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SCREENING, DIAGNOSIS AND LIFESTYLE INTERVENTION PROGRAM FOR GESTATIONAL DIABETES MELLITUS IN AN URBAN PRIMARY HEALTH CLINIC IN SOUTH AFRICA

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SUPERVISORS

Professor Shane A Norris
Professor Eckhart Buchmann

A THESIS

Submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfilment of the requirements for the degree of

Doctor of Philosophy

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

i. Declaration by Student

I, Lynnsay M Dickson, Student Number 8312389, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my Thesis. It is being submitted for the Degree of Ph.D. at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____ (Signature of candidate)

__17____ day of _December_____ 2019, at__Johannesburg_____

ii. Dedication

For Ging, with love.

iii. Acknowledgements

Thanks to my Ph.D. supervisors Prof Eckhart Buchmann and Prof Shane Norris for initiating a most remarkable journey. I am grateful for the time and attention, the most limited of resources, that they have generously given to this research project.

Diabetes West staff made considerable adjustments to the routine operations of the private practice, with very little notice, to allow me the few years needed for this Ph.D. Specifically, Dr KarNeen Tam, Dr Deshree Janneker and Dr Shahista Khan generously absorbed my patient load. In addition to providing additional support to patients previously under my care, nurses Charmaine Moyo and Vuyisa Jobela also assisted with study procedures. Tammy Winskill kindly shared her experience with qualitative research methods that she acquired in her MSc. The Zola project would not have been possible without the support of this team.

Ms. Nandi Mtshali, with minimal training, excelled as our research assistant. She tirelessly engaged with participants and staff of Zola Community Health Clinic and ensured we all remained focused on a common goal, namely, to contribute towards enabling gestational diabetes screening for all women. She never backed down from the many challenges encountered. It was a privilege to have Nandi at my side, every step of the way.

Thanks to Dr. Thabi Maitin and Mr Thobile Mabuya of the South African Medical Research Council for their support, the research skills training and for facilitating the opportunity to interact with fellow MSc and Ph.D. students from across the country. Thanks to KarNeen, Werner and Ido for taking the time to read drafts of the manuscripts. Deon, your encouragement in those overwhelming moments was invaluable. None of this would be

possible without my first and most important mentor, Dr. Suliman Jhazbhay, who inspired me to study medicine and gave me a lifelong love of reading, all those years ago.

iv. Thesis material

A. Publications

Dickson, L. M., Buchmann, E. J., Janse van Rensburg, C. & Norris, S. A. Accuracy of five plasma calibrated glucometers to screen for and diagnose gestational diabetes mellitus in a low resource clinic setting. J. Clin. Transl. Endocrinol. 16: 100174 (2019) https://doi.org/10.1016/j.jcte.2018.12.003

Dickson, L. M., Buchmann, E. J., Janse Van Rensburg, C. & Norris, S. A. The impact of differences in plasma glucose between glucose oxidase and hexokinase methods on estimated gestational diabetes mellitus prevalence. Sci. Rep. 9:7238 (2019). https://doi.org/10.1038/s41598-019-43665-x

Dickson, L. M., Buchmann, E. J., Janse Van Rensburg, C. & Norris, S. A. Fasting plasma glucose and risk factor assessment: comparing sensitivity and specificity in identifying gestational diabetes in urban African women.
This manuscript is accepted for publication by the South African Medical Journal. The letter of acceptance from the editor is attached in Appendix IV.

B. Presentations arising from this research project

Oral presentations

1. Annual Johannesburg District Research Conference held on the 17th November 2016 at the Bytes Conference Centre, Midrand, Gauteng, South Africa.

Title: "Women's accounts of the gestational diabetes experience - a South Africa perspective."

2. Netcare West Rand and South African Medical Association West Rand Symposium, 26–27 August 2017, Misty Hills Conference Centre, Muldersdrift, Johannesburg, Gauteng, South Africa.

Title: "A universal screening program for gestational diabetes mellitus in Zola Community Health Clinic, Soweto."

3. Work in Progress Seminar, 25 June 2017, MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom.

Title: "Screening diagnosis and lifestyle intervention program for gestational diabetes in an urban primary health clinic in South Africa"

4. Gestational Diabetes Symposium, 25 July 2018, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng, South Africa.

Title: "Universal screening for gestational diabetes mellitus in a low resource setting"

5. 34th World Congress of Internal Medicine, 18–21 October 2018, Cape Town, Western Cape, South Africa.

Title: "Validation of Five Plasma Calibrated Glucometers to Screen for and Diagnose Gestational Diabetes Mellitus in a Low Resource setting."

6. 18th International Congress of Endocrinology, 1–4 December 2018, Cape Town, Western Cape, South Africa.

Title: "Validation of Five Plasma Calibrated Glucometers to Screen for and Diagnose Gestational Diabetes Mellitus in a Low Resource setting."

Poster presentations

1. 18th International Congress of Endocrinology, 1–4 December 2018, Cape Town, Western Cape, South Africa.

Title: "Systematic bias between glucose oxidase and hexokinase laboratory methods significantly affects the estimated prevalence of gestational diabetes."

2. 18th International Congress of Endocrinology, 1–4 December 2018, Cape Town, Western Cape, South Africa.

Title: "Accuracy of plasma calibrated glucometers to screen for and diagnose gestational diabetes in a low resource setting."

3. 18th International Congress of Endocrinology, 1–4 December 2018, Cape Town, Western Cape, South Africa.

Title: "Women's accounts of the gestational diabetes experience – A South African perspective."

C. Nomenclature

ADA – American Diabetes Association

AUROC – Area Under Receiver Operating Curve

BMI – Body Mass Index

C&C – Carpenter and Coustan

c.f.a.s – Calibrator for Automated Systems

CHBAH – Chris Hani Baragwanath Academic Hospital

CHC – Community Health Clinic

CI – Confidence Interval

cm – centimeter

CJVR – Charl Janse van Rensburg

CV – Coefficient of variation

DCM – Diabetes Conversation Map

DM – Diabetes Mellitus

DPHRU – Developmental Pathways to Health Research Unit

e.g. – for example

EASD – European Association for the Study of Diabetes

EJB – Eckhart J Buchmann

F – Fisher's exact test

FDA – Food and Drug Administration

FGD – Focus Group Discussions

FIGO – International Federation of Gynaecology and Obstetrics

FPG – Fasting Plasma Glucose

g – gram

GCT – Glucose Challenge Test

GDM – Gestational Diabetes Mellitus

GOx – Glucose Oxidase method

HAPO – Hyperglycaemia and Adverse Pregnancy Outcome study

HbA1c – Haemoglobin A1c

HK – Hexokinase method

IADPSG – International Association of Diabetes and Pregnancy Study Groups

IDF – International Diabetes Federation

IFG – Impaired Fasting Glucose

IGT – Impaired Glucose Tolerance

IOM – Institute of Medicine

ISO – International Standards Organization

K – Kappa statistic

kg – kilogram

kg/m^2 – kilogram per meter squared

LoA – Limits of Agreement

Lab – laboratory

LGA – Large for Gestational Age

LMD – Lynnsay M Dickson

LMIC – Low-middle income countries

mmHg – millimetres of mercury

mmol/l – millimole per litre

MRC – Medical Research Council

MUAC – Mid-Upper Arm Circumference (≥ 33 cm is associated with obesity)

