four (45.8%) patients had at least one risk factor for GDM. The presence of one or more risk factors had a poor sensitivity (58.7%) and specificity (58.6%) for the detection of gestational diabetes in our study population.

Conclusion:

The prevalence of gestational diabetes would be substantially increased if universal screening with the IADPSG criteria is employed. Risk factors are a poor screening test for gestational diabetes.

Introduction:

Globally there is an alarming increase in the incidence of type 2 diabetes mellitus (T2DM) and obesity. South Africa (SA) is now regarded as one of the world's most obese nations. [1] Pregnancy is characterised by insulin resistance and hyperinsulinaemia, thus predisposing some women to develop gestational diabetes (GDM). It is well recognised that women who develop GDM in pregnancy are at an increased risk of pregnancy complications as well as DM in later life. In addition, poor glycaemic control in pregnancy impacts adversely on the neonatal outcome and puts the child at increased risk of developing obesity and T2DM. [2]

Over the decades global organisations have recommended a plethora of algorithms for the screening and diagnosis of GDM. In 2010 the International Association of Diabetes in Pregnancy Study Groups (IADPSG) proposed consensus derived cut-off values for the diagnosis of GDM. Their thresholds are derived from the 1.75 increase in odds of having a complication in pregnancy based on the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study population. The IADPSG criteria has now been adopted by International Federation of Gynecology and Obstetrics (FIGO) and most international organisations, with The American Congress of Obstetricians and Gynecologists (ACOG) and The National Institute for Health and Care Excellence (NICE) being notable exceptions. [3]

The prevalence of GDM in SA is estimated to be 1.6-8.8% based on scant data and selective risk factor-based screening. [4] Whilst it is well known that women with GDM have certain definable risk factors, there is concern that a significant proportion of women with GDM will be missed if screened by risk factors alone, as has been

illustrated in numerous studies. [5-7] Current international opinion favours the universal screening of all pregnant women for GDM, where local circumstances allow.

The screening and diagnosis of GDM in South Africa (SA) remains disorderly. There are disparities in protocols between the various provinces and hospitals. In 2012 the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) had recommended risk factor-based selective screening at 24 to 28 weeks gestation using the World Health Organisation (WHO) 1999 criteria [8]. Risk factors include advanced maternal age, obesity, family history of DM, prior adverse pregnancy outcome (congenital abnormality, recurrent miscarriages, delivery of a stillborn child), delivery of a macrosomic baby in a prior pregnancy, certain ethnic backgrounds, or significant or persistent glycosuria. Their new guidelines recommend universal screening, according to which all pregnant women will be screened for GDM, with the IADPSG criteria (personal communication). At present risk factor-based selective screening is the predominant practice in South Africa. However, each centre has decided independently on which diagnostic criteria to use. In Pretoria the IADPSG criteria [3] is used; Johannesburg utilises the NICE criteria [3], whilst the Western Cape uses a combination of the Western Cape criteria [9] and the NICE guidelines. [3] The variation in diagnostic criteria utilised results in discrepancies in prevalence and the women classified as GDM. Thus, many women with GDM will not receiving appropriate treatment. The most commonly used criteria in SA are the NICE, IADPSG and the WHO 1999 diagnostic criteria.

Objectives:

Our study aimed to determine the prevalence of GDM in a South African population. The prevalence of GDM was compared using the various diagnostic criteria. The risk factors associated with GDM were also evaluated.

Methods:

This paper is part of a larger study investigating screening strategies for GDM in a South African population. A prospective cohort observational study was carried out at a level 1 clinic in Johannesburg. One thousand pregnant women that were less than 26 weeks pregnant were recruited. Patients known with diabetes mellitus or greater and 26 weeks pregnant were excluded. Gestational age was based on the patient's last normal menstrual period, ultrasound determined gestation or on palpation of the symphysis fundal height.

At recruitment the women completed a questionnaire including demographic data and an evaluation of risk factors for GDM. A random glucose and HbA1c was tested at recruitment. If the random glucose was greater than 11.1 mmol/L or HbA1c was greater than 6.5% the patient was referred to the local hospital for further management of diabetes mellitus. Else, a 75 g – 2-hour oral glucose tolerance test (OGTT) was scheduled for between 24 and 28 weeks gestation. At the time of the OGTT an HbA1c was drawn again. All blood was drawn by a registered nurse and was stored on ice until it was delivered to the laboratory on the same day.

The diagnosis of GDM was compared using the following diagnostic criteria (Table 1):

Table 1: Diagnostic criteria for gestational diabetes commonly used in South Africa

	IADPSG	NICE	WHO 1999	Western Cape
0h glucose (mmol/L)	5.1	5.6	7.0	• Random glucose 8-11 mmol/L → fasting glucose • Fasting glucose ≥6 mmol/L → for glucose profile
1h glucose (mmol/L)	10			
2h glucose (mmol/L)	8.5	7.8	7.8	

The data was analysed using the Stata 13 statistical package (StataCorp, College Station, TX USA). Descriptive statistics was used to describe the population. The student's t-test was calculated for continuous variables and the chi-squared test for categorical data. Graphically, the data was found to be evenly distributed and thus parametric tests were used. The presence of any one risk factor was considered a positive finding. Risk factors considered were obesity (BMI ≥30 kg/m^2), age ≥35 years, delivery of a baby ≥4 kg in a prior pregnancy, glycosuria, a history of GDM in a prior pregnancy, or a history of a baby with a congenital abnormality, an unexplained stillbirth or recurrent pregnancy losses. The sensitivity and specificity for having at least one risk factor as a screening tool for GDM was calculated. Statistical significance level and confidence interval were set at a p-value less than 0.05 and 95% respectively.

Approval for this study was obtained from the University of Pretoria, Faculty of Health Sciences Ethics Committee (Protocol 180/2012).

Results:

One thousand (1000) pregnant women were recruited. Eighty-two (8.2%) women had fetal losses and did not continue with the study, 163 (16.3%) women moved away from the area and were thus lost to follow up, 194 (19.4%) women were unreachable and 7 (0.7%) women withdrew consent for the study. Thus 554 (55.4%) women had complete data available for analysis.

The clinical and biochemical characteristics of the women with and without GDM based on the IADPSG criteria are given in Table 2. The mean age, weight, body mass index (BMI), HbA1c at recruitment and random venous glucose at recruitment were significantly higher in women with GDM compared to those without GDM.

Table 2: Clinical and biochemical characteristics of subjects stratified by GDM based on IADPSG criteria

Variable		No GDM* (n=411)	GDM* (n=143)	P
Age (years) (mean, range, SD)		26.8 15 - 42 4.56	28.4 13 – 42 6.40	0.004
Weight (kg) (mean, range, SD)		68.5 42.9-124 13.66	72.1 45.3 – 122.2 15.78	0.010
Height (m) (mean, range, SD)		1.65 1.45 – 1.74 0.8	1.62 1.47 – 1.78 0.06	0.590
BMI† (kg/m2) (mean, range, SD)		26.1 14.6 – 46.2 5.08	27.9 17.5 – 47.2 6.03	0.001
MUAC‡ (cm) (mean, range, SD)		28.5 18 - 42 3.93	29.8 17 – 45 4.68	0.003
Parity (mean, range, SD)		1.05 0 - 4 0.95	1.2 0 – 5 1.01	0.096
Haemoglobin (g/dL) (mean, range, SD)		12.3 6.1 – 17.2 1.89	12.5 7.5 – 16.1 1.52	0.370
HbA1c§ (%) (mean, range, SD)	**Booking**	5.1 3.8 – 6.3 0.40	5.3 4.1 – 6.5 0.37	0.001
	OGTT¶	5.1 4.0 – 7.7 0.37	5.6 4.4 – 6.4 4.6	0.027
Random glucose (mmol/L) (mean, range, SD)	**Capillary**	4.7 2.3 – 8.6 1.03	4.7 2.8 – 9 0.86	0.565
	Laboratory	4.5 2.9 – 9.3 0.76	4.7 3.3 – 6.5 0.56	0.002
Fasting glucose (mmol/L) (mean, range, SD)	**Capillary**	4.3 2.8 – 6.3 0.56	4.6 2.7 – 8.4 0.80	<0.001
	Laboratory	4.3 2.1 – 5.8	5.8 3.9 – 10.7	<0.001

		0.44	1.01	
OGTT – 1 hour glucose (mmol/L) (mean, range, SD)	**Capillary**	6.4 2.6 – 12.9 1.29	7.0 3.6 – 11.2 1.50	<0.001
	Laboratory	5.6 1.7 – 9.9 1.33	6.7 3.9 – 12.1 1.65	<0.001
OGTT – 2 hour glucose (mmol/L) (mean, range, SD)	**Capillary**	5.8 3.3 – 10.4 1.01	6.4 4.4 – 15.5 1.43	<0.001
	Laboratory	5.2 1.8 – 8.4 1.03	6.5 3.4 – 13.8 1.67	<0.001
HIV ‖ **(n, %)**	**Negative** **Positive** **Unknown**	296 (72.0%) 111 (27.0%) 4 (1.07%)	93 (65.0%) 49 (34.2%) 1 (0.7%)	0.252
Anaemia (<11 g/dL) (n, %)	**No** **Yes**	245 (59.6%) 79 (19.2%)	104 (72.7%) 18 (12.6%)	0.500
Hypertension (>135/85 mmHg) (n, %)	**No** **Yes**	311 (75.7%) 100 (24.3%)	94 (65.7%) 49 (34.3%)	0.210
Education (n, %)	**<Grade 12** **≥Grade 12**	231 (56.2%) 163 (39.7%)	81 (56.6%) 60 (42.0%)	0.807
Employment (n, %)	**Unemployed** **Employed** **Scholar**	257 (62.5%) 144 (35.0%) 7 (1.7%)	73 (51.0%) 64 (44.8%) 5 (3.5%)	0.037
Risk factors (n, %)	**0 (n=300)** **≥1 (n=254)**	241 (58.6%) 170 (41.4%)	59 (41.3%) 84 (58.7%)	<0.001 <0.001

Abbreviations: *GDM, Gestational diabetes mellitus; † BMI, Body mass index; ‡MUAC, Mid-upper arm circumference; § HbA1c, Glycated haemoglobin; ¶ OGTT, Oral glucose tolerance test; || HIV, Human immunodeficiency virus

All the women would have had an OGTT if universal screening was employed. Only 254 (45.8%) women would have had an OGTT if selective risk factor-based screening was employed. The prevalence of GDM based on the different diagnostic criteria is illustrated in Graph 1 and 2.

The prevalence of GDM was 25.8% with universal screening and 15.2% with selective screening when the IADPSG criteria were used. If the NICE criteria was used and universal screening was applied the prevalence was 17%. If selective screening was

used the prevalence was 3.6%. With the WHO 1999 criteria the prevalence of GDM was 7.2% with universal screening and 3.6% with selective screening. The Western Cape criteria would have diagnosed no woman in our study population as having gestational diabetes.

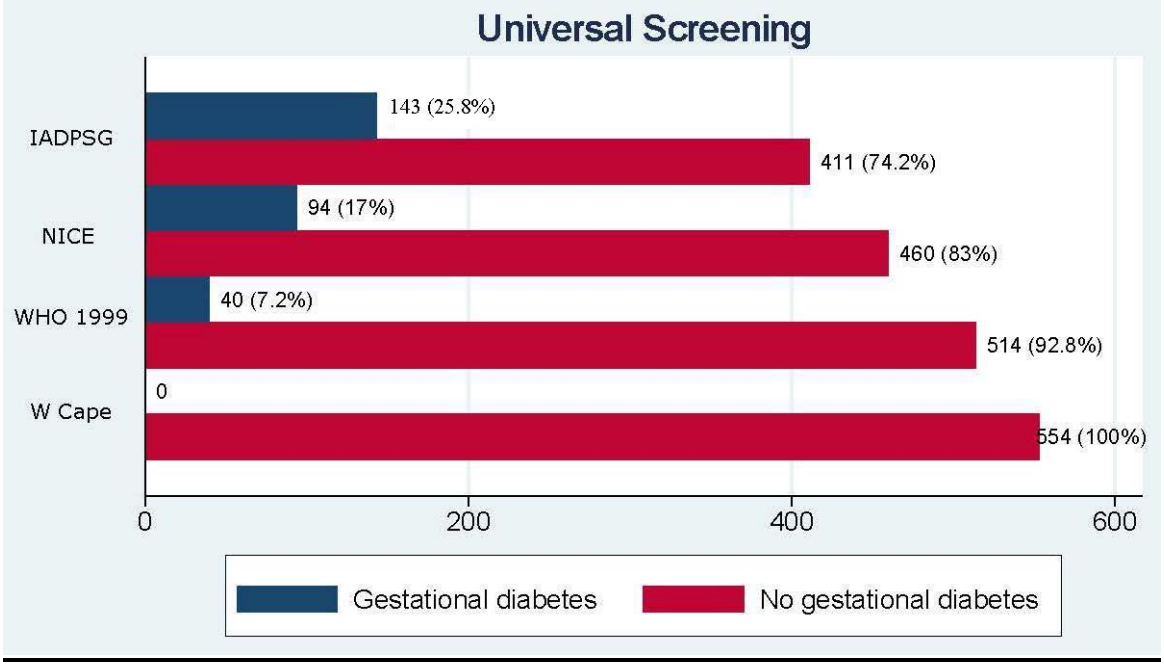

Figure 1: Prevalence of GDM based on universal screening

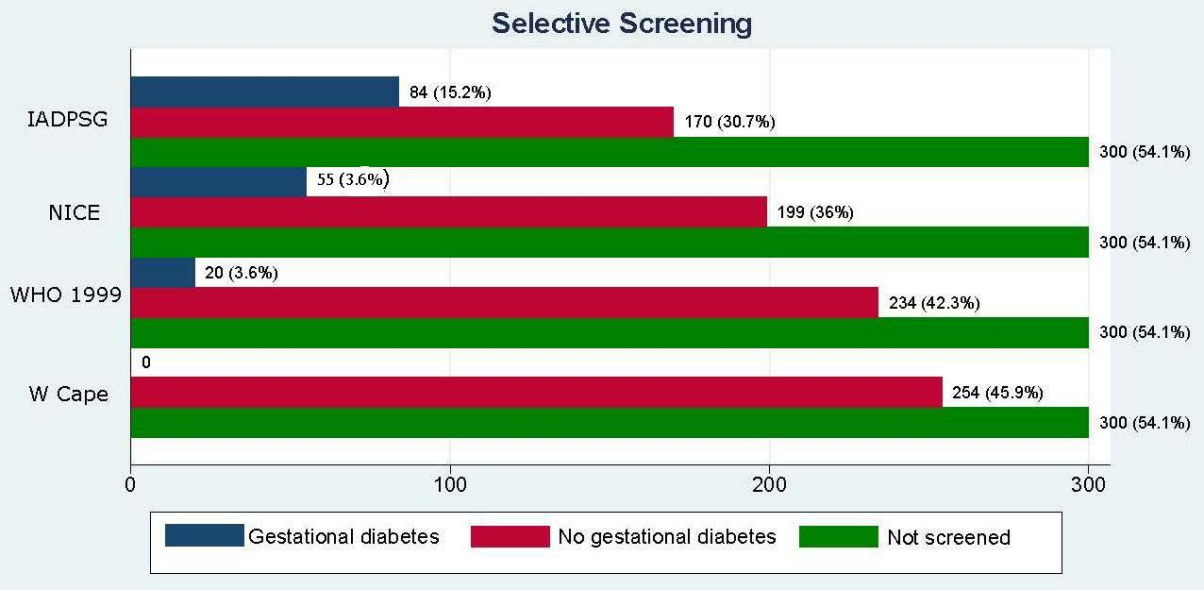

Figure 2: Prevalence of GDM based on selective screening

Table 3: Comparison of subjects with GDM based on IADPSG and NICE criteria

Variable		IADPSG GDM* (n=143)	NICE GDM (n=94)	P
Age (years) (mean, range, SD)		28.4 13 – 42 6.40	28.7 13 – 42 6.81	0.010
Weight (kg) (mean, range, SD)		72.1 45.3 – 122.2 15.78	72.5 45.3 – 122.2 17.13	0.030
Height (m) (mean, range, SD)		1.62 1.47 – 1.78 0.06	1.61 1.47 – 1.76 0.06	0.851
BMI† (kg/m2) (mean, range, SD)		27.9 17.5 – 47.2 6.03	28.3 17.5 – 47.2 6.61	<0.001
MUAC‡ (cm) (mean, range, SD)		29.8 17 – 45 4.68	30 20 – 45 4.98	0.010
Parity (mean, range, SD)		1.2 0 – 5 1.01	1.3 0 – 5 1.06	0.060
Haemoglobin (g/dL) (mean, range, SD)		12.5 7.5 – 16.1 1.52	12.5 8.3 – 15.7 1.49	0.570
HbA1c§ (%) (mean, range, SD)	**Booking**	5.3 4.1 – 6.5 0.37	5.3 4.2 – 6.5 0.38	<0.001
	OGTT¶	5.6 4.4 – 6.4 4.6	5.9 4.4 – 6.8 5.56	0.020
Random glucose (mmol/L) (mean, range, SD)	**Capillary**	4.7 2.8 – 9 0.86	4.7 2.8 – 9 0.94	0.750
	Laboratory	4.7 3.3 – 6.5 0.56	4.7 3.3 – 9.3 0.76	<0.001
Fasting glucose (mmol/L) (mean, range, SD)	**Capillary**	4.6 2.7 – 8.4 0.80	4.6 2.7 – 8.4 0.87	<0.001
	Laboratory	5.8 3.9 – 10.7 1.01	6 3.9 – 10.7 1.16	<0.001