N/n number

NACB – National Association of Clinical Biochemistry

NDDG – National Diabetes Data Group

NHLS National Health Laboratory Service (South Africa)

NICE – National Institute for Health and Care Excellence

NIH – American National Institutes of Health (NIH)

NLR – Negative Likelihood Ratios

NPV – Negative Predictive Value

OGTT – Oral Glucose Tolerance Test

Ph.D. – Doctor of Philosophy

PLR – Positive Likelihood Ratios

POC – Point of Care

PPV – Positive Predictive Value

RIQAS – Randoxy International Quality Assessment Scheme

RMMCAH – Rahima Moosa Mother and Child Academic Hospital

ROC – Receiver Operating Curve

T1D – Type one diabetes mellitus

T2D – Type two Diabetes Mellitus

SADH – South African Department of Health

SAMRC – South African Medical Research Council

SAN – Shane A Norris

SANAS – South African National Accreditation Service

SD – Standard deviation

SEMDSA – Society of Endocrinology, Metabolism, and Diabetes of South Africa

SMBG – self monitoring of blood glucose

T – Time

t – t-test

TAE – Total Allowable Error

μl – microliter

U – Mann-Whitney U test.

UK – United Kingdom

USA – United States of America

WHO – World Health Organization

χ – Chi-square test

D. List of Tables and Figures

Figures

Number	Figure Title	Page
Figure 1.1	Patient Centred Conceptual Framework: Factors Influencing Patient Centeredness.	30
Figure 1.2.	Top Ten Leading Causes of Death of South Africans.	33
Figure 1.3.	The Spectrum of Hyperglycaemia in an Urban Black South African Population	33
Figure 2.1.	Mean Glucose Concentrations as Measured by the Reference Laboratory and Each Glucometer Brand at Different Time Points of the OGTT.	87
Figure 3.1.	Venn Diagrams Illustrating the Number of GDM Positive Cases Identified at Various Time Points of the OGTT by the GOx (Glucose Oxidase) and HK (Hexokinase) Laboratory Methods. (WHO 2013 test positivity cut-offs).	107
Figure 3.2.	Bland Altman Plots of the Paired Plasma Glucose Results (mmol/l) Measured by the GOX (Glucose Oxidase) and HK (Hexokinase) Methods at 120 Minutes of the 75 g Oral Glucose Tolerance Tests for 592 Women Screened for Gestational Diabetes.	108
Figure S 1.	Venn Diagram Illustrating the Distribution of GDM Positive Participants as Defined by the Different Test Methods.	203

Tables

Number	Table Title	Page
Table 1.1	Maternal and Fetal Morbidity and Mortality Associated with GDM.	36
Table 1.2	Evolution of criteria for GDM diagnosis.	38
Table 1.3	Features of the WHO 2013 GDM diagnosis and classification recommendations.	40
Table 1.4	Modified Wilson and Junger Criteria for Screening.	44
Table 1.5	Selection of Strategies for GDM Screening.	45
Table 1.6.	Controversies associated with the OGTT.	50
Table 1.7	Number and type of Laboratories Accredited to Internationally Recognized Quality Standards.	53
Table 1.8.	Advances in glucometer functionality from 1966 to present.	57
Table 2.1.	Participant Characteristics.	86
Table 2.2.	Results of Statistical Analysis of Agreement Between the Glucometer Brands and the Reference Laboratory at OGTT Time Point.	88
Table 2.3.	Statistical Analysis of Agreement in Gestational Diabetes Diagnosis Between the Glucometers Against the Hexokinase Method Laboratory Reference.	90
Table 3.1.	Participant characteristics, with comparison of GDM positive and with GDM negative women.	106
Table 4.1.	Participant Characteristics.	125
Table 4.2.	Validity measures of FPG and Risk Factors as a GDM screening Strategy.	127
Table 5.1.	Quotes of participant's responses to their diagnosis of GDM.	137
Table 5.2.	Quotes of participant's experience of the health care service.	138
Table 5.3.	Quotes of participant's lifestyle adjustments in pregnancy.	140
Table 5.4.	Quotes of participant's need for support during pregnancy.	142
Table 5.5.	Quotes of participant's understanding of diabetes.	143
Table 5.6.	Quotes of unexpected themes.	144
Table 6.1.	Summary of research questions and major aligned empiric findings.	153
Table 6.2.	NICE recommended disclosures for informed consent prior to GDM screening.	162
Table S 1.	Statistical Analysis Results of the Plasma Calibrated Glucometers	203

	Against the Composite Laboratory Reference Test.	
Table S 2.	Area Under ROC values by Glucometer Brand Against the Composite and Individual Reference Test at Different Time Points in the OGTT.	204

v. Table of contents

i. Declaration by Student....3
ii. Dedication....4
iii. Acknowledgements....5
iv. Thesis material....7
A. Publications....8
B. Presentations arising from this research project....9
C. Nomenclature....11
D. List of Tables and Figures....15
v. Table of contents....18
Preface....21
Abstract....24
The Organization of the Thesis....27
Chapter 1. Introduction and review of the literature....29
1.1 Conceptual framework....30
1.2 Significance of Gestational Diabetes Mellitus in context of Diabetes Mellitus....31
1.3 Prevalence of GDM....33
1.4 Pathogenesis of GDM.....34
1.5 Sequelae of GDM....34
1.6 Diagnostic criteria and screening strategies for GDM....37
1.6.1 Evolution of diagnostic criteria for GDM....37
1.6.2 Global and local response to the IADPSG and WHO recommendation....40
1.7 Screening strategies for GDM....42
1.7.1 Features of a public health screening program....43
1.7.2 GDM screening strategies....44
1.7.3 Fasting plasma glucose to screen for and diagnose GDM....47
1.8 The Oral Glucose Tolerance Test....49
1.9 Measurement of blood glucose concentrations in the OGTT....51
1.9.1 Laboratory measurement of plasma glucose....51
1.9.2 Glucometer measurement of plasma glucose....53
1.10 GDM screening in low resource settings....58
1.11 Interventions for GDM....59
1.11.1 Benefits of treating GDM....59
1.11.2 GDM Interventions....60
1.11.3 Local adaptation of existing interventions....61
1.12 Thesis rationale....63