HIV ‖ **(n, %)**	**Negative** **Positive** **Unknown**	93 (65.0%) 49 (34.2%) 1 (0.7%)	66 (70.2%) 28 (29.8%) 0	0.080
Anaemia (<11 g/dL) (n, %)	**No** **Yes**	104 (72.7%) 18 (12.6%)	65 (69.1%) 10 (10.6%)	0.080
Hypertension (>135/85 mmHg) (n, %)	**No** **Yes**	94 (65.7%) 49 (34.3%)	61 (64.9%) 33 (35.1%)	0.060
Education (n, %)	**<Grade 12** **≥Grade 12**	81 (56.6%) 60 (42.0%)	53 (56.4%) 40 (42.6%)	0.210
Employment (n, %)	**Unemployed** **Employed** **Scholar**	73 (51.0%) 64 (44.8%) 5 (3.5%)	53 (56.4%) 36 (38.3%) 4 (4.3%)	0.080
Risk factors (n, %)	**0** **≥1**	59 (41.3%) 84 (58.7%)	39 (41.5%) 55 (58.5%)	<0.001

Abbreviations: *GDM, Gestational diabetes mellitus; † BMI, Body mass index; ‡MUAC, Mid-upper arm circumference; § HbA1c, Glycated haemoglobin; ¶ OGTT, Oral glucose tolerance test; || HIV, Human immunodeficiency virus

Table 3 illustrates the differences between patients who have GDM based on either the IADPSG criteria or the NICE criteria. There is a significant difference in age, weight, body mass index (BMI), HbA1c at booking and at the time of the OGTT, random and fasting glucose, and in the number of patients with at least one risk factor for GDM.

In our study 254 (45.8%) patients had at least one risk factor for GDM. Of these patients 26% had GDM. However, the presence of 1 or more risk factors had a poor sensitivity (58.7% 95% CI 50.2 – 66.9) and specificity (58.6%; 95% CI 53.7 – 63.4) for the detection of gestational diabetes in our study population (Table 4). The positive likelihood ratio was 1.42 and the negative likelihood ratio was 0.704. Risk factors had a positive predictive value of 33.1%, a negative predictive value of 80.3% and an odds ratio of 2.02.

The McNemar test showed a relative difference of 0.107 (95% CI 0.0756 – 0.1374) when the prevalence of GDM diagnosed with the IADPSG criteria was compared to the prevalence of GDM diagnosed by the NICE criteria. The exact odds ratio was 10.8 (95% CI 4.35 – 4.35), meaning that a pregnant woman is 10.8 times more likely to be diagnosed with GDM if the IADPSG criteria is used.

Table 4: Performance of risk factors as a screening tool for GDM

		Risk factors ≥1		TOTAL
		Yes	No	
Gestational diabetes	**Yes**	84 (15.2%)	59 (10.6%)	143 (25.8%)
	No	170 (30.7%)	241 (43.5%)	411 (74.2%)
TOTAL		254 (45.8%)	300 (54.2%)	554 (100%)

Discussion:

This study aimed to determine the prevalence of GDM and its associated risk factors in a South African population. To our knowledge this is the first study to evaluate the IADPSG criteria in a South African population.

Screening for GDM in South Africa is chaotic. SEMDSA (2012) had recommended risk factor-based selective screening using the WHO 1999 criteria. [8] Their new guidelines recommend universal screening with the IADPSG criteria (personal communication). The change in recommendation would translate to a greater than 100% increase in the number of pregnant women that would need to be screened, and an increase in the prevalence of GDM from 3.6% to 25.8%, i.e. 7.2-fold increase in the prevalence of GDM.

The incidence of GDM is increasing worldwide. The IADPSG diagnostic criteria were extrapolated from the population screened in the HAPO study. Although there was no clear inflection point above which the adverse effects of GDM increased, the IADPSG recommends diagnostic criteria based on an odds ratio of 1.75. [3, 10] When the IADPSG criterion was applied to the HAPO population a GDM prevalence of 18% was found. However, a GDM prevalence of 25.8% was found in our study population when the IADPSG criterion was used. The markedly increased prevalence of GDM found with the IADPAG criteria is greater than the prevalence found in other countries. [3]

The significant increase in the prevalence of GDM reported in this study compared to previous South African studies can be attributed to the lower diagnostic threshold and the use of universal screening. [4] The IADPSG criteria were used as it is now recommended in an attempt to standardise the diagnosis of GDM globally [3] and is recommended in the proposed SEMDSA guidelines.

Secular changes in lifestyle in South Africa have contributed to the increasing risk of obesity. Whilst modifiable, these changes have contributed to the increasing prevalence of DM in the general population. [1] Similarly, obesity is also associated with an increased likelihood of having GDM. It is known that women with GDM are at an almost 50% increased risk of developing DM within 10 years. The increasing incidence of GDM is of concern as these women and their offspring are at increased risk of cardiometabolic disease. It has also been demonstrated that the partners of women with GDM are at increased risk of developing Type 2 DM. [11, 12] Hence, there is a need for large scale awareness and lifestyle modification programmes to alter these risks.

Currently the most widely used criterion for screening for GDM in South Africa is the NICE guidelines. The NICE criteria seem like an attractive alternative for the diagnosis of GDM. The use of these diagnostic criteria will result in a 17% prevalence of GDM. However, the application of the NICE criteria may not be ideal. Meek et al. [13] have found that women who did not have GDM if the NICE criteria were applied, but had GDM if the IADPSG criteria were used were still at an increased risk of adverse obstetric outcomes such as an increased caesarean section rate, polyhydramnios and fetal macrosomia.

Risk factor-based screening has been widely utilised to identify women at high risk of having GDM. If selective screening was used in our study 59 (10.6%) patients with GDM would have not been diagnosed if the IADPSG diagnostic criteria had been used, and 39 (7%) women would have remained undiagnosed had the NICE diagnostic criteria been used.

Historically risk-factor based selective screening has been recommended for the screening of GDM as it was not considered to be cost-effective to subject all women to laboratory testing. Risk factor-based screening performs poorly as a screening tool for GDM. The poor sensitivity and specificity of risk factor-based screening has also been found in other studies. [14, 15] Furthermore, a major challenge of selective screening is that it places a high demand on the health care worker to identify patients that should be screened. The increased workload in effect results in a lower compliance and inadequate screening and testing.

Universal screening and the low diagnostic threshold proposed by the IADPSG, on the other hand, may have the potential to over diagnose GDM, which has both financial and workload implications that has been the subject of much debate. [16]

The Western Cape guidelines propose a novel approach to screening for GDM. In our study no patients were diagnosed with GDM when these criteria were applied. This result may be due to the low socio-economic status of the population in which this study was conducted. Due to the poor social circumstances many pregnant women present to the antenatal clinic without having eaten an adequate breakfast, as can be seen by the similar random and fasting glucose measurements.

Selective screening still remains an alluring option for South Africa. In addition to being a low-middle income country, we are faced with a dual burden of disease – malnutrition, poverty and communicable diseases, whilst obesity and lifestyle-related non-communicable diseases are increasing. However, if we are to consider risk factor-based screening we would have to define appropriate, simply applied risk factors and evaluate the efficacy of such a strategy.

The strengths of this study were that it prospectively assessed the prevalence of GDM and its associated risk factors in a low risk South African population, and that universal screening and the IADPSG criteria were applied. The limitations are that this study was conducted in a local study in a Black African population and there was a large loss to follow-up.

Conclusion:

Universal screening is the only strategy by which the majority of women with GDM will be diagnosed. There will be a substantial increase in the prevalence of GDM in South Africa with the use of the IADPSG criteria regardless of whether universal or selective screening is implemented. There is a need to investigate and standardise the ideal strategy for the screening of GDM in the South African context. Due to the varied health priorities in South Africa it is evident that an appropriate set of diagnostic criteria needs to evolve from a consensus approach based on balancing obstetric and long-term health risks and benefits within our unique socio-economic and clinical context.

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Chapter 3

Selective screening strategies for gestational diabetes, a prospective cohort observational study

Adapted from:

Adam S, Rheeder P. Selective screening strategies for gestational diabetes, a prospective cohort observational study. Journal of Diabetes Research (2017): 3:1-9 Article ID 2849346, 9 pages. doi.org/10.1155/2017/2849346

Abstract

Aim:

The aim of this study was to develop a prediction model for the diagnosis of gestational diabetes, and to evaluate the performance of published prediction tools on our population.

Methods:

A cohort study was conducted on women <26 weeks gestation at a level 1 antenatal clinic in Johannesburg, South Africa. Women with diabetes mellitus were excluded. Participants completed a questionnaire and had a random basal glucose (RBG) and glycated haemoglobin (HbA1c) drawn at enrolment. A 75 g 2-hour oral glucose tolerance test was scheduled between 24-28 weeks gestation. GDM was diagnosed as per FIGO criteria. A score was derived using multivariate logistic regression. Published scoring systems were tested by deriving ROC curves.

Results:

In 554 women included RBG, BMI and a history of baby ≥4000 g were significant risk factors for GDM, which were used to derive a nomogram-based score. The logistic regression model for prediction of GDM had R^2 0.143, Somer's D_{xy} rank correlation 0.407, and Harrell's c-score 0.703. HbA1c did not improve predictive value at any threshold (e.g. at a probability >10% 25.6% of cases were detected without the HbA1c, and 25.8 cases would have been detected if the HbA1c was included in the prediction model. There was no interaction between HIV and other variables (p=0.974). The 9 published scoring systems performed poorly.

Conclusion:

A nomogram-based score that can be used at first antenatal visit to identify women at high risk of GDM was proposed.

Introduction:

Gestational diabetes mellitus (GDM) is regarded as glucose intolerance with first onset in pregnancy. The diagnosis of GDM infers an increased risk of both short- and long-term adverse outcomes for the mother and fetus. [1] The current guidelines of the International Federation of Gynecology and Obstetrics (FIGO) recommends universal screening of pregnant women for GDM with a 75g-2-hour oral glucose tolerance test (OGTT). [2] The lower thresholds recommended by FIGO are derived from the findings of the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study. The HAPO study found that the adverse events associated with GDM increase along a continuum with increasing hyperglycaemia. [3] The estimated prevalence of GDM based on the FIGO guidelines varies between 11.1 - 44.3%. [4-5]

Universal screening for GDM has the advantage that all pregnant women are screened as part of routine antenatal care. However, the screening of all pregnant women for GDM will place an added burden, both financial and personnel, on the health care system. Selective screening based on risk factors such as advanced maternal age, obesity, family history of diabetes, and previous adverse pregnancy outcomes such as recurrent or unexplained pregnancy losses, large-for-gestational-age babies or congenital abnormalities, has been proposed as a screening strategy for GDM. Selective screening based on risk factors performs poorly as a screening tool with up to one-sixth of women with GDM diabetes being missed. [6] Furthermore, recall of historical risk factors is poor, medical records are often incomplete or unavailable, or the recorded history is not often considered by clinical staff to trigger screening for GDM. Thus, the current risk factor-based screening is ineffective.

Whilst the traditional risk factor-based screening program performs poorly for the screening of GDM there are several published risk scoring systems that hold promise. These models combine maternal characteristics and medical history into a simple clinical prediction tool. The scoring system approach may assist in identifying women who require an OGTT with greater efficacy, accuracy and efficiency. [7-15] However, these models were developed on non-African populations in tertiary centres using data obtained from a selective-screening approach in most instances. [7-15]

The purpose of this study was to develop a clinical prediction model for GDM in a South African population, and to evaluate the performance of the published prediction tools on our study population. The introduction of such a prediction tool would reduce the number of OGTTs, hence decreasing the workload and financial burden on an overburdened healthcare system.

Materials and Methods:

This paper forms part of a larger study investigating screening strategies for GDM in a South African population. A prospective cohort observational study was carried out at a level 1 primary healthcare clinic in Johannesburg. One thousand consecutive pregnant women that were less than 26 weeks pregnant were recruited. Patients known with diabetes mellitus or greater than 26 weeks pregnant were excluded.

At recruitment each patient completed a questionnaire including demographic data and an evaluation of risk factors for GDM. Risk factors considered were obesity, i.e. a body mass index (BMI) ≥30 kg/m^2, age ≥35 years, a family history of diabetes mellitus, a history of a delivery of a baby ≥4000 g in a prior pregnancy, glycosuria, a history of GDM in a prior pregnancy, or a history of a baby with a congenital abnormality, an unexplained stillbirth or recurrent pregnancy losses. Gestational age was based on the patient's last normal menstrual period, ultrasound determined gestation or by measuring of the symphysis to fundal height.

A random blood glucose (RBG) and glycated haemoglobin (HbA1c) level were measured at recruitment on a Roche Accuchek Active® point-of-care device (Roche Diagnostics, Mannheim, Germany) and at the laboratory. The glucometer was regularly calibrated as per manufacturer guidelines and glucose was measured on whole capillary blood. Measurements on the glucometer were not influenced by haematocrit. If the random glucose was greater than 11.1 mmol/l or HbA1c was greater than 6.5% the patient was referred to the local hospital for further management of overt diabetes mellitus. The patients returned after 2 weeks for a fasting glucose measurement. Thereafter, a 75 g – two-hour oral glucose tolerance test (OGTT) was scheduled for between 24 and 28 weeks gestation. GDM was diagnosed based on

the FIGO criteria. [2] All blood was drawn by a registered nurse and was stored on ice until it was delivered to the laboratory on the same day. Point-of-care tests were performed on-site.

R version 3.3.0 [16] with packages PredictABEL [17] and rms [18] was used. In order to compare the different prediction models the missing values were imputed using multivariate imputation by chained equations. [19] Because our dataset is large enough all clinically relevant predictors were used in a logistic regression model. [16] Random serum glucose demonstrated a non-linear relationship with the log odds of outcome and a restricted cubic spline with two knots in the model was used. The other continuous variables were not transformed in the model. In order to determine the degree of optimism with the model, the model was calibrated and validated with 200 bootstrap samples according to Harrell. [18]

To reduce the number of variables for a more parsimonious model, the method of approximation as suggested by Harrell (to remove the variables that would have the smallest effect on the R^2 co-efficient of determination of the linear regression model of variables on the linear predictor of the logistic regression model as outcome) [18] was used. The interaction of HIV with the other variables was investigated.

Thereafter, the effect of having a model with and without HbA1c was investigated as some centres may and some may not have HbA1c testing readily available. These models were compared using Harrell`s C index, Somer's Dxy rank correlation, the Brier score, R^2, the net reclassification index (NRI) (at probabilities of 10, 50 and 100%) as well as the integration discrimination improvement (IDI). [16] The Harrell's c-index (C-index >0.5 shows good predictive ability) and the Somer's Dxy (where Dxy =1 when the model is perfectly discriminating) are measures of the general predictive

power of a regression model. In effect they are a natural extension of ROC curve areas. The Brier score (where the best possible score is 0 for total accuracy) measures the accuracy of probabilistic predictions, i.e. it is the average gap between the calculated probability and the actual outcome. R^2 (where 1 fits the regression line perfectly) provides information on the goodness of fit of the model. The NRI is an index of how well a new model classifies subjects (i.e. in this study how well does the prediction model identify patients at high risk of GDM). The IDI similarly is a tool that evaluates the capacity of a marker or model to predict the outcome (i.e. how well can the prediction model identify patients with GDM).

Categorical NRI equal to x% means that compared with individuals without outcome, individuals with outcome were almost x% more likely to move up a category than down. The function also computes continuous NRI, which does not require any discrete risk categories and relies on the proportions of individuals with outcome correctly assigned a higher probability and individuals without outcome correctly assigned a lower probability by an updated model compared with the initial model. IDI equal to x% means that the difference in average predicted risks between the individuals with and without the outcome increased by x% in the updated model (according to PredictABEL help function). Finally, for ease of use nomograms were generated for the model with and without HbA1c. [18]

Furthermore, nine published risk prediction models for GDM were identified. [7-15] The risk prediction model from each study was applied to our study population and a receiver operating curve (ROC) was generated to evaluate its performance as a screening tool. Thereafter the two ROC curves derived from independent samples were compared to assess if there was a significant difference in the area under the curve.

Approval for this study was obtained from the University of Pretoria, Faculty of Health Sciences Ethics Committee (Protocol 180/2012), and was performed in accordance with the 1964 Declaration of Helsinki and its amendments. Informed consent was obtained from every patient prior to entry into the study.

Results:

One thousand (1000) pregnant women were recruited. Eighty-two (8.2%) women had fetal losses and did not continue with the study, 163 (16.3%) women moved away from the area and were thus lost to follow up, 194 (19.4%) women were unreachable and seven (0.7%) women withdrew consent for the study. Thus 554 (55.4%) women had complete data available for analysis. One hundred and forty-four (25.8%) women had GDM.

The mean age of the population was 27.3 years (SD 5.84; IR 13-42), parity 1.1 (SD 0.96; IR 0-5), BMI 26.5 kg/m^2 (SD 5.37; IR 14.8-47.2), random glucose 4.5 mmol/l (SD 0.72; 2.9-9.3), and HbA1c 5.2% (33.3 mmol/mol) (SD 0.39; IR 3.8-6.5%/18-47.5 mmol/mol). One hundred and sixty (28.9%) women were HIV positive of which 59 (36.9%) were on highly active antiretroviral therapy (HAART), 78 (14.1%) women had a positive family history of diabetes mellitus, 55 (9.9%) had a history of a previous stillborn or congenitally abnormal baby, and 44 (7.8%) women had previously delivered a baby >4000 g.

The role of the random glucose (AUROC 0.63, 95%CI 0.58-0.68), and fasting glucose (AUROC 0.93, 95% CI 10.86-31.24) as a screening tool was considered. One hundred and sixty two women would have been diagnosed with GDM based on the fasting glucose measured at the second visit (i.e. fasting glucose ≥5.1 mmol/l). However, 40 (24.7%) of these women later had a normal OGTT, i.e. had a false positive based on the fasting glucose.

Furthermore, following univariate analysis, clinically relevant predictors, viz. delivery of a previous baby ≥4000 g, random glucose, BMI, family history of diabetes mellitus, HbA1c, history of a previous stillbirth or previous baby with a congenital abnormality

and age, were included in a logistic regression model. [2] The odds ratio of the full model including all the clinically relevant factors (named above) is illustrated in Figure 1a and the odds ratio of the smaller model is shown in Figure 1b. The performance of this full model (Figure 1a) including all clinical variables is illustrated in Table 1.

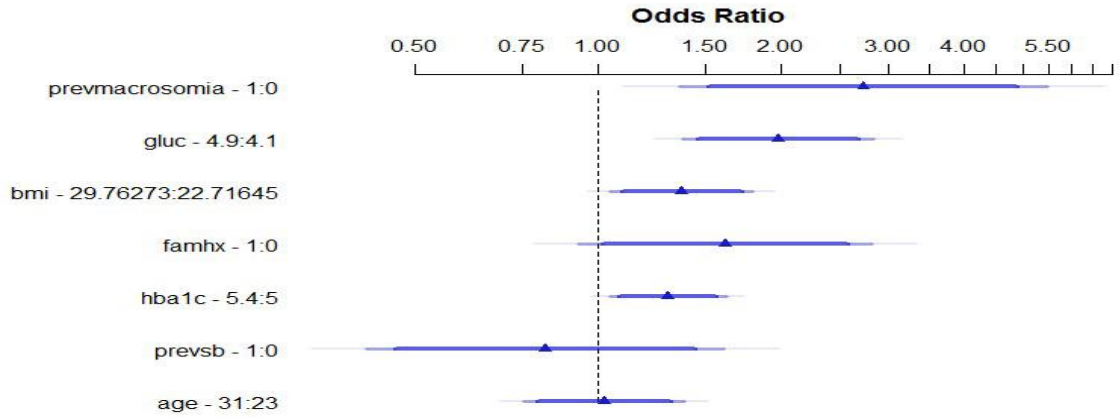


Figure 1a: Odds ratio of full model including all clinical variables (continuous variables: 75th versus 25th percentile)

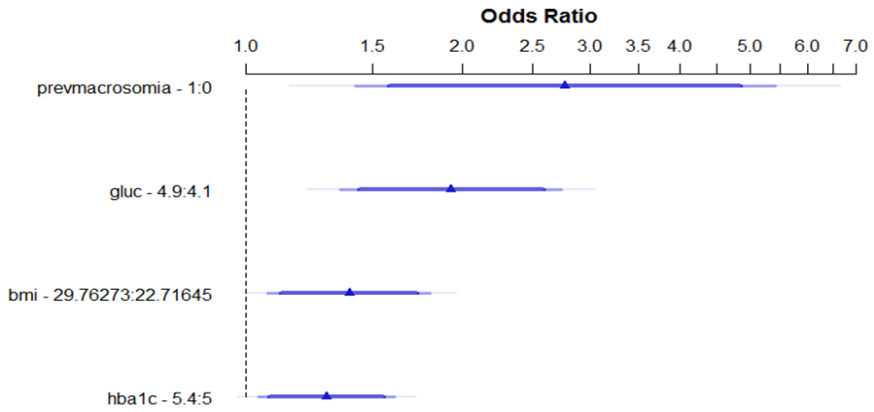


Figure 1b: Odds ratio of smaller model including only significant clinical variables (continuous variables: 75th versus 25th percentile)

Table 1: Discrimination indices of the full predictive model including all clinical risk factors

Discrimination Index	Full model with all clinical variables	Validated model
R^2	0.143	0.109
Harrell's C index	0.703	
Somer's Dxy rank correlation	0.407	0.362
Brier score	0.173	0.178

The full model including all clinical variables was then validated and calibrated with 200 bootstrap samples according to Harrell. [18] One can observe that at higher predicted probabilities the actual probabilities are less in the optimism corrected model indicating a fair degree of optimism as demonstrated in Figure 2. At higher predicted probabilities the actual probabilities are less in the optimism corrected model indicating a fair degree of optimism. The discriminatory indices for the validated model are illustrated in Table 1. The quantile absolute error was 0.029. The slope of the bias-corrected model was 0.870, it has a 0.130 difference when corrected for optimism.

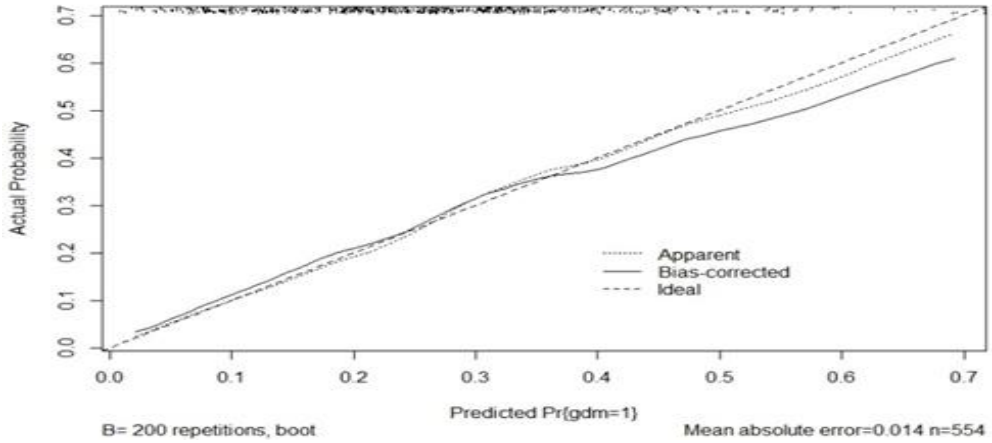


Figure 2: Correcting the model for optimism

In order to get a smaller model with fewer clinical variables, an approximation method was used as suggested by Harrell [18] to remove variables that would have the smallest effect on R^2 of the linear regression model (Table 2). Family history of diabetes mellitus, history of a previous stillbirth or previous baby with a congenital abnormality and age was removed and the model still maintained 95.7% of R^2.

Table 2: B-coefficient of predictive variables in model (random glucose, BMI, previous baby >4000 g) with and without HbA1c

		Model Without HbA1c[1]	Model With HBA1c[1]
Previous baby ≥4 kg		1.02	1.01
Rgluc[2]/ Rgluc'[3]		1.99/ -2.17	2.17/ -2.28
BMI[4]		0.05	0.05
HbA1c[1]		0.65	
R^2 co-efficient of determination		0.14	0.12
Somer's Dxy rank correlation		0.38	0.36
Harrell's C-index/ AUROC[5]		0.69	0.68
Brier score		0.18	0.17
NRI[6]	**Categorical**	0.036 (-0.002 – 0.073); p-0.060	
	Continuous	0.253 (0.066 – 0.440); p-0.016	
IDI[7]		0.108 (0.002 – 0.020); p-0.016	

Abbreviations: HbA1c[1], glycated haemoglobin; Rgluc[2], random glucose first spline; Rgluc[3], random glucose second spline; BMI[4], body mass index; AUROC[5], area under the receiver operating curve; NRI[6], net reclassification index; IDI[7], integrated discrimination improvement

The interaction of random glucose and HbA1c was evaluated via regression analysis and no interaction was found. Hence both variables were considered in the development of the model.

The interaction of HIV and HAART with the clinical variables was analysed by regression analysis. HIV nor the HAART had any interaction with a history of a delivery of a previous baby greater than 4000 g (p=0.066), the random glucose (p=0.835), or BMI (p=0.801). Overall, HIV nor HAART had an effect on our proposed model (p=0.974)

Thereafter a smaller model was used to determine whether adding HbA1c would add any predictive value to the model as demonstrated in Figure 3. It was found that adding an HbA1c did not significantly improve the predictive value of the model (Table 2). The slope of the bias-corrected model was 0.933, and it has a 0.067 difference when corrected for optimism.

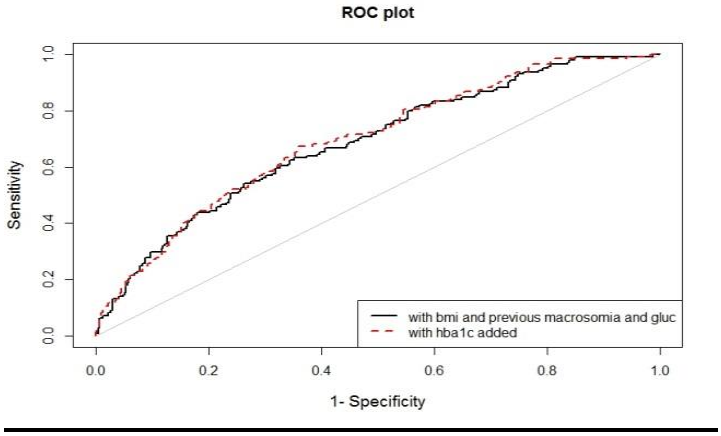


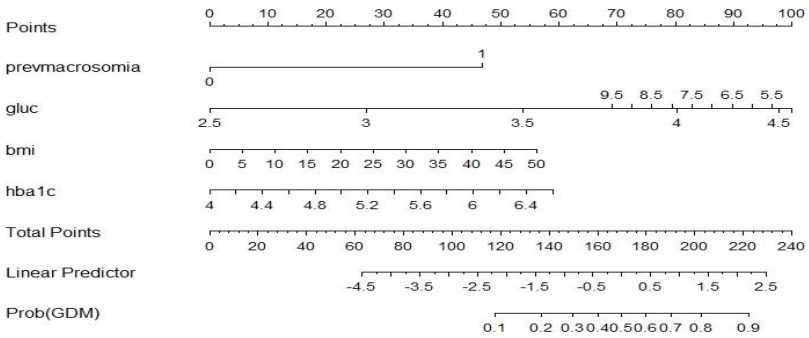
Figure 3: Comparison of predictive value of model with and without HbA1c

When considering the categorical NRI, 12%, 4%, and 9% of patients will be down-classified to being at low risk of GDM at 10, 50, and 100% respectively, by adding the HbA1c to the model. Similarly, 0%, 4%, and 0% will be up-classified to being at high risk of GDM at 10, 50, and 100% respectively when HbA1c was added to the model. The integrated discrimination improvement (IDI) shows that the discrimination slope of the updated model with the added HbA1c was 10.8% higher than the original model.

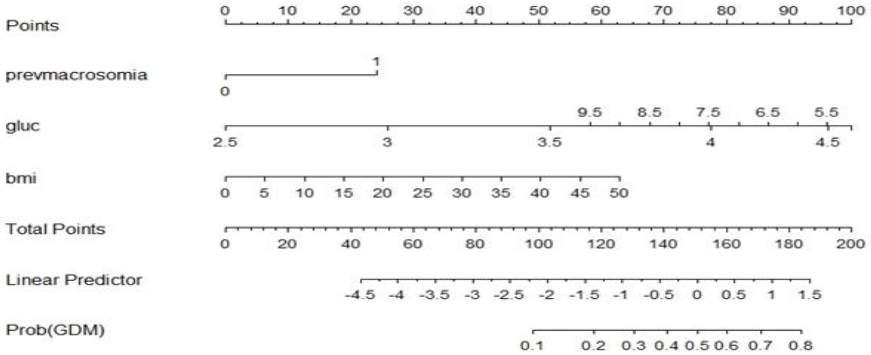
The le Cessie - van Houwelingen - Copas - Hosmer unweighted sum of squares test for global goodness of fit for the model with HbA1c gave a p value of 0.87 and for the model without HbA1c 0.81.

Finally for ease of use nomograms were generated for the model with and without the HbA1c (Figure 4).

(a)



(b)



Abbreviations: prevmacrosomia, history of delivering a baby >4000 g; gluc, random glucose; bmi, Body mass index; hba1c, glycated hemoglobin; Prob(GDM), probability of developing gestational diabetes

[a]The nomograms consider the history of delivery of a previous baby >4000 g (prevmacrosomia: 0=no, 1=yes), random glucose (gluc: measurement in mmol/l), and BMI (bmi: mass in kilograms/height in metre^2). Two nomograms are illustrated to show the difference with and without and HbA1c measurement being included. The score is derived by aligning the points on each number line with the 'points' line at the top. The total score is then calculated and plotted on the 'total points' line. When the total score is compared to the 'prob(GDM)' line the probability of developing GDM is derived. For example, a 30-year-old woman who is now para 2 gravida 3, with a BMI of 35 kg/m2, who previously delivered a 4.3 kg baby, has an HbA1c of 5.8% and now has a random glucose of 6.7 mmol/l will have a score of 155 and thus a 50% chance of developing GDM in this pregnancy based on the nomogram without the HbA1c. Her score is 182 and thus a 52% risk of developing GDM if the HbA1c is incorporated into the prediction model.