1.12.1 Problem statement....63
1.12.2 Thesis Objectives....64
Chapter 2. Validation of Glucometer Accuracy....67
2.1 Abstract....69
2.2 Introduction....71
2.3 Study participants, materials and methods....72
2.4 Results....77
2.5 Discussion....80
2.6 Conclusion....85
2.7 Acknowledgements....85
2.8 Tables and Figures....87
Chapter 3 Comparison of Results Between Laboratory Methods....93
3.1 Abstract....95
3.2 Introduction....96
3.3 Study subjects, methods, and materials....97
3.4 Results....101
3.5 Discussion....104
3.6 Tables and Figures....107
Chapter 4. Fasting Plasma Glucose to Screen for GDM....111
4.1 Abstract....113
4.2 Introduction....115
4.3 Study methods....116
4.4 Results....119
4.5 Discussion....121
4.6 Conclusion....125
4.7 Tables....127
Chapter 5. Women's experience of GDM....131
5.1 Abstract....133
5.2 Introduction....135
5.3 Methods....136
5.4 Results....138
5.5 Discussion....147
Chapter 6. Integrated Discussion....154
6.1 Summary of results....155
6.2 Reflection on challenges encountered to universal GDM screening....156
6.2.1 Barriers to women participating in GDM screening....158
6.2.2 Technical challenges encountered in implementing GDM screening....160

6.3 Conceptual framework revisited 161
6.3.1 Government Policy: GDM Screening Procedures 161
6.3.2 Patient centred care 163
6.4 Recommendations based on research results 165
6.5 Strengths and limitations of this research 167
6.6 Future research 169
6.6.1 Measurement of glucose 169
6.6.2 Assumption of false positive results 169
6.6.3 Intervention development 170
6.6.4 Multicentre GDM screening 171
6.7 Conclusion statement 172
6.8 Executive Summary 173
REFERENCES 179
APPENDICES 204
I. Human Research Ethics Committee Clearance Certificate 205
II. Johannesburg District Department of Health 207
III. Supplementary data 209
A. Bland Altman Plots of Glucose concentrations (mmol/l) measured by specific glucometer brands against the HK method at t=0, t=60 and t=120 of the OGTT. 209
B. The HK method and composite laboratory results serve as the reference test o evaluate the accuracy of the glucometers. 215
C. Passing Bablok analysis of comparison between methods 221
D. Deming regression analysis of comparison between methods 225
E. Pitmans Test Results 229
F. Analysis of Cutpoints of Fasting Plasma Glucose Concentrations 230
IV. Published manuscripts and/or letter of acceptance 233
V. Turnitin Report 236

Preface

I am a specialist physician and the founder and director of Diabetes West. This private practice, which includes two large diabetes clinics based in Johannesburg, South Africa, was formed in 2003. Holistic support with a comprehensive range of services are offered to patients and this includes the services of doctors, diabetes nurse educators, dieticians, and podiatrists. Special interests of this practice are the use of continuous insulin infusion pump therapy and the management of gestational diabetes. In 2013, I co-founded Leto, a non-profit, public benefit organization. Leto enabled diabetes education and other supportive services to approximately 100 paediatric patients with diabetes attending the state-sector Rahima Moosa Mother and Child Academic Hospital.

Donald J Coustan, the academic giant and doyen of gestational diabetes was the international speaker at the SEMDSA (Society of Endocrinology, Metabolism, and Diabetes of South Africa) conference in South Africa in April 2014. At the end of his presentation, a member of the audience asked what the best way to screen for gestational diabetes. Donald Coustan's response was 'There is no reason for orthodoxy.' My initial idea was simple and remarkably naïve. It was my intention that Leto adopt a single, local, state-sector antenatal clinic, and screen for and manage gestational diabetes (intermediate hyperglycaemia) as a public-private initiative. Inexpensive glucometers rather than a laboratory service would be used to measure blood glucose levels in the oral glucose tolerance test. Women affected would be offered a blood glucose monitoring and lifestyle education program for the duration of their pregnancy.

I met with Prof Eckhart Buchmann, an obstetrician in the Johannesburg District Department of Health and at his suggestion, wrote a formal proposal for the project. This was presented to the executive committee of the Johannesburg District Department of Health in October 2014.

Eckhart also introduced me to Prof Shane Norris, who suggested that this project was suitable for a Ph.D. Arrangements were made to temporarily relieve me of my responsibilities at the Diabetes West clinics. I registered as a Ph.D. student at the University of the Witwatersrand in January 2015 with Eckhart and Shane as my co-supervisors.

Following this impulsive decision, I found myself constantly on steep slopes of many learning curves. Retrospectively, I appreciated that my supervisors allowed me to find solutions to the many challenges I encountered. Throughout the process, Eckhart and Shane were supportive and provided strategic road maps. They invited me to statistics training sessions, academic meetings and introduced me to academics with similar interests. Their kind encouragement and support facilitated my development of essential research skills. Shane enabled my three-month participation in a Ph.D. student exchange program, which was funded by the Research Councils United Kingdom Newton Fellowship. As part of this program, I was nested within the Intervention Development team at the Medical Research Council-Epidemiology Unit at the University of Cambridge in England in 2017. From this experience, I gained some insight into the complexity of functioning of their Medical Research Council (MRC) unit.

I feel privileged to have had the opportunity to be a Ph.D. candidate. These experiences have allowed me to develop confidence in my ability to plan, implement and report the findings of an academic research project. The rigor of the peer review process necessary for publication of the manuscripts included in this thesis, has transformed my appreciation of the academic literature. I've had unique opportunities to interact with my peers and have a renewed appreciation of my intellectual heritage. I believe this work represents a significant

contribution to medical knowledge and will lead to improved medical care of gestational diabetes affected women in low resource settings.

Abstract

We investigated the feasibility of implementing a universal screening program for gestational diabetes mellitus (GDM) in an urban low resource setting, using glucometers rather than a calibrated laboratory to measure blood glucose concentrations of the 75 g oral glucose tolerance test (OGTT). In this prospective, pragmatic, cross-sectional study, 592 consecutive women underwent an OGTT at 24–28 weeks' gestation. The World Health Organization (2013) diagnostic thresholds were applied. Five plasma-calibrated glucometer brands were evaluated against two independent laboratories, which used either the glucose oxidase (GOx) or hexokinase (HK) method to measure plasma glucose levels. Also, retrospectively, the validity of a universally applied fasting plasma glucose (FPG) of ≥ 4.5 mmol/l was evaluated against a risk factor assessment, which is current standard care, as a method of screening for GDM. In addition, as part of formative work to develop an intervention that may be applied locally, the experience of women previously affected by GDM was examined through a series of focus group discussions (FGD). In this qualitative component of this study, the Diabetes Conversation Map educational instrument was used to examine the experiences of women previously affected by GDM, and these FGD were recorded, transcribed and thematically analysed.

GDM prevalence determined by the glucometers was 12.7%. Three of the five glucometer brands evaluated were within the predetermined total allowable error, but only at fasting of the OGTT. All glucometers were inaccurate at one and two hours. Glucometer results were significantly positively biased relative to both laboratories results at all time points of the test, meaning, they potentially over-diagnosed GDM. GDM prevalence determined by GOx and HK methods were 6.9% and 5.1% respectively. Unexpectedly, there was a significant bias of 0.20 mmol/l between laboratories, with a low agreement of 34% on GDM positive diagnoses.

The absence of a true gold standard, and the ambivalent results provided by the calibrated laboratories that served as the reference test, created clinical diagnostic uncertainty in determining participants GDM status. Nevertheless, an elevated fasting glucose of ≥ 5.1 mmol/l defined ≥ 80% of GDM positive diagnoses by all methods of measurement. The use of a universally applied FPG (GOx laboratory method served as reference) would mean 25.8% of women would be identified as medium to high risk and would need to undergo a complete OGTT and 97.6% of GDM affected women would be identified. If risk factor based selective screening were applied, only 34.6% of women would require an OGTT, however, 43.9% of GDM positive cases would have been missed.

Results of the qualitative study suggested women affected by GDM reacted with shock, anxiety, confusion, and disbelief to their diagnosis of GDM. They were aware of inconsistent diagnostic procedures applied at clinics and hospitals. Despite difficulty adjusting to a diet initially perceived to be unpalatable and more expensive, changing to a healthier lifestyle was considered an overall positive consequence of their diagnosis. Lifestyle changes were partially retained postpartum and were reported to have a positive effect on other family members. Unexpectedly, women reported that being HIV (Human Immunodeficiency Virus) positive was preferable and less stressful than having GDM.

In conclusion, the thesis research found that there is no ideal method to measure plasma glucose concentrations of the OGTT in a low resource setting. Reliance on routine laboratory methods to measure blood glucose concentrations of the OGTT may miss GDM positive women. Acknowledgement of the limitations of the different methods of measurement is an important consideration when developing GDM screening strategies. In this study population, FPG measured by glucometers may be a superior screening strategy for GDM, over the

current practice of selective screening with a laboratory-dependent OGTT. Regarding women's experience of GDM, consistency in health messaging, diagnostic criteria and diagnostic procedures will be essential to a successful roll out of GDM screening in low resource South Africa settings.

The Organization of the Thesis

The first chapter includes a brief, critical review of the literature on GDM, in order to contextualize research gaps and justify the purpose of this study. The problem statement, study purpose, research questions as well as the conceptual framework is presented.

Results of this research have been and will be submitted to academic journals for publication. Consequently, each manuscript will be presented as an individual chapter:

Chapter 2: the aim of this chapter is to validate glucometers as an alternative to laboratory measurement of blood glucose concentrations. The title of this manuscript is 'Accuracy of five plasma calibrated glucometers to screen for and diagnose gestational diabetes in a low resource setting'. This was published in the Journal of Clinical and Translational Endocrinology in June 2019.

Chapter 3: the aim of this chapter is to report the unexpected research finding of significant differences between laboratory methods to measure plasma glucose concentrations. The title of this manuscript is 'The impact of differences in plasma glucose between glucose oxidase and hexokinase methods on estimated gestational diabetes mellitus prevalence'. This was published in Scientific Reports - Nature in May 2019.

Chapter 4: the aim of this chapter is to explore the utility of the FPG to identify GDM affected women. The title of this manuscript is 'Fasting plasma glucose and risk factor assessment: comparing sensitivity and specificity in identifying gestational diabetes in urban African women'. This was accepted for publication by the South African Medical Journal.

Chapter 5: the aim of this chapter is to report the subjective experiences of local women previously diagnosed with GDM. The title of this manuscript is ‘Women’s accounts of the gestational diabetes experience – a South African perspective’.’ This is submitted for consideration for publication.

Finally, the thesis concludes with the integrative chapter where I revisit the overall aim and objectives of the PhD against what was found. I reflect on the research findings, tying up the individual publications and highlighting key themes. The strength and limitations of the research and recommendations for future research are discussed. This chapter ends with an overarching conclusion statement of the thesis.

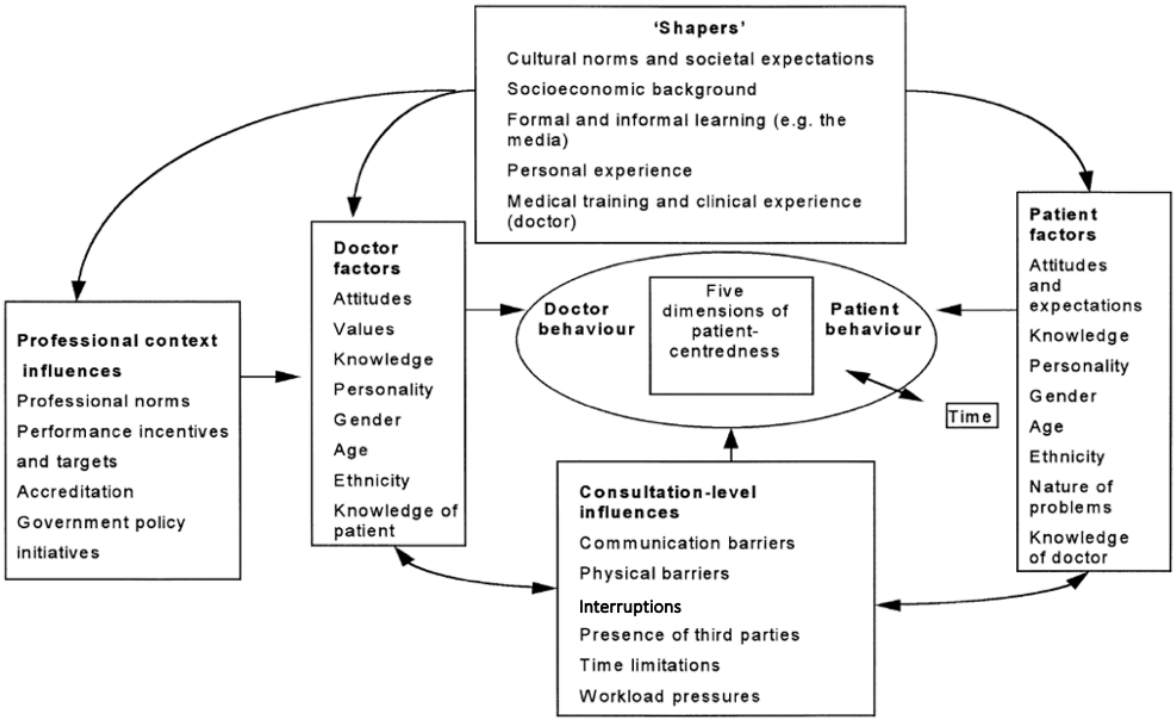
Chapter 1.