Figure 4: Nomograms (a) with HbA1c and (b) without HbA1c[a]

The efficacy of the nomograms at >10% and >15% probabilities of GDM was then compared (Table 3) as the cut-off risk above which a woman is deemed at high risk of developing GDM had to be established. At a cut-off of 10%, 58/554 (10.5%) and 50/554 (9.0%) fewer OGTTs would be carried out if HbA1c was or was not incorporated into the nomogram, respectively. Two (0.4%) and one (0.2%) cases of GDM would be missed if the nomogram with and without the HbA1c was applied, respectively. Similarly, at a 15% cut-off 124/554 (22.4%) and 103/554 (18.6%) fewer OGTTs would be carried out if HbA1c was or was not incorporated into the nomogram, respectively. Nine (1.6%) cases of GDM would be missed whether or not HbA1c was incorporated into the nomogram.

Table 3: Comparison of the efficacy of nomograms at probabilities of 10 and 15%

Nomogram	With HbA1c[1]				Without HbA1c[1]			
	High risk		Low risk		High risk		Low risk	
Probability of GDM[2]	GDM[2]	No GDM[2]	GDM[2]	No GDM[2]	GDM[2]	No GDM[2]	GDM[2]	No GDM[2]
>10%	142 (25.6%)	354 (63.9%)	2 (0.4%)	56 (10.1%)	143 (25.8%)	361 (62.5%)	1 (0.2%)	49 (8.8%)
>15%	135 (24.3%)	304 (54.9%)	9 (1.6%)	115 (20.8%)	135 (24.3%)	316 (57.0%)	9 (1.6%)	94 (17%)

Abbreviations: HbA1c[1], glycated haemoglobin; GDM[2], gestational diabetes

Table 4 demonstrates the performance of each published prediction model for GDM once it was applied to our study population as compared to the population that it was derived from.

Table 4: Comparison of the performance of scoring systems for the screening of GDM in our population

Study	Risk factors	Risk calculation	AUROC[a] (study population)	AUROC[a] (original)	P[20]
Caliskan[7]	• Age (years) • Body mass index (BMI) • Family history of diabetes mellitus (DM) • Previous baby >4000 g • Previous adverse pregnancy outcome	• <25=0; ≥25=1 • <25=0; ≥25=1 • No=0; Yes=1 • No=0; Yes=1 • No=0; Yes=1	0.594 (0.537 – 0.650)	0.832 (0.793-0.867)	0.001

Naylor[8]	• Age (years) • Body mass index (BMI) • Race	• <30=0; 31-34=1; ≥35=2 • <22=0; 22.1-25=2; >25.1=3 • White/Black=0; East Asian=5; South Asian=2	0.590 (0.532 – 0.647)	0.733 (0.711-0.755)	0.001
Van Leeuwen[9]	• Body mass index (BMI) • Race • Family history of diabetes mellitus (FamHx) • Gestational diabetes in previous pregnancy (GDMHx)	=1/[1+exp(-β)] B=[-6.1+(0.83xnon-caucasian) + (0.57 x FamHx) – (0.67xmultipara no GDMhx) + (0.5xmultipara GDMhx) +(0.13xBMI) (Non-Caucasian: No=0; Yes=1 Famhx: No=0; Yes=1 Nullipara=0; MultiparaNoGDMhx=1; MultiparaGDMhx=2)	0.568 (0.510 – 0.630)	0.770 (0.690-0.850)	0.002
Phaloprakan[10]	• Age (years), body mass index (BMI), • Family history of diabetes mellitus (FH), • Previous baby >4000 g, • Previous adverse pregnancy outcome	6 age + 11 BMI + 109FH + 42 baby >4000 g + 49 adverse pregnancy outcome ≥380 is positive screen	0.5182 (0.487 – 0.550)	0.769 (0.746-0.792)	<0.001
Teede[11]	• Age (years) • Body mass index (BMI) • Race	• <25=0; 25-34=1; ≥35=2 • <20=0; 20-34.9=1; ≥35=2 • White=0; East Asian/South Asian/African=1 • No=0; Yes=1	0.586 (0.529 – 0.643)	0.703 (0.679-0.727)	0.001

	• Family history of diabetes mellitus • Gestational diabetes in previous pregnancy	• No=0; Yes=2			
Harrison[12] Model 1 Model 2	• Age (years) • Body mass index (BMI) • Race • Family history of diabetes mellitus • Gestational diabetes in previous pregnancies • Fasting plasma glucose (FPG)	• <25=0; 25-34=1; ≥35=2 • <20=0; 20-34.9=1; ≥35=2 • White=0; East Asian/South Asian/African=1 • No=0; Yes=1 • No=0; Yes=2 • If score ≥3 assess FPG: • FPG 4.61-4.89 mmol/l • FPG ≥4.9 mmol/l	0.4751 (0.451-0.4995) 0.8662 (0.8336 – 0.89869)	0.753 (0.675-0.832) 0.83 (0.77-0.90)	<0.001 0.1846
Syngelaki[13]	Gestational diabetes in previous pregnancy	No formula available in article	Could not be calculated as	0.823 (0.820-0.826)	

	Family history of DM Age (years) Weight (kg) Height (cm) Race Method of conception Birth weight of previous pregnancy		inadequate information on last pregnancy birth weight available		
Nanda[14]	Age (years) Body mass index (BMI) Race Gestational diabetes in previous pregnancy Previous baby's birth weight >90th centile (prevBW)	= 1/[1+exp(-β)] B= {-8.68947 + (0.05365*age) + (0.10852*BMI) + (1.00312 * South Asian) + (0.88785* east Asian) + (3.72259 * previous GDM) + (0.67673*prevBW >90th centile)	0.622 (0.563 – 0.681)	0.788 (0.759-0.817)	<0.001
Capula[15]	Age (years) Pregravid body mass index (BMI) Previous gestational diabetes (GDM), polycystic ovarian syndrome (PCOS) Fasting plasma glucose (FPG) 5.6-6.9 mmol/l before pregnancy	= Constant-2.2532*(Age/10) + 0.4128*(Age/10)^2 + 0.0795*pregravid BMI Constant is intercept depending on previous GDM, PCOS, FPG 5.6-6.9 mmol/l before pregnancy	0.534 (0.48 - 0.59)	(information not available)	

Abbreviations: a AUROC, area under receiver operating curve

Discussion:

This study aimed to evaluate the use of risk indicators to develop a statistical prediction model for GDM. Traditionally identified risk factors such as BMI, age, or family history of diabetes mellitus have been associated with GDM in other populations. [21-24] Data on GDM in Africa, especially since the introduction of the FIGO criteria is scant. Available data found an association with GDM and obesity, family history of diabetes mellitus, previous stillbirth, previous macrosomic child and age >30 years in some sub-Saharan African populations. [23]

The fasting glucose appears to be a very attractive tool for screening pregnant women for GDM. However, all pregnant women would have to present in a fasted state for screening, thus this approach can only take place on the second antenatal visit, and would require all pregnant women to be tested. While this approach may not seem unrealistic, it can prove to be challenging in a low income country where women have to travel a great distance to the healthcare facility and they often do not have funds for transport. Thus an alternate screening tool that could be used easily on the first antenatal visit to stratify a women's risk for GDM in the current pregnancy was investigated.

It was found that a previous history of delivering a baby weighing ≥4000 g and an elevated random blood glucose were independent predictors of developing GDM. Church et al. [25] and Meek et al. [26] found that the random glucose was a promising screening tool for GDM with AUROC of 0.8 and 0.86 respectively. By comparison these retrospective studies employed a 2-stage screening protocol for GDM and did not use the currently widely accepted FIGO diagnostic criteria. However, by comparison the basal random glucose alone was a poor predictor of women likely to

develop GDM in our study. Thus it was proposed that this nomogram-based scoring system, by adding other variables to the random blood glucose, will better identify women at risk at GDM compared to the random blood glucose alone. This premise requires prospective validation of the nomogram in a real-world setting.

Other studies have also identified risk factors. [18, 19, 21-24] Only nine of these studies summarised the significant risk factors into a score or a clinical prediction model, of which eight (8) were tested on our study population (Table 4). These tests performed poorly as a screening tool in our study population compared with their derivation populations. This poor performance may be a result of testing these scores on a low risk pregnant population. Risk factors may play a less significant role in predicting GDM when universal screening is applied and the FIGO diagnostic criteria are used. By contrast most of the afore-mentioned scoring systems used a selective screening approach and used criteria other than that recommended by FIGO for the diagnosis of GDM in the derivation and the validation of their scores. [7-14] Furthermore, many of these scores use logarithmic equations in their calculations, thus necessitating a computer in the clinic, which is not always available in South African antenatal clinics. [9, 13, 14, 15]

As South Africa is a resource-restricted country that faces a dual burden of disease, i.e. communicable and non-communicable diseases, a selective screening approach is an attractive option for the diagnosis of GDM as it seems the more cost effective approach. As a risk-factor based approach performs inconsistently, a scoring system that incorporates the more significant risk factors in a population may be a better option. Thus, a nomogram that incorporates the significant factors in a South African population was proposed. The BMI and history of previous deliveries are currently part of routine antenatal practice. The random blood glucose can easily be tested at

the first antenatal visit, making the random glucose a clinically applicable tool for early in pregnancy. In some settings an HbA1c may be available. However, it was demonstrated that including the HbA1c into the risk stratification tool does not significantly influence the patients' risk of GDM. South Africa has a high burden of HIV. In our study HIV did not influence the incidence nor did it contribute as a predictive marker of GDM.

The risk stratification system proposed by Harrison et al. [12] performed well in our study population. This score suggested by Harrison et al. [12] is based on the patient's age in years, BMI, race, family history of diabetes mellitus, a history of GDM in a prior pregnancy and fasting plasma glucose. The advantage of Harrison's [12] system is that it is a scoring system rather that a logarithmic equation, and it incorporates information that is routinely obtained on the first antenatal visit. However, it will require the patient to present to the clinic in a fasted state for a second visit before the risk stratification can be completed. This may be problematic in our setting of a low-middle income population that may not live close to the clinic. In addition, a selective screening approach may not be complied with if it requires the healthcare worker to recalculate the risk on multiple visits. Our proposed nomogram incorporates only two historical factors and a random glucose, thus making it quick and easy to use at the first antenatal visit.

There is an increasing health burden related to obesity and type 2 diabetes mellitus in sub-Saharan Africa, yet little is known about the prevalence of GDM. [27] In South Africa and many other countries worldwide screening programs are based on risk factors. However, it has been demonstrated that a selective screening approach shows a low compliance to guidelines. Hence, many women are not screened and GDM remains under-diagnosed. [28] The FIGO criteria have been criticised for its low

diagnostic thresholds. Several studies have shown that women diagnosed with GDM based on the IADPSG criteria had higher adverse outcomes such as fetal macrosomia, risk of primary caesarean delivery and pre-eclampsia compared with women with no GDM. [29-30]

Screening for GDM is necessary as it has both short- and long-term implications for mother and child. The FIGO diagnostic criteria have been adopted almost universally. [2] A simple nomogram that can be used for predicting the probability of developing GDM at the first antenatal visit was proposed. A limitation of this study is that the prediction model needs to be tested prospectively in the screening and diagnosis of GDM so that it can be validated, and a threshold of clinical usefulness can be determined before it can be widely implemented.

Conclusion:

Universal screening for GDM may be an unachievable ideal in low-middle income countries. Random glucose and risk factors alone perform poorly as screening tools. Ideally women should be stratified as high- or low-risk for GDM at their first antenatal visit, thus avoiding repeated clinic visits which may negatively influence compliance to care. As an alternative to improve the model of selective screening a nomogram-based score that can be used at first antenatal visit to identify women at high risk of GDM was proposed.

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Chapter 4

Evaluating the utility of a point-of-care glucose meter for the diagnosis of gestational diabetes

Adapted from:

Adam S, Rheeder P. Evaluating the utility of a point-of-care glucose meter for the diagnosis of gestational diabetes. Int J Gynaecol Obstet (2017) Nov 21. doi:10.1002/ijgo.12399 [Epub ahead of print]

Keywords: Glucometer; Gestational diabetes; Accuracy; Point-of-care testing

Synopsis: The Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) was found to perform poorly for the diagnosis of gestational diabetes mellitus as compared with the gold-standard laboratory test.

Abstract

Objective:

To investigate the performance of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) in diagnosing gestational diabetes mellitus (GDM) versus the gold-standard laboratory test.

Methods:

In a prospective cohort observational study at a primary healthcare clinic in Johannesburg, South Africa, 1000 pregnant women, excluding known diabetics, were recruited between 2013 and 2016. A 75 g 2-hour oral glucose tolerance test (OGTT) was scheduled at 24–28 gestational weeks. Glucose was measured in venous blood (laboratory) and capillary blood (glucometer). GDM was diagnosed via FIGO criteria. Diagnostic accuracy was evaluated by calculating the sensitivity, specificity, and coefficient of variance (CV) of the glucometer test, and by Bland–Altman plots.

Results:

Data from 529 women were analyzed. Of these, 141 (26.7%) and 79 (14.9%) were diagnosed with GDM by laboratory and glucometer measurements, respectively. The results were concordantly positive for GDM on the glucometer and laboratory for 38 (7.2%) women. In 103 (19.5%) GDM would have been diagnosed on laboratory measurement, but not if the glucometer was used. Forty-one (7.8%) women would have been diagnosed with GDM had the glucometer been used, but not on laboratory analysis of glucose. The CV of the glucometer ranged from 15% to 17%. Bland–Altman plots showed a positive bias of the glucometer results at 0 hours, but a

negative bias at 1 and 2 hours of the OGTT. The sensitivity and specificity of the glucometer for the diagnosis of GDM were 27.0% and 89.4%, respectively.

Conclusion:

Use of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) for the diagnosis of GDM cannot be recommended.

Introduction

After decades of research, there is now almost universal consensus regarding the screening and diagnostic criteria for gestational diabetes mellitus (GDM). [1] Hyperglycemia in pregnancy is associated with adverse perinatal outcomes and increases long-term risks for both mother and child. [2-4] Despite investigations into other screening and diagnostic tests, the 75 g 2-hour oral glucose tolerance test (OGTT) remains the cornerstone of diagnosis. [5] Furthermore, there is a shift away from conducting traditional risk-factor-based screening among high-risk women only to universal screening for GDM among all pregnant women. [1]

The OGTT is not without limitations. Both a trained phlebotomist and laboratory facilities for glucose measurement are required. In addition, the results of the OGTT are available only several days later, potentially necessitating more clinic visits by the woman. With over a million pregnancies registered in South Africa every year, this approach to screening for GDM places an enormous burden on the healthcare system and the pregnant women. [6]

To make universal screening for GDM feasible, a point-of-care (POC) test for glucose with good accuracy and precision is required, especially in low-resource settings. [1] It is generally accepted in clinical practice that capillary blood glucose and venous plasma glucose measurements are comparable. [7-9] However, laboratory tests are performed on venous plasma, whereas POC tests are usually performed on capillary whole blood. Glucose levels vary depending on the source of the blood sample used for analysis; the variation is attributed to differences in glucose extraction by tissues, perfusion, oxygenation, pH, and temperature. [10] The increased volume of distribution associated with pregnancy may further influence these measurements.