Introduction and review of the literature

1.1 Conceptual framework

The researcher has selected the Patient-Centred Conceptual Framework as the overarching conceptual framework for this thesis. This framework was previously described with the purpose of facilitating communication between researchers and clinicians.[1] The five dimensions of patient-centeredness identified in this framework include a biopsychosocial perspective, the 'patient-as-person', sharing power and responsibility, the therapeutic alliance as well as the 'doctor-as-person'. Included in this framework are important shapers of the patient's health care experience, such as government policies, medical training and cultural norms. (Figure 1.1)

Figure 1.1: Patient Centred Conceptual framework. Factors Influencing Patient Centeredness. Source: Mead, et al. (2000)[1]



1.2 Significance of Gestational Diabetes Mellitus in context of Diabetes Mellitus

Gestational diabetes mellitus (GDM) may be regarded as one of the "great obstetrical syndromes" because the associated morbidity and mortality to mother and child are secondary to pathology that develops at the maternal-placental-fetal interface.[2] GDM, the most common metabolic disorder that occurs in pregnancy, is a usually asymptomatic condition that manifests in the mid-second to early-third trimester.[3] Typically, GDM is an intermediate hyperglycaemia that resolves spontaneously post-partum. However, type 2 diabetes (T2D), or less frequently, type one diabetes (T1D) may be unmasked.[4] With the increasing global prevalence of T2D and an increasingly younger age of disease onset, women of reproductive age are more likely to be affected by hyperglycaemia in pregnancy, and this includes GDM and overt diabetes mellitus (DM).[5,6] Together with the pre-diabetes states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), GDM is a T2D precursor.[4]

The World Health Organization (WHO) estimated that the global prevalence of DM is 8.5% and it is the seventh leading cause of death.[7] More than 90% of DM is classified as T2D. The global prevalence of DM has doubled since 1980.[6] A United States National Health and Nutrition Examination Survey (NHANES) reported an increase in pre-diabetes of 24% between 1999–2002 and 2007–2010 in non-pregnant adults aged >18 years.[8] A rapid increase in T2D prevalence is occurring in low and middle-income countries (LMIC), which now bear 80% of the burden of disease.[4,6,9–12] There is a continuum of risk for the development of DM which begins at glycaemic levels below 6.1 mmol/l, which is the WHO diagnostic threshold for IFG.[13] The risk of future development of T2D is similar for IFG, IGT and GDM, and this occurs at a rate of approximately 5% per year.[14,15]

The global increase in DM is associated with decreased physical activity, excessive calorie intake and the increase in overweight and obesity.[16] Obesity is associated with low-grade inflammation and increased insulin resistance which, together with a genetic predisposition, result in progressive pancreatic β-cell failure. The consequence of this progressive β-cell failure is reduced insulin secretion and an inability to maintain euglycaemia. There is a tendency toward progression through the phases of IFG and IGT. Eventually, in up to 70% of individuals with obesity, T2D develops.[16,17] However, there is evidence that T2D is preventable and if identified in the early stages of the disease, may be reversible.[18,19]

Age-standardized mean body mass index (BMI) and the prevalence of obesity and T2D have increased consistently across Africa for the past three decades. South African estimates of obesity are higher than the global average across all age groups.[20,21] The youth are also affected with 18.8% of males and 26.3% of females < 20 years of age being obese or overweight.[20] Sub-Saharan Africa has a historically undernourished population that is currently affected by a high prevalence of overweight and obesity.[22] This may have predisposed South Africans to the rapid emergence of DM as a public health concern.[23]

DM is the leading cause of death of South African women and is the second leading cause of death of all South Africans.[24] (Figure 1.2) Recent studies confirm a rising trend in DM in South Africa with prevalence reports of 4–33%. Significantly, both rural and urban populations are at risk.[25–27] Age-standardized IGT and DM prevalence increased in an urban black South African population by 67% and 53% respectively between 1990 and 2008/9.[28] The increasing prevalence of pre-diabetes in younger, reproductive age groups, suggests that South African women may be at high risk for GDM. (Figure 1.3)

Figure 1.2. Causes of Death of South Africans.

Source: Statistics South Africa.[29]

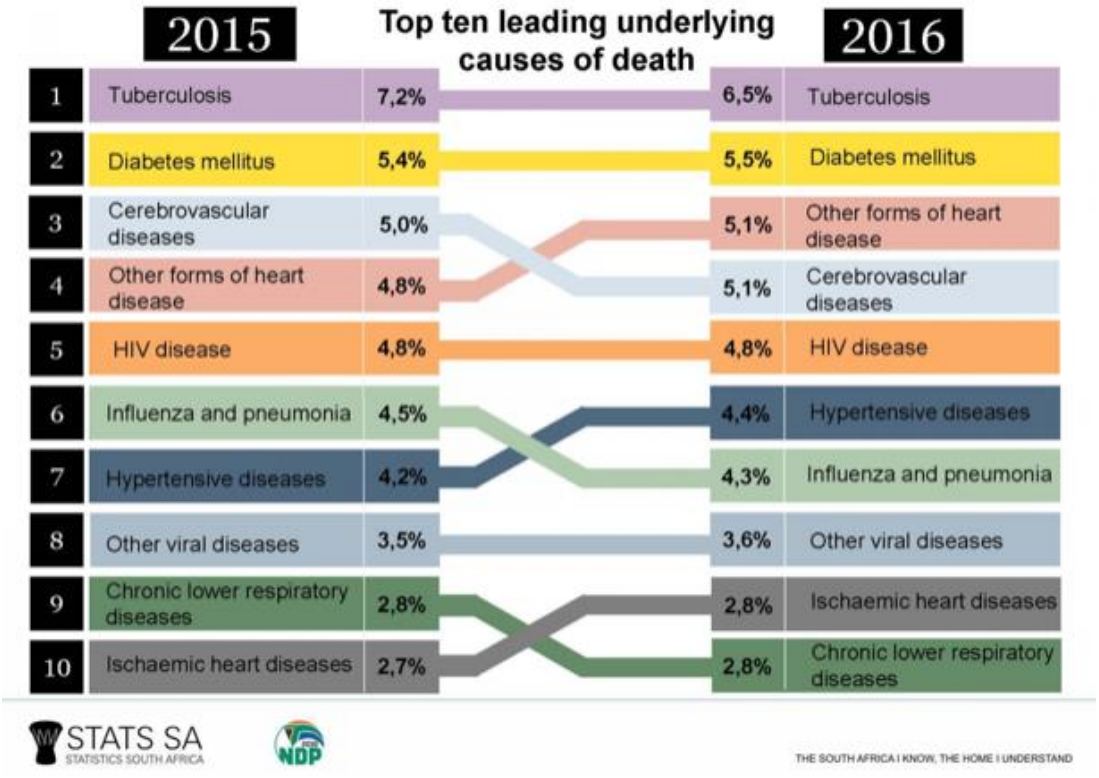
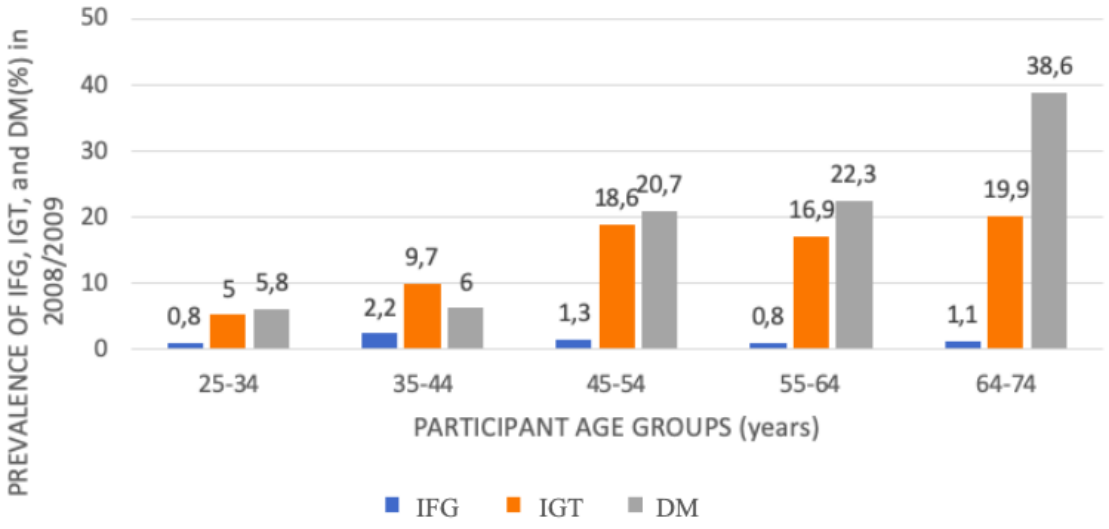


Figure 1.3 The spectrum of Hyperglycaemia in an Urban Black South African Population.

Source: Peer, et al (2012).[28]



1.3 Prevalence of GDM

GDM prevalence increases in parallel with that of T2D and is proportionate to that of obesity for a given population.[30–32] GDM prevalence increases by an estimated 0.9% per one unit increase in BMI.[33] The WHO estimates that 16% of pregnancies are affected by GDM globally.[6] LMIC contribute to 85% of global annual births and 90% of maternal and perinatal deaths.[4] The burden of GDM in South Africa is difficult to estimate due to the inconsistency of GDM criteria and screening strategies used. Recently, urban South African GDM prevalence of 9.1% and 26.7% have been reported.[34–36]

1.4 Pathogenesis of GDM.

Pregnancy is a physiological, natural stress test for the reserve capacity of endocrine pancreas function.[37,38] Normally, in the latter half of pregnancy, a 40–50% reduction in insulin sensitivity occurs, which is usually compensated for by a 200–250% increase in insulin secretion by the β-cells.[39] Supra-physiological increases in insulin resistance in the latter half of pregnancy are linked to maternal pre-conception obesity and excessive maternal weight gain in pregnancy.[39] Third trimester increases in placental hormones such as human placental lactogen, affect maternal lipid metabolism, but a direct link to insulin sensitivity is not yet demonstrated.[4,37,39] Individuals with compromised pancreatic β-cell reserve function are unable to meet the rising demand for insulin in the third trimester of pregnancy. A usually transient and intermediate hyperglycaemia develops which persists until the birth. Reduced maternal pancreatic β-cell reserve and insulin resistance persist postpartum.[37]

1.5 Sequelae of GDM

The transient nature of diabetes in pregnancy was described in the 19th century.[40] In 1952, Jackson of the University of Cape Town reported that women who subsequently developed diabetes post-partum, frequently had a history of macrosomia and stillborn infants.[40] More recent studies have confirmed that both mother and offspring are at risk of future development of T2D which predispose to macrovascular disease, microvascular disease and premature death.[19,37,41]

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study found a linear relationship between maternal blood glucose concentration and the risk of poor fetal outcomes.[42] A strong continuous association, with no clear threshold at which risks increased, was found between maternal glycaemia and pre-eclampsia, increased fetal birth-weight, increased cord-blood serum C-peptide levels and increased risk of shoulder dystocia or birth injury. The HAPO Follow-Up Study evaluated the carbohydrate metabolism status of 4160 children aged 10–14 years and found that maternal levels of hyperglycaemia are positively associated with child glucose and insulin resistance levels.[43] These outcomes were independent of both mother and child BMI or a family history of diabetes. Increased obesity in the offspring of women affected by GDM is also previously reported.[44] A possible mechanism for this is an epigenetic modification in the developing fetus.[37,45,46]

The most common obstetric complications associated with GDM are preeclampsia and fetal macrosomia, which may necessitate a caesarean birth.[47] Hypertensive disorders, obstructed labour and haemorrhage are leading causes of maternal mortality globally, and these are also sequelae of GDM.[48] While universal screening for hypertension, which affects 10% of pregnancies, is standard, GDM is not routinely screened for and is often missed.[48] Additional maternal, perinatal and fetal sequelae of GDM are presented in Table 1.1.

Table 1.1. Maternal and fetal morbidity and mortality associated with GDM. (modified from Hod, et al. (2015) [4]

Maternal	**Fetal**
Early pregnancy	Stillbirth
Spontaneous abortions	Neonatal death
Pregnancy	Non–chromosomal congenital malformations
Pre–eclampsia	Shoulder dystocia
Gestational hypertension	Respiratory distress syndrome
Excessive fetal growth	Cardiomyopathy
Hydramnios	Neonatal hypoglycaemia
Urinary tract infections	Neonatal polycythaemia
Delivery	Neonatal hyperbilirubinaemia
Preterm labour	Neonatal hypocalcaemia
Obstructed labour	Erb's palsy (a consequence of birth injury)
Traumatic labour	Programming and imprinting
Instrumental birth	(fetal origin of disease:
Caesarean birth	obesity, diabetes, hypertension)
Postoperative/postpartum infection	
Postoperative/postpartum haemorrhage	
Thromboembolism	
Maternal morbidity and mortality	
Puerperium	
Failure to initiate/maintain breastfeeding	
Body weight retention	
GDM in subsequent pregnancies	
Future overt diabetes	
Future cardiovascular disease	

In addition to maternal, obstetric and fetal morbidity and mortality, placental changes in GDM affected pregnancies are subtly different from those associated with either T1D or T2D. The placenta is often heavier in pregnancies affected by hyperglycaemia and this

includes GDM and overt DM.[49] Placental dysfunction causes increased production of inflammatory cytokines and oxidative stress that can lead to chronic fetal hypoxia.[2,46] Placental changes in GDM are characterized by up-regulation of genes involved in a multitude of cellular functions. These include changes to the immune system, organ development, the regulation of cell death and programming of obesity.[46,50]

DM is the second leading cause of death of South Africans. However, the effect of DM and GDM on maternal deaths and stillbirths in South Africa is unknown.[51,52] An audit of results for 1087 pregnancies, managed at a combined specialist diabetes in pregnancy clinic of a single academic hospital in Soweto, South Africa (1983 –1992 and 1992 –2002), indicated poor outcomes for untreated GDM. The perinatal mortality for those treated for GDM was 4.5% and for those with a late referral, who received ≤ two weeks of intensive management before the birth, the perinatal mortality was 19.9%.[53] It is possible that the effect of untreated GDM on perinatal mortality is underestimated in South Africa. There are missed opportunities for identifying and treating GDM in South Africa, and this may adversely affect pregnancy-associated morbidity and mortality.