[11] Capillary blood glucose concentrations have been shown to be significantly higher than venous glucose concentrations. [10]

Despite advances in glucometer technology over the past decade, the glucose POC device does not perform consistently on statistical analysis. [12, 13] Most studies have focused on evaluating use of the glucometer for monitoring and guiding insulin management for known patients with diabetes mellitus [12, 13], and few have investigated use of the POC glucometer for the diagnosis of GDM. [14-16] The POC glucometer represents an attractive option for the diagnosis of GDM, especially in low-resource settings where laboratory services and transportation may not be readily available. Furthermore, a POC device would facilitate timely diagnosis of GDM and initiation of its management. In turn, this on-site diagnosis might improve adherence to screening guidelines, especially if universal screening for GDM is implemented. A POC glucometer would also facilitate a diagnosis of GDM based on elevated fasting glucose levels alone [17], which is important for populations where most cases of GDM are currently diagnosed on the basis of an elevated fasting plasma glucose alone, including the present study population.

The use of glucometers for monitoring and management of diabetes mellitus has been extensively studied and is generally accepted as part of care of the diabetic patient, despite variations in the performance of POC devices relative to the gold-standard laboratory test. [12, 13, 14-20] Although FIGO guidelines recommend use of the glucometer for the diagnosis of GDM in low-resource settings [1], there is less robust, and often conflicting, evidence regarding their use for GDM diagnosis. [14-16] The aim of the present study was therefore to investigate the performance of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany), which is

the most commonly available POC device in the study setting, in the diagnosis of GDM.

Materials and Methods

The present analysis formed part of a larger study of screening strategies for GDM in South Africa. In a prospective cohort observational study, 1000 pregnant women were recruited at a primary healthcare clinic in Johannesburg, South Africa, between September 1, 2013, and June 30, 2016. Approval for the study was obtained from the University of Pretoria, Faculty of Health Sciences Ethics Committee (Protocol 180/2012). Informed consent was obtained from every woman prior to enrollment in the study.

The sample size was calculated by using a 5% margin of error and a 95% confidence interval (CI), which determined that 400 women would be needed to complete the study. Considering loss to follow-up (50%), pregnancy loss (15%), and patient migration (20%), a sample size of 1000 (to the nearest 100) was calculated.

Women at less than 26 gestational weeks were recruited. Those known to have diabetes mellitus or were more than 26 weeks pregnant were excluded.

At recruitment, each woman completed a questionnaire of demographic data and underwent an evaluation of risk factors for GDM. Gestational age was determined by the woman's last normal menstrual period, ultrasound scan, or measurement of fundal height. Random blood glucose was measured at recruitment on both a POC device and at the laboratory. If the random glucose level was greater than 11.1 mmol/L (199.8 mg/dL), the woman was referred to the local hospital for further management of overt diabetes. Otherwise, a 75 g 2-hour OGTT was scheduled at 24–28 gestational weeks. GDM was diagnosed on the basis of FIGO criteria: namely, any one glucose value corresponding to 5.1 mmol/L (91.8 mg/dL) or higher at 0 h, 10 mmol/L (180 mg/dL) or higher at 1 hour, or 8.5 mmol/L (153 mg/dL) or higher at 2 hours. [1]

Venous blood was drawn by a trained research nurse into a fluoridated tube and was stored on ice until delivery to the laboratory as soon as possible, simulating the real clinical situation. The sample was centrifuged on arrival at the laboratory, unlike other studies in which it was centrifuged within 5–30 minutes. [21] The laboratory is accredited by the South African National Accreditation System, and uses the Beckman DXc hexokinase method to measure glucose. The laboratory test had a mean imprecision (co-efficient of variation) of 1.68%, 1.38%, and 1.48% at glucose levels of 2.4 mmol/L (43.2 mg/dL), 12 mmol/L (216 mg/dL), and 22 mmol/L (396 mg/dL), respectively. The mean bias was 3.65, 1.36, and 1.27 at glucose levels of 2 mmol/L (36 mg/dL), 7 mmol/L (126 mg/dL), and 15 mmol/L (270 mg/dL), respectively.

At the same visit, capillary glucose was tested on the Roche Accuchek Active® POC device (Roche Diagnostics, Mannheim, Germany). Two trained research nurses performed the POC glucose measurements. The woman's hands were cleaned with alcohol and allowed to dry prior to obtaining the capillary sample. The test was carried out within 5 minutes of venipuncture.

The Roche Accuchek Active® meter (Roche Diagnostics, Mannheim, Germany) measures glucose by reflective photometry using the hexokinase method. The glucose values displayed correspond to the estimated plasma glucose concentration even though the device measures glucose in whole blood. The POC device was calibrated in accordance with the manufacturer's guidelines and test strips were stored appropriately. During the study, four different lot numbers were used so that all test strips remained within their expiration date; however, differences in test strips used for glucometers might diminish analytical quality because studies have shown that significant variability exists between test strips. [22, 23]

The study data were analyzed by using Stata version 13 (StataCorp, College Station, TX USA). Continuous variables were analyzed by Student *t* test. Glucose measurements taken at 0 hours, 1 hour, and 2 hours were analyzed separately. Laboratory glucose measurements were regarded as the “gold standard”.

Capillary glucometer results were evaluated in accordance with ISO 15197:2013 guidelines. [24] These recommend that, for a blood glucose level of 4.2 mmol/L (75.6 mg/dL) or less on laboratory testing, glucometer results should be within 0.83 mmol/L (14.94 mg/dL) for at least 99% of samples tested. For blood glucose levels above 4.2 mmol/L (75.6 mg/dL) on laboratory testing, glucometer results should be within 15% for at least 99% of samples tested. [24]

Multiple statistical methods were used to analyze the accuracy of the glucometer. Bland-Altman plots were generated for glucose measurements at 0 hours, 1 hour, and 2 hours to assess agreement between the glucometer and laboratory assays. Acceptable limits of agreement were defined as –0.5 to +0.5. The coefficient of variation (CV), defined as the ratio of the SD to the mean, was determined to assess variability, and a CV of less than 5% was taken as acceptable. The Youden index (J) was used to evaluate the performance of the glucometer test, and was calculated by the formula J = sensitivity + specificity – 1. The sensitivity and specificity of the glucometer for the diagnosis of GDM in clinical practice was determined. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Of the 1000 pregnant women recruited, 82 (8.2%) experienced fetal loss and did not complete the study, 163 (16.3%) moved from the area, 194 (19.4%) were lost to follow-up, and 7 (0.7%) withdrew consent. In addition, the paired glucose data were incomplete for 25 (2.5%) women. Thus, 529 (52.9%) women had complete data and formed the study population (Table 1).

Table 1 Clinical characteristics of the study population (n=529).

Characteristic	Mean value	Standard deviation	95% CI	Range
Age, years	27.3	5.84	26.8–27.8	13 – 42
Gestational age at recruitment, week	18.7	5.3	18.2–19.1	5 – 26
BMI (kg/m$^{2)}$	26.5	5.37	26.1–27.0	14.8 – 47.2
Hemoglobin, g/dL (mmol/L)	12.3 (7.7)	1.81	12.2–12.5 (7.5–7.8)	6.1 – 17.2
Glycated hemoglobin/HbA1c, % (mmol/mol)	5.2 (33)	0.39	5.2–5.2 (33.0–34.0)	3.8 – 6.5

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval

Gestational age was determined by last normal menstrual period for 443/529 (83.7%) women and by early ultrasound for 86/529 (16.3%) women. A hemoglobin level of less than 11 g/dL (6.8 mmol/L) was considered to indicate anemia. Ninety-five (18%) women were considered anaemic. The presence of anemia had no significant effect on the glucometer measurement (P=0.903 at 0 hours, P=0.331 at 1 hour, and P=0.045 at 2 hours), but had an effect on the laboratory measurement of glucose (P=0.006 at 0 hours, P=0.162 at 1 hour, and 0.068 at 2 hours) according to regression analysis.

Among the 529 women, 141 (26.7%) women were diagnosed with GDM via the gold-standard laboratory measurement. By contrast, 79 (14.9%) women were diagnosed with GDM via glucometer measurement. The results were concordantly positive for GDM on the glucometer and laboratory for 38 (7.2%) women. In 103 (19.5%) GDM would have been diagnosed on laboratory measurement, but not if the glucometer was used. Forty-one (7.8%) women would have been diagnosed with GDM had the glucometer been used, but not on laboratory analysis of glucose. The mean glucose levels at 0 hours, 1 hour and 2 hours of the OGTT measured by the laboratory and the glucometer are shown in Table 2.

Table 2 Mean glucose levels in OGTT.

Test	Glucometer, capillary		Laboratory, venous		*P* value
	mmol/L	mg/dL	mmol/L	mg/dL	
0 hour					
Mean (95% CI)	4.4 (4.3–4.5)	79.0 (78.1–80.1)	4.8 (4.7–4.8)	85.5 (83.9–86.9)	0.162
Range	2.7–8.4	48.6–151.2	2.1–13.4	37.8–241.2	
1 hour					
Mean (95% CI)	6.6 (6.4–6.7)	118.1 (115.9–120.2)	5.9 (5.8–6.0)	105.8 (103.5–108.2)	<0.001
Range	2.6–12.9	46.8–232.2	2.7–12.1	48.6–217.8	
2 hour					
Mean (95% CI)	6.0 (5.9–6.1)	107.8 (106.0–109.6)	5.6 (5.4–5.7)	99.0 (97.7–101.7)	<0.001
Range	3.3–15.5	59.4–279.0	2.8–13.8	50.4–248.4	

Abbreviation: OGTT, oral glucose tolerance test

The CV of the glucometer test was 16%, 17%, and 15% at 0, 1, 2 hours, respectively, indicating poor precision of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) relative to laboratory measurements, which range from 0.97% to 3.41%.

The glucometer results were evaluated in terms of the ISO guidelines (Table 3). Overall, 216/290 (74.5%) glucometer readings were within 0.83 mmol/L (14.94 mg/dL) of the corresponding laboratory measurement for glucose levels of 4.2 mmol/L (75.6 mg/dL) or less, and 758/1297 (58.4%) glucometer measurements were within 15% of the laboratory measurement for glucose levels above 4.2 mmol/L (75.6 mg/dL).

Table 3 Stratification of glucometer readings as per ISO guidelines [a].

Test	No. (%) of samples ≤4.2 mmol/L (75.6 mg/dL) within 0.83 mmol/L (14.94 mg/dL) of lab value	No. of samples >4.2 mmol/L (75.6 mg/dL) within 15% of lab value)
0 h	140/161 (87.0)	232/368 (63.0)
1 h	43/53 (28.3)	218/476 (45.8)
2 h	33/76 (44.4)	308/453 (68.0)
Overall	216/290 (74.5)	758/1297 (58.4)

[a] ISO 15197:2013 guidelines [24]

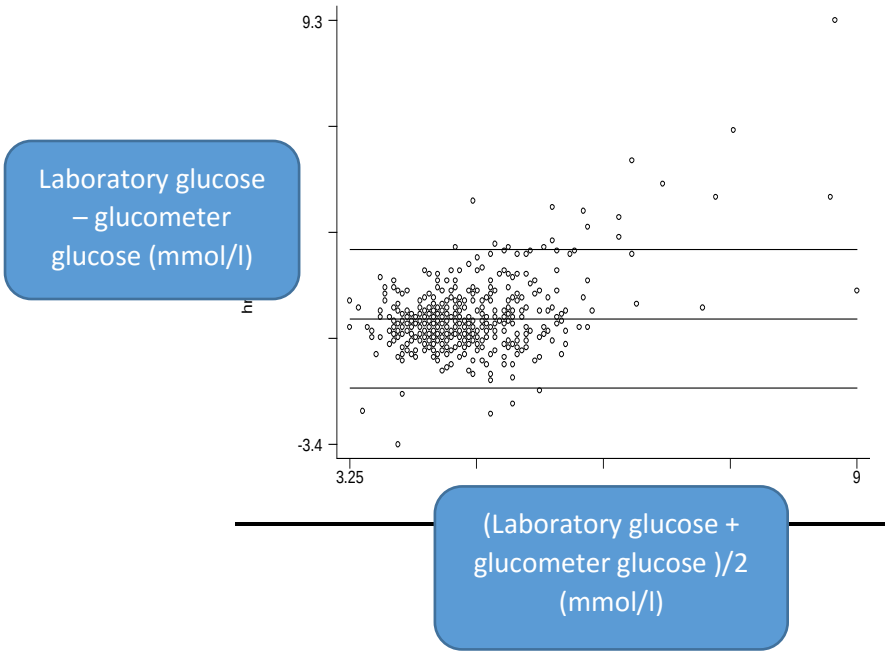
Bland–Altman plots were used to assess agreement between the glucometer and laboratory measurements of glucose (Figure 1). The plot at 0 hours (Figure 1a) showed an average glucose level (across laboratory and glucometer measurements) of 3.3–9.0 mmol/L (58.5–162.0 mg/dL). There was an acceptable positive bias of 0.35 (95% confidence interval [CI], 0.26–0.44); in other words, the laboratory measurements were higher on average than the glucometer results. The difference between the laboratory measurement and the glucometer measurement ranged from 1.7 to 2.4 mmol/L (30.7–43.3 mg/dL).

The Bland-Altman plot at 1 hour (Figure 1b) showed an average glucose level of 3.4–11.0. mmol/L (61.2–197.1 mg/dL). There was an unacceptable negative bias of –0.68 (95% CI, –0.78 to –0.59); in other words, the laboratory measurements were lower on average than the glucometer results. The difference between the laboratory

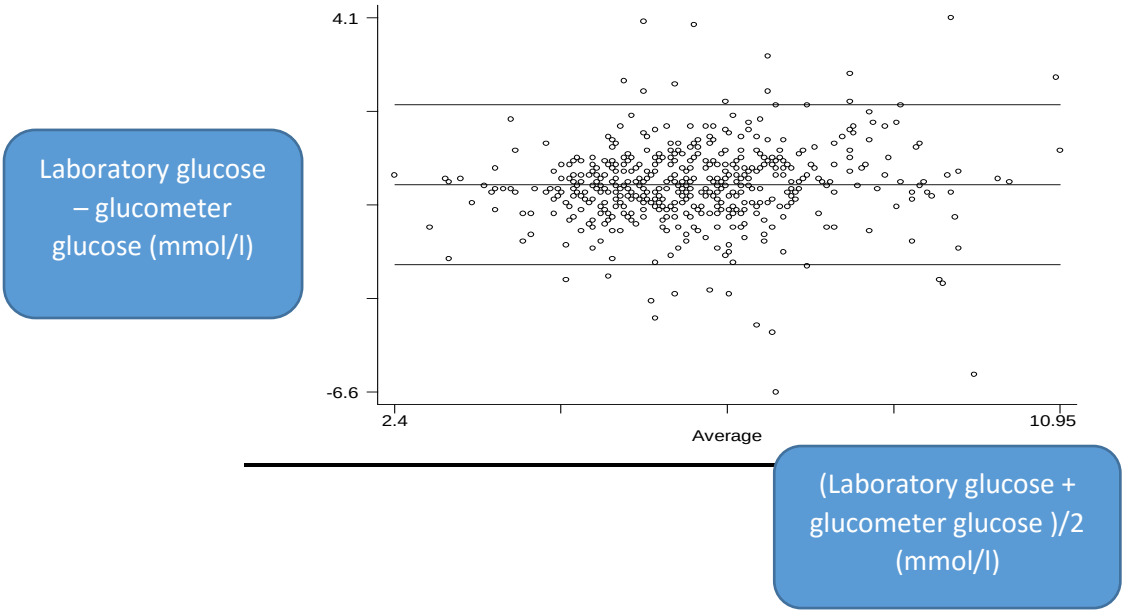
measurement and the glucometer measurement ranged from –3.0 to 1.6 mmol/L (–53.5 to 28.8 mg/dL).

The Bland–Altman plot at 2 hours (Figure 1c) showed an average glucose level of 3.8–11.3 mmol/L (67.5–202.5 mg/dL). There was an acceptable negative bias of –0.45 (95% CI, –0.54 to –0.36); in other words, the laboratory measurements were lower on average than the glucometer results. The difference between the laboratory measurement and the glucometer measurement ranged from –2.6 to 1.7 mmol/L (–47.4 to 31.3 mg/dL).

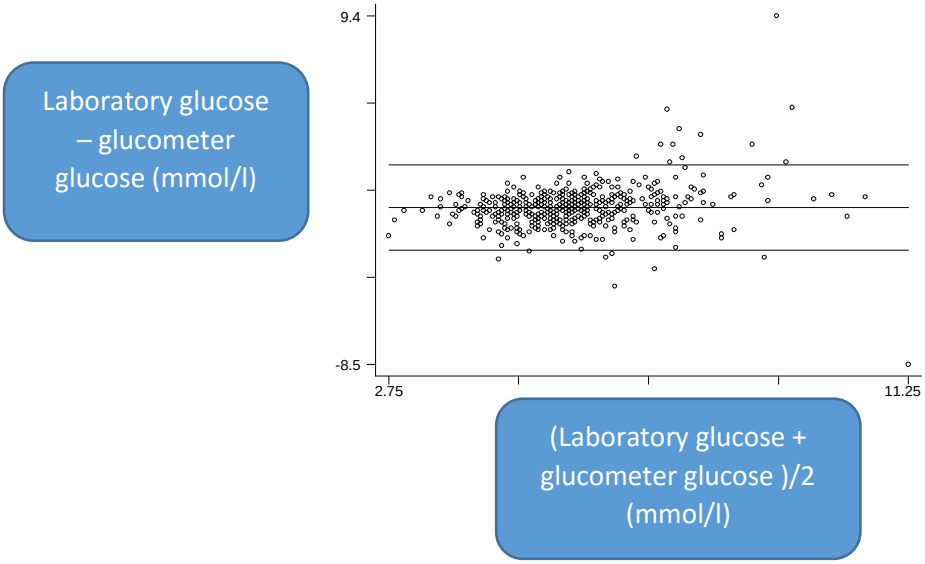
a) <u>0-hour</u>



b) <u>1-hour</u>



c) <u>2-hour</u>



<u>Figure 1: Bland-Altman plots for glucose (mmol/l) at (a) 0 hour, (b) 1 hour, and (c) 2 hour measurements of 75 g OGTT</u>

If the diagnosis of GDM was based on the glucometer readings as compared to the laboratory gold-standard, the diagnosis of GDM with the glucometer would have a sensitivity of 27.0% (95% CI 19.8 – 35.1) and specificity of 89.4% (85.9 – 92.3%) (Table 4). The Youden index was 0.16 and accuracy was calculated to be 72.8%.

Table 4 Diagnostic characteristics of point-of-care device in the diagnosis of GDM (n=529) [a]

Diagnosis by lab test	Diagnosis by glucometer [b]		
	GDM	No GDM	Total
GDM	38 (7.2)	103 (19.5)	141 (26.7)
No GDM	41 (7.7)	347 (65.6)	388 (73.3)
Total	79 (14.9)	450 (85.1)	529 (100)

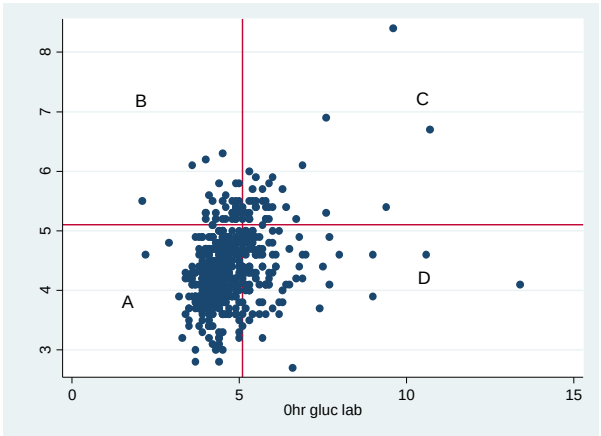
[a] Values are given as number (percentage)

[b] Receiver operator characteristic curve analysis of glucometer diagnosis: area under curve, 0.58; sensitivity, 27.0%; specificity, 89.4%; positive predictive value, 48.1%; negative predictive value, 77.1%.

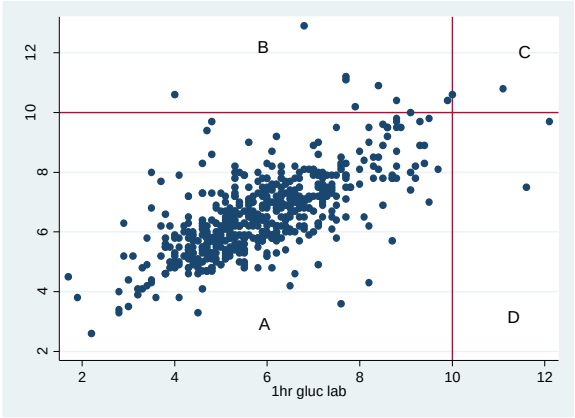
The McNemar test showed a relative difference of 0.138 (95% CI 0.089 – 0.186) when the diagnosis of GDM using laboratory analysis was compared to the diagnosis of GDM using a glucometer. The exact odds ratio was 2.5 (95% CI 1.733 – 3.702), meaning that a pregnant woman is 2.5 times more likely to be diagnosed with GDM if the glucose measurement is analyses at the laboratory rather than a glucometer.

Clinical accuracy was further evaluated by scatter plots (Figure 2). Overall, 137 of the 141 (97.2%) women with an abnormal OGTT by laboratory test had a fasting glucose level of ≥5.1 mmol/L (≥91.8 mg/dL). The fasting plasma glucose had a good predictive value for the diagnosis of GDM with an area under the ROC curve (AUC) of 0.99. By contrast, the capillary glucose measurement performed poorly with an AUC of 0.58; in other words, only 68 (48.2%) measurements were 5.1 mmol/L (91.8 mg/dL) or above on the glucometer.

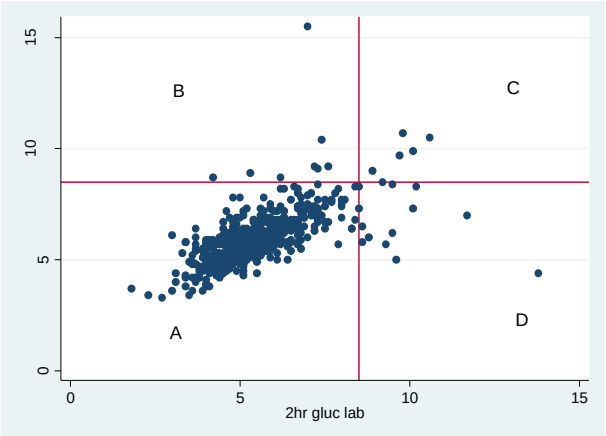
a) 0-hour*



b) 1-hour*



c) 2-hour*



2-

Region	0-hour (a) (n=529)	1-hour (b) (n=529)	2-hour (c) (n=529)
A	374 (70.7%)	517 (97.7%)	504 (95.3%)
B	34 (6.4%)	9 (1.7%)	8 (1.5%)
C	31 (5.9%)	1 (0.2%)	5 (0.9%)
D	90 (17%)	2 (0.4%)	12 (2.3%)

*Footnote: The reference lines on the scatter plots are in keeping with the FIGO diagnostic criteria for GDM. [1] Regions A and C on the graphs show concordance between glucose readings in the laboratory and on the glucometer, i.e. both methods report measurement above or below the thresholds thus not influencing the diagnosis of GDM. Regions B and D demonstrate the discordant sample sets that would lead to misdiagnosis of GDM.

Figure 2: Scatter plots of laboratory glucose measurements versus glucometer measurements at (a) 0-hour, (b) 1-hour, and (c) 2-hour of the OGTT*

Discussion

The present study found that the glucometer performed poorly as compared with the laboratory when used for the diagnosis of GDM. It did not meet the ISO criteria and so has poor analytic accuracy. [24] It also has poor clinical accuracy, as demonstrated by the large number of women with GDM who would not have been diagnosed if their glucose level had been measured only by glucometer (Table 4).

Previous studies investigating a POC glucometer for the diagnosis of GDM have recommended its use in clinical practice. [14-16] A recent South African study found that most glucometers were acceptable, although the authors warned about the variability among different meters and the need for independent comparison. [25] The present study found that the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) performed poorly when used for the diagnosis of GDM. This finding is consistent with a review of POC glucometers that found that a reliable glucose reading relative to the laboratory reference is achieved only by approximately 50% of POC meters. [26]

In the present study, the glucometer was found to have poor sensitivity and specificity for the diagnosis of GDM. Overall, 103 (19.5%) cases of GDM would not have been diagnosed by the glucometer alone. Numerous variables can influence the measured glucose level, including the POC device or test strips, patient medications, hematocrit level, blood pH, the site from which blood was obtained, and the detection method used by the POC device [27]. Bhavadharini et al. [19] also investigated the use of a glucometer in a low-resource setting, and reported a poor correlation between the glucometer and the laboratory. They suggested using a lower cut-off for the capillary reading; however, their proposal to use the glucometer as a screening tool would

necessitate two OGTTs, which would increase the number of visits to the clinic and might also deter women from have the test at all owing to the adverse effects of the oral glucose load.

It was previously demonstrated that capillary glucose values are higher than venous glucose readings. [10] In the present study, however, the venous glucose measurements at 0 hours were higher. This discrepancy in glucose measurements may be due to oxidation in the sample caused by the longer time between sampling and centrifugation. Alternatively, the variation in glucometer strips might have led to altered enzyme activity or enzyme coverage, thus resulting in lower values measured on the glucometer. [28]

Most cases of GDM in the study were diagnosed on the basis of fasting glucose. The possibility of applying a correction factor to the glucometer was considered, but a simple user-friendly formula could not be derived. Furthermore, correction factors do not perform well when applied to the general population, and thus would not be feasible in a universal screen for GDM.

The advantages of the study include its large patient numbers in a low-resource real-world setting. In addition, two research nurses were used to minimize variability (two research nurses were needed to accommodate their other commitments during the study period). The study also has limitations. First, only one POC glucometer system was tested, and four lots of test strips were used, thereby increasing variability. For the laboratory test, blood was not centrifuged within the recommended 30 minutes owing to the distance between the laboratory and the clinic. Last, citrate tubes were not used for the collection of venous blood for glucose measurements.

The use of a POC device remains an alluring tool for the diagnosis of GDM. There have been conflicting results from recent studies. [19, 20] Whereas Bhavadharini et al. [19] found a poor correlation, Jadhav et al. [20] reported 100% correlation between the glucometer and the laboratory. It can be concluded that glucometers have variable performance and should be used cautiously for the diagnosis of GDM.

On the basis of the present study, use of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) for the diagnosis of GDM cannot be recommended. There is a need to test and improve the accuracy and precision of POC glucometers for the diagnosis of GDM. Newer technologies, such as smartphone measurements of glucose or continuous glucose monitoring, might have to be considered as alternatives to the OGTT for the diagnosis of GDM.

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Chapter 5

Association between gestational diabetes and biomarkers: A role in diagnosis

Adapted from:

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Abstract

Background:

The use of markers of insulin resistance, chronic inflammation, and adipokines has been investigated as a tool for the prediction of GDM. However, it has been illustrated that there are differences in these markers between ethnic groups. Data regarding gestational diabetes and especially the related biomarkers in an African population is sparse

Objectives:

The association between markers of insulin resistance, chronic inflammation, and adipokines and gestational diabetes (GDM) were investigated.

Methods:

In this case-cohort study in Johannesburg women with GDM and controls without GDM were included. The ability of biomarkers to identify women at high risk of GDM was tested.

Results:

Of the 262 pregnant women, 83 (31.7%) had GDM. Women with GDM had a higher BMI ($p=0.04$) and had more clinical risk factors ($p=0.008$). It was found that a significant difference in fasting insulin ($p <0.001$), adiponectin ($p=0.046$), HOMA-IR ($p <0.001$) and QUICKI ($p <0.001$). HOMA-IR (AUROC=0.82) as well as QUICKI (AUROC=0.82) improved the ability of risk factors to identify women at high risk of GDM.

Conclusion:

Women with GDM had a higher BMI and more clinical risk factors present. Fasting insulin, HOMA-IR, QUICKI and adiponectin were significantly different in women with GDM. Adiponectin levels seem to be influenced by adiposity. The addition of HOMA-IR or QUICKI to clinical risk factors may improve the ability to predict women at risk of GDM. In the future these biomarkers should be investigated for the early identification of pregnant women at risk of GDM.

Background:

The International Diabetes Federation (IDF) reports that the incidence of gestational diabetes (GDM) is increasing at an alarming rate with recent studies reporting an incidence as high as 30%. [1] This increase in GDM parallels the obesity epidemic. Furthermore, the diagnosis of GDM infers the long-term risk of developing type 2 diabetes mellitus (T2DM) on the pregnant women. [2] In addition, the offspring of a mother with GDM has an increased risk of developing glucose intolerance and obesity in later life. [3]

The 2-hour-75-grams oral glucose tolerance test (OGTT) remains the gold-standard for the diagnosis of GDM. Universal screening for GDM is now recommended by most international organisations. [4] Hence, all pregnant women will require an OGTT which is an unpleasant time-consuming test. The associated nausea, vomiting and bloating will make it more likely that women will not complete the test. [5] It is advised that the OGTT be conducted at 24 to 28 weeks of gestation. At this gestation in the late second trimester GDM has already developed and the hyperglycaemia may have already caused adverse effects. [6] Thus there is a need for a simpler more effective test that can either identify women at high risk of developing GDM or diagnose GDM earlier in pregnancy.

Pregnancy is characterised by increasing insulin resistance from mid-gestation. The relative hyperglycaemia of pregnancy is an important source of nutrition and is vital for the development of the fetus. In women with GDM insulin secretion is inadequate to compensate for the characteristic insulin resistance of pregnancy. Insulin resistance most likely exists before pregnancy in women who develop GDM. Thus GDM is partly a result of chronic insulin resistance. [2]

GDM and T2DM have similar predisposing factors leading to dysglycaemia. Obesity is a major risk factor and it may contribute to the pathogenesis of both conditions via chronic subclinical inflammation, low grade activation of the acute phase response and the dysregulation of adipokines. [7]

The use of markers of insulin resistance, chronic inflammation, and adipokines has been investigated as a tool for the prediction of GDM. [8-12] However, it has been illustrated that there are differences in these markers between ethnic groups. [13] Data regarding gestational diabetes and especially the related biomarkers in an African population is sparse. However, the incidence of obesity, T2DM, and GDM in Africa continues to increase. [14, 15] The aim of this study was to investigate the association between the concentrations of biomarkers associated with glucose homeostasis and GDM in a South African population.

Methods:

This study formed part of a larger prospective cohort observational study investigating screening strategies for GDM in a South African population. Informed consent was obtained from all participants prior to enrolment into the study. The protocol for this study was approved by the University of Pretoria Health Sciences Ethics Committee (180/2012).

One thousand (1000) pregnant women that were less than 26 weeks pregnant were recruited at a primary healthcare clinic in Johannesburg, South Africa, between September 2013 and June 2016. Women known to have diabetes mellitus were excluded. The women completed a demographic questionnaire and had a random glucose and glycated haemoglobin (HbA1c) measured at the first visit. They returned within two weeks for a fasting glucose measurement. At the second visit serum and whole blood were stored for future testing. The blood was centrifuged at 4000 rpm for 15 minutes and serum was extracted. The samples were stored at -40 ºC. An OGTT was scheduled between 24- and 28-weeks of gestation. GDM was diagnosed based on the criteria recommended by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), i.e. any one abnormal value was diagnostic of GDM – fasting glucose ≥5.1 mmol/l, one-hour glucose ≥10 mmol/l, or two-hour glucose ≥8.5 mmol/l. [4]

For the analysis of the biomarkers a case-cohort study was conducted. HIV negative patients with GDM were selected. Twice the number of HIV negative patients without GDM were selected as the control group. The groups were matched for age, parity and gestational age. HIV positive women were excluded as HIV may be a confounder.

HIV has an effect on insulin resistance, chronic inflammation, and is associated with lipodystrophy thus influencing the adipokines. [16]

At the time of analysis, the frozen serum specimens were thawed and diluted. Insulin, C-reactive protein (CRP), and adiponectin were measured in the serum sample. These biomarkers were selected for analysis as they have been found to be significant in women with GDM, and thus hold the potential as being early markers for GDM, thus allowing earlier identification of women at risk of developing GDM. However, there has been little investigation into the use of these biomarkers in a Black African population.