1.6 Diagnostic criteria and screening strategies for GDM

1.6.1 Evolution of diagnostic criteria for GDM

Jackson of the University of Cape Town established reference ranges for a 50 g glucose challenge test administered at 36 weeks' gestation to identify diabetes in pregnancy in the 1950s.[40] Later, O'Sullivan and Mahan described the first set of diagnostic thresholds for the 100 g oral glucose tolerance test (OGTT) that identified women at risk of later

developing T2D.[40,54] The United States of America (USA) has remained at the forefront of the DM pandemic. Prior to 2010, the American Diabetes Association's (ADA) definition of GDM was commonly accepted internationally, namely, "any degree of glucose intolerance with onset or first recognition during pregnancy". This definition is attractive because it has no specific diagnostic thresholds, and these may vary both between and within countries.[55–57] The evolution of the diagnostic thresholds of GDM is presented in Table 1.2.

Table 1.2. Evolution of criteria for GDM diagnosis

Criteria	Approach	n. of increased	Year	Glucose load (g)	Glucose thresholds (mmol/l)			
					0 h	1 h	2 h	3 h
O'Sullivan	2-step	2	1964	100	5.0	9.2	8.1	6.9
NDDG	2-step	2	1979	100	5.8	10.6	9.2	8.0
C&C	2-step	2	1982	100	5.3	10.0	8.6	7.8
ADA	2-step	2	2000	100	5.3	10.0	8.6	7.8
WHO	1-step	1	1999	75	7.0	-	7.8	-
SEMDSA	1-step	1	2007	75	7.0	-	7.8	-
NICE	1-step	1	2008	75	7.0	-	7.8	-
IADPSG	1-step	1	2010	75	5.1	10.0	8.5	-
WHO	1-step	1	2013	75	5.1	10.0	8.5	-
NICE	1-step	1	2015	75	5.6	-	7.8	-
ADA	1-step	1	2011	75	5.1	10.0	8.5	-
ADA	1-step or C&C/ND	1 2	2016	75 100	5.1 5.3/5.8	10.0 10.0/10.6	8.5 8.6/9.2	- 7.8/8.0
SEMDSA	1-step	1	2017	75	5.1	10.0	8.5	-

Abbreviations:

O'Sullivan, O'Sullivan and Mahan; NDDG, National Diabetes Data Group; C&C, Carpenter and Coustan; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; WHO, World Health Organisation; IADPSG, International Association of

Diabetes in Pregnancy Study Group; NICE, National Institute of Health and Care Excellence, SEMDSA, Society of Endocrinology Metabolism and Diabetes of South Africa.

Modified from source: DB Sacks. Clin Chem 60(1) 2014:141-145 [47,54,58–62]

The HAPO study was designed to clarify the risk of adverse perinatal outcomes associated with intermediate levels of maternal hyperglycaemia. Data were analysed for the 75 g OGTT at 24–32 weeks' gestation for 23316 participants from 15 centres across nine countries. These predominantly northern hemisphere, developed countries included the USA, UK, Canada, Hong Kong (Peoples Republic of China), Australia, Israel, Thailand, Singapore and Barbados.[63] All blood samples were processed in a central laboratory with rigorous standardization at each field centre as well as at the central laboratory, for the duration of the study.[64] Primary outcomes included birth weight above the 90th percentile for gestational age, primary caesarean birth, clinical neonatal hypoglycaemia and cord-blood serum C-peptide level above the 90th percentile. Results were evaluated by the International Association of Diabetes and Pregnancy Study Groups (IADPSG).

In the absence of clear risk thresholds, the IADPSG based their recommendations for a positive GDM diagnosis on a 1.75 odds ratio for the adverse pregnancy outcomes of large for gestational age and infant hyperinsulinaemia, as indicated by the HAPO study results.[3] In 2013, the WHO adopted the diagnostic thresholds for GDM recommended by the IADPSG.[3,47] The definition of dysglycaemia in pregnancy is now more stringent than in the non-pregnant population. IFG is defined by a fasting plasma glucose (FPG) $\geq$ 5.6 mmol/l by the ADA or $\geq$ 6.1 mmol/l by the WHO.[13,60] This step toward international consensus on diagnostic thresholds was intended to facilitate the collection of epidemiological data on GDM, as well as investigate feasible, sustainable screening strategies and interventions.[47] Important features of the WHO recommendations are listed in Table 1.3.

Table 1.3 Features of the WHO 2013 GDM diagnosis and classification recommendations

1. Gestational Diabetes is now separated into 2 distinct clinical entities:
   - GDM which is an intermediate level of hyperglycaemia
   - Diabetes in Pregnancy (considered to be overt DM by the IADPSG) which most likely represents pre-conception diabetes.
2. A single phase 75 g OGTT at 24–28 weeks' gestation is the recommended standard diagnostic procedure.
3. The diagnostic criteria of (overt) Diabetes in Pregnancy remain the same as that for DM in the general population (FPG ≥ 7 mmol/l and/or 2-hour plasma glucose of ≥11.1 mmol/l).
4. Only one abnormality of the OGTT is sufficient for the diagnosis of GDM. A FPG of 5.1–6.9 mmol/l, one-hour glucose ≥10.0 mmol/l and/or two-hour glucose of 8.5–11.0 mmol/l is 100% specific for a diagnosis of GDM.
5. GDM diagnostic criteria are now based on perinatal fetal outcomes rather than the maternal future risk of developing DM2.

1.6.2 Global and local response to the IADPSG and WHO recommendation

International response to the WHO GDM recommendations has been varied. A survey by the European Board and College of Obstetrics and Gynaecology on GDM screening practice found that 67.9% of European countries had adopted the WHO 2013 diagnostic thresholds.[57] The United Kingdom's (UK) National Institute of Health and Care Excellence (NICE) reduced their diagnostic thresholds from 7.0 mmol/l to 5.6 mmol/l at fasting of the OGTT, however, a selective screening strategy for GDM was retained.. A subsequent UK audit found that those women with a FPG between 5.1–5.6 mmol/l were at increased risk of large for gestational age infant birth weights, caesarean delivery and polyhydramnios, although the

increase in GDM prevalence was only 0.49% based on the WHO 2013 rather than the NICE 2015 diagnostic thresholds.[65]

The ADA recommendations for GDM screening include options for either a one-step 75 g OGTT or the two-step 50 g glucose challenge test (GCT) followed by a diagnostic 100 g OGTT if the GCT is positive.[60] In 2013, the American National Institutes of Health (NIH) reviewed the IADPSG recommendations and elected to retain the commonly used two-step Carpenter and Coustan (C&C) GDM criteria with a universal screening strategy applied.[60] It is possible that Coustan's position on GDM diagnostic thresholds had changed since 1982, considering he was an investigator in the HAPO study.[66] Reasons given for the NIH decision were:

- the "medicalization" of a substantially higher proportion of pregnancies,
- an increased cost to health care systems
- lack of evidence demonstrating the benefits of clinical interventions based on the IADPSG diagnostic thresholds.[60]