During a normal pregnancy the insulin levels are increased due to insulin resistance caused by placental hormones, the C-reactive protein remains unchanged, and adiponectin is expected to decrease, but this difference disappears when corrected for body fat and insulin resistance. In a pregnancy affected with GDM it is expected that the insulin levels will increase, the C-reactive protein will increase most likely due to sub-clinical inflammation, and adiponectin levels will usually decrease. [2, 8, 10, 11]

The Insulin Sensitivity Index (HOMA-IR) was calculated from the fasting insulin and fasting glucose values using the equation: fasting insulin (microU/L) x fasting glucose (mmol/L) / 22.5. [17] The Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated by the following equation: $1 / [\log (I_0) + \log (G_0)]$. [17].

Data was analysed using STATA 13 software (StataCorp, College Station, TX USA). The women were stratified into two groups based on the presence or absence of GDM as we were investigating biomarkers that were influenced by GDM. Means or proportions were calculated for the two groups and the one-sided Students t-test and x^2 were used to assess univariate differences between the groups for continuous and categorical variables respectively. Statistical significance was set at 0.05. The groups

were further stratified according to obesity as obesity may have an effect on the adipokines. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Analysis of variance (ANOVA) tests were used to test for differences between the groups. Logistic regression was performed to assess the independent association of the BMI, fasting glucose, fasting insulin, adiponectin, and CRP with GDM as this was a case-control study. The odds ratio for fasting glucose, fasting insulin, HOMA-IR, QUICKI, adiponectin, and CRP were calculated in order to assess its usefulness in predicting GDM. The biomarkers were added to clinical variables that were previously identified as being significant in being able to detect GDM, viz. BMI, random venous glucose, and a history of delivery of a baby >4000 g, to assess whether the use of biomarkers would improve the predictive ability of the model. Statistical significance was set at $p < 0.05$. All datasets used in this study are available on request.

Results:

One thousand (1000) pregnant women were recruited. Eighty-two (8.2%) women had fetal losses and did not continue with the study, 163 (16.3%) women moved away from the area and were thus lost to follow up, 194 (19.4%) women were unreachable and 7 (0.7%) women withdrew consent for the study. Thus 554 (55.4%) women had complete data available for analysis. Four hundred and eleven (74.2%) women had a normal OGTT and 143 (25.8%) women were diagnosed with GDM.

One hundred and sixty (28.9%) women were HIV positive, and five (2.6%) had an unknown HIV status and were thus 165 women were excluded. Three hundred and eighty-nine women (70.2%) were included in this nested case cohort study. One hundred and twenty-seven (29.8%) women were excluded as there was no serum sample available for analysis or the specimen was haemolysed and unsuitable for analysis.

Thus, two hundred and sixty-two women were included in this study. In this cohort 179 (68.3%) women had a normal OGTT and 83 (31.7%) were diagnosed with GDM. Table 1 describes the demographic data of the study population.

Table 1: Demographic description of GDM vs non GDM women*

	GDM[a] (n=83)	No GDM[a] (n=179)	P
Age (years) (mean, range, SD)	27.5 15 - 41 6.42	26.3 15 - 42 6.06	0.150
Gestational age (weeks) (mean, range, SD)	18.7 7 – 26 5.45	19.3 5 – 26 5.39	0.640
Parity (mean, range, SD)	1 0 – 3 0.90	1.02 0 – 4 0.96	0.820
Body mass index at 1st visit (kg/m^2) (mean, range, SD)	27.7 18.9 – 47.1 5.53	26.1 14.8-45.6 5.57	0.040
Haemoglobin (g/dl) (mean, range, SD)	12.8 8.7 – 16.1 1.43	12.4 8.1 – 16.8 1.85	0.190
HbA1c[b] (%, mmol/mol) (mean, range, SD)	5.3 (34.4) 4.1 – 6.5 (21.3 – 47.5) 0.40	5.1 (32.2) 4 – 6.3 (20.2-45.4) 0.37	<0.001
Random glucose (mmol/l) (mean, range, SD)	4.7 3.3 – 6.5 0.55	4.4 2.9 – 9.3 0.79	0.004
≥1 Risk factors[c] present (n, %)	47 (56.60%)	70 (39.10%)	0.008

Abbreviations: GDM[a], gestational diabetes; HbA1c[b], glycated haemoglobin; Risk factors[c], advanced maternal age (age ≥35 years), obesity (BMI ≥30 kg/m2), family history of diabetes mellitus, history of delivery of a baby >4000 g, glucosuria, previous recurrent pregnancy loss, stillbirth, or birth of a baby with congenital abnormalities

* Non-GDM group not double the GDM group as some samples were inadequate or unsuitable for analysis due to haemolysis

Women with GDM had a higher BMI than the control group at their first antenatal clinic visit. The HbA1c and random glucose were also significantly higher compared with women who did not have GDM. Women with GDM were more likely to have at least one of the traditional risk factors for GDM, i.e. advanced maternal age (age ≥35 years),

obesity (BMI ≥30 kg/m^2), family history of diabetes mellitus, delivery of a previous baby more than four kilograms, glucosuria, previous recurrent pregnancy loss, stillbirth, or birth of a baby with congenital abnormalities.

Table 2 illustrates the comparison of biomarkers between women with and without GDM. The fasting insulin, HOMA-IR, QUICKI, and adiponectin were significantly different between the groups.

Table 2: Markers of insulin resistance, chronic inflammation, and adipokines

	GDM[a] (n=83)	No GDM[a] (n=179)	P
Fasting glucose (mmol/l) (mean, range, SD)	5.9 5.64 – 10.7 1.11	4.4 2.1 – 8.1 0.60	<0.001
Fasting insulin (uU/ml) (mean, range, SD)	9.68 1.8 – 56.5 9.77	6.36 1.0 – 29.3 3.84	0.001
Fasting insulin >10.4 uU/ml (n, %)	20 (24.10%)	11 (6.10%)	<0.001
Fasting glucose/ fasting insulin (mean, range, SD)	0.94 0.10 – 2.56 0.55	0.91 0.16 – 4.7 0.55	0.650
QUICKI[b] (mean,range, SD)	0.636 0.38 – 1.09 0.12	0.746 0.47 – 1.49 0.15	<0.001
HOMA-IR[c] (mean, range, SD)	2.67 0.37 – 18.58 3.17	1.26 0.21 – 5.99 0.82	<0.001
CRP[d] (mg/dl) (mean, range, SD)	7.7 0.6 – 73.6 8.53	7.3 0.4 – 74.8 8.16	0.700
CRP[d] >5 mg/dl (n, %)	49 (59.00%)	85 (47.50%)	0.140
Adiponectin (mmol/l) (mean, range, SD)	9.29 1.71 – 40.49 6.08	11.89 1.38 – 89.26 9.90	0.046

Abbreviations: GDM[a], gestational diabetes; QUICKI[b], Quantitative Insulin Sensitivity Check; HOMA-IR[c], Insulin Sensitivity Index; CRP[d], C-reactive protein

Women with GDM were stratified by their BMI. Forty-five women were categorised as non-obese, i.e. BMI <30 kg/m^2, and twenty-three women were obese, i.e. BMI ≥30 kg/m^2. Information on the height for fifteen women who were excluded from this analysis was unavailable. The concentrations of biomarkers between these two groups were compared, as illustrated in Table 3. The concentration of adiponectin was significantly lower in the obese group with GDM.

Table 3: Concentrations of biomarkers in women with GDM stratified by weight

	Non-obese[d] (n=45)	**Obese[e] (n=23)**	**P**
Age (years) (mean, range, SD)	26.7 17 – 41 6.01	29.1 15 – 40 6.52	0.128
Gestational age (weeks) (mean, range, SD)	18.7 7 – 26 5.85	20.3 9 – 28 4.73	0.262
Parity (mean, range, SD)	0.9 0 – 3 0.89	1.3 0 – 3 0.88	0.107
Body mass index (kg/m^2) (mean, range, SD)	24.6 18.9 – 29.8 3.21	33.6 30.08 – 47.14 4.02	<0.001
Fasting glucose (mmol/l) (mean, range, SD)	5.93 4.5 – 10.7 1.37	5.9 4.7 – 7.7 0.83	0.233
Fasting insulin (uU/ml) (mean, range, SD)	10.05 1.8 – 56.5 10.36	11.47 2.4 – 55 11.06	0.621
Fasting glucose/ fasting insulin (mean, range, SD)	0.98 0.10 – 2.56 0.14	0.75 0.14 – 2.13 0.45	0.140
QUICKI[a] (mean, range, SD)	0.64 0.40 – 1.09 0.14	0.60 0.38 – 0.92 0.10	0.230
HOMA-IR[b] (mean, range, SD)	2.82 0.37 – 14.56 3.29	3.13 0.54 – 18.58 3.78	0.738
CRP[c] (mg/dl)	6.64	7.83	0.301

(mean, range, SD)	0.6 – 17.3 4.0	1.5 – 18.3 4.85	
Adiponectin (mmol/l) (mean, range, SD)	10.57 2.94 – 40.49 6.83	6.28 2.72 – 15.37 3.40	0.013

Abbreviations: QUICKI[a], Quantitative Insulin Sensitivity Check; HOMA-IR[b], Insulin Sensitivity Index; CRP[c], C-reactive protein; Non-obese[d], BMI <30 kg/m^2; Obese[e], BMI ≥30 kg/m^2

The usefulness of the biomarkers as a screening tool for GDM was evaluated. (Table 4). The addition of biomarkers to clinical factors available at the first antenatal visit, viz. BMI, history of delivery of baby >4000 g, and random venous glucose greatly improved the predictive ability of the model to identify women at risk of developing GDM. The AUROC of the predictive model incorporating only the clinical factors was 0.69. The addition of biomarkers to the clinical factor-based model improved the predictive ability of the model, especially the addition of either the HOMA-IR or QUICKI.

Table 4: Performance of biomarkers in the prediction of gestational diabetes

Biomarker	AUROC[a]	OR[b]	SE[c]	p	95% CI[d]	AUROC[a] (Biomarker + clinical markers[e])
Fasting insulin (uU/ml)	0.62	1.10	0.03	0.003	1.03 – 1.16	0.77
Fasting glucose/ fasting insulin	0.52	1.12	0.28	0.650	0.68 – 1.84	0.72
QUICKI[f]	0.73	0.0006	0.0009	<0.001	0.00 – 0.01	0.82
HOMA-IR[g]	0.73	2.11	0.38	<0.001	1.48 – 3.01	0.82
CRP[h] (mg/dl)	0.55	1.01	0.02	0.700	0.97 – 1.04	0.73
Adiponectin (mmol/l)	0.60	0.95	0.02	0.048	0.90 – 0.99	0.75

Abbreviations: AUROC[a], area under receiver operating curve; OR[b], odds ratio; SE[c], standard error; CI[d], confidence interval; Clinical biomarkers[e], body mass index, random venous glucose, history of delivery of baby >4000 g as described in Chapter 3; QUICKI[f], Quantitative Insulin Sensitivity Check; HOMA-IR[g], Insulin Sensitivity Index; CRP[h], C-reactive protein

Discussion:

Pregnancy is a physiologically hyperglycaemic state, due in part to several circulating maternal and placental diabetogenic hormones such as oestrogen, progesterone, human placental lactogen, placental ACTH, and placental growth hormone variant. This relative hyperglycaemia results in a compensatory pancreatic insulin production leading to hyperinsulinaemia, which is an essential event preceding the development of GDM. When the pancreas fails to mount an appropriate insulin response maternal hyperglycaemia results. [9]

The pathogenic phenomenon was illustrated in our study by the statistically significant differences detected in the fasting insulin concentration, HOMA-IR and QUICKI in patients with and without GDM. Similar findings were found in other studies. [4, 9] We, like Endo et al. [18], have illustrated that the insulin insensitivity was significantly different between the women with GDM and normoglycaemia, and the difference was not attributed to obesity. Insulin insensitivity is a hallmark feature in the development of GDM and thus these tests show potential as a screening and diagnostic tool for GDM.

Currently the OGTT is the gold-standard for the diagnosis of GDM. An ideal screening test should be accessible, affordable, and acceptable. The OGTT is labour- and time-consuming, and unpleasant for the pregnant women who may already be experiencing nausea. Insulin sensitivity tests such as the HOMA-IR and QUICKI offer an attractive alternative tool for identifying women at high risk of developing GDM.

It was also demonstrated that adiponectin is significantly decreased in women with GDM suggesting that an adiponectin deficiency is necessary for the pathogenesis of GDM. Previous studies have identified adiponectin as having anti-diabetic activity.

[10, 19] Adiponectin is strongly correlated with insulin sensitivity across a wide range of glucose tolerance. [19] However, adiponectin levels are negatively correlated with maternal BMI in addition to insulin sensitivity. [8] Several studies have shown that adiponectin is decreased independent of BMI or insulin sensitivity in pregnancies affected by GDM. [20-22] When obese women (BMI ≥30 kg/m^2) with GDM were considered there was a significant difference in adiponectin concentrations, indicating that adiponectin levels were influenced by the presence of obesity in our study population.

Low grade inflammation is associated with T2DM and GDM. [11] This low-grade inflammation, as measured by the CRP, has also been associated with the presence of obesity in pregnancy. [23] Wolf et al. [24] demonstrated that CRP concentrations in the first trimester predicted the development of GDM. Other studies found inconsistent results regarding the association between inflammatory markers and the incidence of GDM, and the interdependence of the degree of adiposity. [23, 25] No significant difference in CRP concentrations was found between women with or without GDM, nor did was a difference in CRP levels found when obese women with GDM were considered. Inconsistent results may be attributed to different populations, socio-economic groups, and the presence of underlying sub-clinical infections.

As we are working towards global consensus on the guidelines for the screening of GDM there has been increasing interest in the role of biomarkers. The strengths of our study were that a large South African Black population cohort was included, and the role of multiple biomarkers was investigated. The limitations of this study were that only HIV negative women were considered, and that the biomarkers were measured at a single point in gestation between 24 and 28 weeks.

The OGTT is a cumbersome test and may lead to decreased compliance by healthcare workers and pregnant women in achieving universal screening for GDM. There is a need to find a simple, more efficient tool that identifies women at risk of GDM before GDM develops. There has been great interest in biomarkers as a tool for the prediction of GDM. The CRP and adiponectin were shown to have promise as biomarkers in other studies [10, 12, 24], but their use was not found to be useful in our population. The tests of insulin sensitivity (HOMA-IR, QUICKI) were shown to be significantly different in women with GDM compared to normoglycaemic controls in our population. The addition of these tests further improved the predictive ability of clinical parameters alone in identifying women at risk of GDM. More research is needed to investigate the use if these indices, especially early in pregnancy, as a tool to identify pregnant women at high risk of developing GDM.

Conclusion:

Women with GDM had a higher BMI and more clinical risk factors present. Fasting insulin, HOMA-IR, QUICKI and adiponectin were significantly different in women with GDM. Adiponectin levels seem to be influenced by adiposity. The addition of HOMA-IR or QUICKI to clinical risk factors may improve the ability to predict women at risk of GDM. In the future these biomarkers should be investigated for the early identification of pregnant women at risk of GDM.

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Chapter 6

Summary and Recommendations

Summary

This study investigated the prevalence of gestational diabetes (GDM) in a South African population. The various diagnostic criteria were compared and the different screening approaches to GDM in our study population was tested.

A prospective cohort observational study was used in order to investigate consecutive pregnant women in a general obstetric population. In order to investigate the association between the concentrations of biomarkers associated with glucose homeostasis and GDM a case-cohort study design was selected.

Chapter 1 includes the background to the research problem, the literature overview related to controversy surrounding screening for GDM both internationally and in South Africa, and the research question that this study addresses. In this chapter the research methodology was outlined in detail, including the inclusion criteria for the study population. The nested case-cohort study that was conducted was also described. Ethical considerations for this study are also given due consideration.

Chapter 2 focussed on the prevalence of GDM in a South African population. In this chapter the prevalence of GDM using the various diagnostic criteria (NICE, IADPSG, WHO 1999, Western Cape criteria) was also compared, and the risk factors (obesity, family history of DM, delivery of a previous baby >4000 g, a poor obstetric history, prior history of GDM) associated with GDM were evaluated. Of the 1000 patients recruited 554 (55.4%) patients completed the 75g-2-hour oral glucose tolerance test (OGTT). It was found that the prevalence of GDM was 25.8% if universal screening and the IADPSG criteria were used. By contrast, if universal screening and the NICE criteria were used the prevalence of GDM was 17%. If selective risk-factor based screening was used only 254 (45.8%) of women would have had an OGTT. The prevalence of

GDM in this instance would have been 15.2% with the IADPSG criteria and 3.6% with the NICE criteria. Two hundred and fifty-four (45.8%) patients had at least one risk factor for GDM. The presence of one or more risk factors had a poor sensitivity (58.7%) and specificity (58.6%) for the detection of gestational diabetes in our study population. Thus it was concluded that the prevalence of GDM would be substantially increased if universal screening with the IADPSG criteria were employed, and that risk factors are a poor screening test for GDM.

In **Chapter 3** a nomogram-based scoring system was developed, that was derived using multivariate regression. This nomogram can be used at the first antenatal visit to identify women at high risk of GDM. In this chapter GDM was defined as per the current FIGO criteria.

It was found that in the 554 women which were used to derive a nomogram-based score, random blood glucose (RBG), body mass index (BMI), and a history of baby ≥4000 g were significant risk factors for GDM. The logistic regression model for prediction of GDM had R^2 0.143, Somer's D_{xy} rank correlation 0.407, and Harrell's c-score 0.703. HbA1c did not improve predictive value at any threshold (e.g. at a probability >10% 25.6% of cases were detected without the HbA1c, and 25.8 cases would have been detected if the HbA1c was included in the prediction model). There was no interaction between HIV and other variables (p=0.974).

The performance of 9 published prediction tools on our study population was also compared by deriving receiver operating characteristic (ROC) curves. The 9 published scoring systems performed poorly in our study population.

Chapter 4 focussed on the performance of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) versus the gold-standard laboratory test

for the diagnosis of GDM. Data from 529 women was analysed. Of these, 141 (26.7%) and 79 (14.9%) were diagnosed with GDM by laboratory and glucometer measurements, respectively. The co-efficient of variation (CV) of the glucometer ranged from 15% to 17%. The Bland–Altman plots showed a positive bias of the glucometer results at 0 hours, but a negative bias at 1 and 2 hours of the OGTT. The sensitivity and specificity of the glucometer for the diagnosis of GDM were 27.0% and 89.4%, respectively. Thus it was concluded that the use of the Roche Accuchek Active® glucometer (Roche Diagnostics, Mannheim, Germany) for the diagnosis of GDM cannot be recommended.

Chapter 5 reports on the nested case-cohort study that was conducted to investigate the association between markers of insulin resistance, chronic inflammation, and adipokines and GDM. Women with GDM and controls without GDM were included. Women who were HIV positive were excluded as HIV was identified as a potential confounder.

Of the 262 pregnant women included in this cohort, 83 (31.7%) had GDM. Women with GDM had a higher BMI (p=0.04) and had more clinical risk factors (p=0.008). A significant difference in fasting insulin (p <0.001), adiponectin (p=0.046), HOMA-IR (p <0.001) and QUICKI (p <0.001) was found. HOMA-IR (AUROC=0.82) or QUICKI (AUROC =0.82) improved the ability of risk factors to identify women at high risk of GDM. It was concluded that markers of insulin sensitivity promising tools to identify women at high risk of GDM, especially in early pregnancy, and warrant further investigation.

Knowledge gained

The diagnosis of gestational diabetes (GDM) has been fraught with controversy for more than half a century. In South Africa, The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) has recently adopted the current FIGO criteria for screening of GDM which recommends universal screening. Our study is the first published study to report on the prevalence of GDM based on universal screening with the application of these criteria. In our study a prevalence of 25% was obtained by employing the current criteria with universal screening.

It was demonstrated that the varying diagnostic criteria for GDM used in South Africa would result in a vast variation in the incidence of GDM. Thus, there is an urgent need to reach consensus on the criteria employed for the diagnosis of GDM at all centres nationally, thus standardising the management of pregnant women.

Furthermore, the screening of GDM is not currently a part of routine antenatal care. In the past selective screening based on the presence of historical and clinical risk factors was recommended. Selective risk-factor-based screening performed poorly as a screening strategy, with a poor sensitivity (58.7%) and specificity (58.6%), even with optimal categorisation of high risk patients. Hence, universal screening is necessary. In order to achieve universal screening, the screening of GDM will need to be included as part of routine antenatal care.

Whilst universal screening is the ideal screening strategy, it has to be considered whether this approach is really viable for the South African healthcare system. Current screening is by means of an OGTT which is only performed at hospitals with laboratories. As all pregnant woman cannot be referred, a paper-based nomogram that requires a random blood glucose performed on a point-of-care device, and a

clinical history and examination that will allow stratification of pregnant women's risk of GDM has been proposed. As only high risk women will require an OGTT the work burden will be decreased. The proposed nomogram requires prospective validation.

Diagnosis of GDM at a primary health care level with the use of point-of-care (POC) devices is very alluring. In our study most patients with GDM had an elevated fasting glucose. Hence, numerous OGTTs would have been avoided had the glucose result been available immediately, on site. However, the POC device performed poorly in our study population and cannot be recommended for on-site diagnosis of GDM. The laboratory glucose measurement still remains the gold-standard.

Ideally, women at risk of developing GDM should be identified as early in pregnancy as possible, thus allowing appropriate surveillance and early intervention for these patients. The OGTT is a cumbersome test that is not always acceptable to pregnant women. Also, the OGTT is a diagnostic test, and not a true screening test. The association between biomarkers viz. adiponectin, C-reactive protein (CRP), and markers of insulin sensitivity (HOMA-IR, QUICKI) in women in GDM was investigated. The markers of insulin sensitivity hold promise as tools that can be used to identify women at high risk of GDM and warrant further investigation, especially early in pregnancy.

South Africa is a low-middle income country with a dual burden of disease. It is projected that the incidence of Type 2 diabetes (T2DM) will more than double in the next 10 years. As GDM has a similar trend to T2DM we can expect a drastic increase in GDM. Thus we need to plan an effective, efficient, acceptable screening strategy for GDM.

There are constraints in adopting universal screening of GDM with the current criteria in a low-middle income country. Some rural areas are remote with lack of access to laboratories or the resources for performing the OGTT. Trained phlebotomists may not be available. Pregnant women have to travel long distances and do not routinely attend the antenatal clinic in a fasted state, nor can they afford repeated visits. Thus it is prudent for us to explore strategies to make screening of GDM accessible to the majority of the pregnant population.

The decision for the best strategy for the screening and diagnosis of GDM needs to be based on the cost and availability of resources within the local context. In order for us to achieve an effective screening policy for GDM the following recommendations need to be implemented and these research areas will require further exploration:

Recommendations for Implementation

1. Incorporate universal screening of GDM into routine antenatal care in South Africa
2. Standardise the diagnostic criteria for GDM nationally
3. Educate health care workers on the screening and management of GDM
4. The use of community health workers and home visits for screening of GDM
5. Formation of a South African Diabetes in Pregnancy Study Group to explore these issues and make appropriate recommendation based on the local context

Recommendations for Future Research

1. Investigate the incidence of GDM in other populations and ethnic groups in South Africa
2. Explore the use of other point-of-care devices, such as glucose measurement on saliva and smartphone technology for the diagnosis of GDM
3. Explore the use of biomarkers as potential screening tools early in pregnancy
4. Prospectively evaluate the nomogram-based scoring system
5. Investigate the outcomes in pregnancies affected with GDM, especially those diagnosed at relatively low levels of hyperglycaemia
6. Cost analysis of the screening for GDM, taking into consideration long-term outcomes in the mother and her offspring

Appendices

A. Ethics Approval

B. Questionnaire

Appendix A: Ethics Approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 13/04/2011 and Expires 13/04/2014.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

1/08/2013

Approval Notice
Amendment

Ethics Reference No.: 180/2012

Title: Comparing screening strategies for gestational diabetes in a South African population

Dear Dr. Sumaiya Adam

The **Amendment** as described in the documents dated June 2013 was approved by the Faculty of Health Sciences Research Ethics Committee on the 31/07/2013.

Please note the following about your ethics amendment:
- Please remember to use your protocol number (180/2012) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committe may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics amendment is subject to the following:

Standard Conditions:
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

The Faculty of Health Sciences, Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

We wish you the best with your research.

Yours sincerely

pp. **Professor Werdie (CW) Van Staden**
MBChB MMed(Psych) MD FCPsych FTCL UPLM
Chairperson: Faculty of Health Sciences Research Ethics Committee

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The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
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Faculty of Health Sciences Research Ethics Committee

25/02/2016

Approval Certificate
Amendment
(to be read in conjunction with the main approval certificate)

Ethics Reference No.: 180/2012

Title: Comparing screening strategies for gestational diabetes in a South African population

Dear Sumaiya Adam

The **Amendment** as described in your documents specified in your cover letter dated 8/02/2016 received on 9/02/2016 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 24/02/2016.

Please note the following about your ethics amendment:
- Please remember to use your protocol number (**180/2012**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committe may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics amendment is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Professor Werdie (CW) Van Staden
MBChB MMed(Psych) MD FCPsych FTCL UPLM
Chairperson: Faculty of Health Sciences Research Ethics Committee

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

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Faculty of Health Sciences Research Ethics Committee

28/09/2017

Dr. Sumaiya Adam
Department of Obstetrics And Gynaecology
University of Pretoria

Dear Dr. Sumaiya Adam

RE.: 180/2012 ~ Letter dated 31 August 2017

NUMBER	**180/2012**
TITLE OF THE PROTOCO	Screening for gestational diabetes in a South African population
PRINCIPAL INVESTIGATOR	Dr. Sumaiya Adam **Dept:** Obstetrics And Gynaecology, University of Pretoria. **Cell:** 0849511773 **E-Mail:** sumaiya1adam@gmail.com

We hereby acknowledge receipt of the following document:

- Extension for study until end of December 2017

which has been approved at 27 September 2017 meeting.

With regards

Dr R Sommers; MBChB; MMed (Int); MPharMed; PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

Appendix B: Questionnaire

STUDY NUMBER

_____

DATA COLLECTION SHEET

AT RECRUITMENT:

1. Date: ☐☐ / ☐☐ / 2 0 1☐
2. Participant's Name: _____
3. Participant's ID Number: ☐☐☐☐☐☐☐☐☐☐☐☐☐
4. Telephone Number: ☐☐☐☐☐☐☐☐☐☐

   Cell Number: ☐☐☐☐☐☐☐☐☐☐
5. Address: _____

   _____
6. Age: ☐☐ years
7. Ethnicity: Black South African ☐ Indian ☐

   Coloured ☐ White ☐ Other ☐ _____
8. Education – highest grade passed? _____
9. Employment: Unemployed ☐ Employed ☐ . . . .

   Formally ☐ Informally
10. Receives grants ☐ Type of grant _____

11. Measure of socio-economic status:

Housing quality index please circle correct number

Variables	*Values*		
Wall	0 = cardboard/plastic bags	1 = metallic sheets (zinc), boards, wood	2 = masonry (bricks, cement blocks)
Floor	0 = dirt, cardboard, plastic bags	1 = cement, tiles, brick, wood	
Roof	0 = cardboard, plastic bags	1 = metallic sheet, wood, asbestos	2 = tiles, cement, brick
Electricity	0 = no	1 = yes	
Water supply	0 = piped in street	1 = piped in yard	2 = piped indoors
Sanitation	0 = in street, neighbour	1 = in yard	2 = inside house
Type of sanitation	0 = homemade pit latrine	1 = non-flush septic tank	2 = flush

12. Parity ☐☐ Gravidity ☐☐

13. Last Normal Menstrual period: ☐☐ / ☐☐ / 201___

14. Gestational age: ☐☐ weeks ☐ days

15. Symphysis Fundal Height: ☐☐ cm

16. Height ☐☐☐ cm Weight ☐☐☐ kg

MUAC ☐☐ cm

17. Blood Pressure ☐☐☐ / ☐☐☐ mmHg

18. Haemoglobin ☐☐ . ☐ g/dL

19. Urine dipstick: Protein ☐ Glucose ☐ Blood ☐ Ketones ☐

20. Acanthosis nigricans: Yes ☐ No ☐

21. Family History of Diabetes Mellitus: Yes ☐ No ☐

If yes, relationship: _____

22. Previous stillbirth or baby with congenital abnormality:

Yes ☐ No ☐ If yes, details: _____

23. Previous baby ≥4 kg: Yes ☐ No ☐

---

24. Gestational Diabetes in prior pregnancy: Yes ☐ No ☐

25. History of Polycystic Ovarian Syndrome: Yes ☐ No ☐

26. HIV Status: ☐ Negative ☐ Positive ☐ Unknown

27. Is the patient on antiretroviral? If so, which drugs: _____

28. Other medical conditions: _____

29. Drug history: _____

30. Random Glucose:

Glucometer (venous) ☐☐ g/dL

Glucometer (capillary) ☐☐ g/dL

Laboratory ☐☐ g/dL

---

31. HbA1C:

On-Site Test ☐☐ g/% Laboratory ☐☐ g/%

2-WEEKS LATER:

32. *Fasting glucose – 2 weeks later:*

Date: ☐☐ / ☐☐ / 2 0 1 ☐

Gestational age: ☐☐ weeks ☐ days

Glucometer (venous) ☐☐ g/dL

Glucometer (capillary) ☐☐ g/dL

Laboratory ☐☐ g/dL

24-28 WEEKS PREGNANT:

33. *OGTT and repeat HbA1C – 24-28 weeks pregnant:*

Date: ☐☐ / ☐☐ / 2 0 1 ☐

Gestational age: ☐☐ weeks ☐ days

HbA1C On-Site Test ☐☐ g/% HbA1C Lab ☐☐ g/%

OGTT – Glucometer (venous):

0hour ☐ 1 hour ☐ 2 hour ☐

OGTT – Glucometer (capillary):

0hour ☐ 1 hour ☐ 2 hour ☐

OGTT - Laboratory: 0hour ☐ 1 hour ☐ 2 hour ☐

STUDY NUMBER
_____

DATA COLLECTION SHEET – 6 WEEKS POST DELIVERY:

1. Date: ☐☐ / ☐☐ / 2 0 1☐
2. Did the mother have Gestational Diabetes in this pregnancy?

   Yes ☐ No ☐

   If yes, what treatment did she receive? _____
3. Did the mother have hypertension in this pregnancy:

   Yes ☐ No ☐
4. Date of delivery: ☐☐ / ☐☐ / 2 0 1☐
5. Gestational age at delivery: ☐☐ weeks
6. Mode of delivery: Normal vaginal delivery ☐

   Forceps/Ventouse ☐

   Caesarean Section ☐ Indication: _____
7. Birth weight: ☐☐☐☐ grams
8. Apgars: 1min ☐ 5 min ☐
9. Neonatal intensive care admission: Yes ☐ No ☐

   If yes, reason: _____
10. <u>Today's visit:</u>
    a. Blood Pressure: ☐☐☐ / ☐☐☐ mmHg
    b. Urine Dipstix: Protein ☐ Glucose ☐ Blood ☐
    c. Mother's Weight: ☐☐☐ kg
11. Gestational diabetic mums – repeat OGTT:

    Glucometer readings: 0 min ☐ 1 hour ☐ 2 hour ☐

    Laboratory readings: 0 min ☐ 1 hour ☐ 2 hour ☐
12. Repeat HbA1C: On-site test ☐☐ g% Lab HbA1C ☐☐ g%