The St Carlos Gestational Diabetes study found that although there was a 3.5-fold increase in the prevalence of GDM using the IADPSG rather than the C&C criteria, there was an estimated cost saving of 14358 Euros per 100 pregnant women evaluated. This cost saving was due to reductions in the need for caesarean births and neonatal intensive care unit admissions.[67] A mathematical model, the GDModel, developed to evaluate the cost-effectiveness of universal GDM screening and lifestyle changes to prevent T2D, found a net cost saving in both Israel and India when the IADPSG criteria were applied.[68] Both the St Carlos study and the GDModel demonstrate clinical benefits and health care cost savings for the IADPSG recommendations, when applied in both developed and LMICs. Although the

majority of the HAPO study centres were based in developed countries in the northern hemisphere, the UK, Spain, Sweden, Norway, Finland and Canada have not as yet adopted the scientifically valid, evidence-based guidelines derived from this data.[57,69]

In addition to variations in diagnostic thresholds, there is also variation in the type of test used to identify GDM globally. The 75 g OGTT is most commonly used in Europe as well as in LMICs.[70] A survey of European countries found the 75 g OGTT was most frequently used, but other test methods used included the 50 g GCT followed by the 100 g OGTT, random glucose, FPG and HbA1c at various stages of pregnancy.[57] The USA applies either a one-step or a two-step procedure.[60] In a survey of LMICs, the 75 g OGTT was most frequently used, but additional test methods included the FPG, random glucose, 50 g GCT, glycosuria, HbA1c, the 100 g OGTT and postprandial testing.[70] International consensus in testing procedures would allow for direct comparisons in GDM prevalence.

Sub-Saharan countries have reported an increase in the prevalence of GDM when the WHO 2013 diagnostic thresholds are applied.[36,71] The South African National Department of Health (SADH) guidelines for maternity care are based on the WHO and the SEMDSA recommendations. The SEMDSA adopted the WHO GDM recommendations in 2017. The SADH guidelines have not been updated since 2015.[72] Currently, the 75 g OGTT at 28 weeks' gestation is the test recommended by the SADH, and WHO 1999 diagnostic thresholds are applied.[72]

1.7 Screening strategies for GDM

1.7.1 Features of a public health screening program

Typically, disease diagnostic thresholds are developed in well-equipped and well-resourced academic/research institutions, far removed from public health care facilities in LMICs. While evidence-based scientific research is essential to create and define diagnostic thresholds, clear and simple directions are necessary for the practical application of these guidelines in clinical settings. An ideal GDM screening tool suitable for use in low-resource settings should be cheap, not require elaborate preparations, have a high sensitivity and specificity, have a short turnaround time to result availability, be easy to administer, with equipment that needs little maintenance or calibration. Currently, no diagnostic device fulfils all these requirements to screen for GDM.[73]

The gold standard of principles and practice for disease screening, originally developed by Wilson and Junger in 1968, were updated by the WHO in 2008. (Table 1.4)[74] According to these criteria, the decision to screen for a disease should be based on the means to detect the condition at an early stage as well as the availability of acceptable treatment for those affected. However, logistical, social and ethical reasons may limit the implementation of public health screening programs. Based on estimated global prevalence, interventions available to reduce perinatal morbidity, the opportunity to prevent future T2D, and the evidence for clinical and cost effectiveness based on the St Carlos and GDmodel studies, GDM screening fulfils criteria 1–4 (Table 1.4). However, criteria 5–9 may have country specific limitations and criterion 10 still attracts controversy.

Table 1.4. Modified Wilson and Junger Criteria for Screening. [74]

1. ‘The screening program should respond to a recognized need.’

2. ‘The objectives of screening should be defined at the outset.’
3. ‘There should be a defined target population.’
4. ‘There should be scientific evidence of screening program effectiveness.’
5. ‘The program should integrate education, testing, clinical services and program management.’
6. ‘There should be quality assurance, with mechanisms to minimize potential risks of screening.’
7. ‘The program should ensure informed choice, confidentiality and respect for autonomy.’
8. ‘The program should promote equity and access to screening for the entire target population.’
9. ‘Program evaluation should be planned from the outset.’
10. ‘The overall benefits of screening should outweigh the harm.’

1.7.2 GDM screening strategies

The IADPSG recommends universal GDM screening, especially in countries with a high prevalence of DM.[3] The WHO suggests that the design and implementation of GDM screening strategies should be determined by individual countries. Strategies should be informed by the prevalence of dysglycaemia and the availability of resources and competing priorities.[47] The American College of Obstetrics and Gynaecology recommends universal screening for GDM because, in their population, an estimated 10% of women would be considered low risk and would not require screening.[62] The International Federation of Gynaecology and Obstetrics (FIGO) urges universal screening for GDM in LMICs.[4] This is because these countries contribute to 85% of annual global deliveries, 80% of the global DM burden and 90% of cases of maternal and perinatal deaths and poor pregnancy outcomes.[4] In addition, the FIGO suggests that selective screening based on risk factors is difficult to implement in low resource settings due to low levels of education, low awareness and poor medical record keeping.[4]

Global GDM prevalence reports are difficult to interpret due to variation in screening strategies, diagnostic thresholds and testing procedures.[75,76] Universal screening for GDM is usually conducted at 24–28 weeks' gestation, at the time of the pregnancy associated physiological increase in insulin resistance.[3] Additional selective screening at the first antenatal visit is recommended in order to identify women who most likely had preconception DM.[3] This may be interpreted as a two-step screening strategy. The commonly used 75 g OGTT serves as both a screening and a diagnostic procedure. Although there is a move towards consensus, progress towards universal GDM screening strategies and procedures that may be applied in routine clinical practice in low resource settings remains elusive. Some strategies used to identify GDM are presented in Table 1.5.

Table 1.5 Selection of Strategies for GDM Screening.[76–78]

1. No screening.
2. Selective screening based on ≥ one traditional risk factor (including but not restricted to: maternal age, body mass index, ethnicity, parity, previous GDM, family history of diabetes, clinical conditions associated with insulin resistance e.g. polycystic ovarian syndrome, large for gestational age fetus, previous unexplained stillbirth).
3. Modified risk factor algorithms to increase the sensitivity of traditional markers.
4. Use of the fasting plasma glucose.
5. Use of random blood glucose.
6. Universal screening using a one-step 75 g OGTT.
7. Universal screening using a two-step model:
   (50 g GCT screening test followed by the diagnostic 100g OGTT).

As well as having a low sensitivity, selective screening programs may be difficult to implement even in well-resourced settings.[78–80] An audit of the GDM screening strategies in 28 European countries published in 2016 found that 64.3% used a risk factor base selective

screening strategy to identify women eligible for an OGTT.[57] An audit of a selective screening program applied to 23270 births in Tuscany, Italy found that 55.6% of women fulfilled eligibility criteria, and that 40% of women screened were at low risk.[80] A multicentre UK audit of 2432 nulliparous women (2007–2011), found 60.8 % were appropriately screened, 38.9% were risk-factor positive but were not screened and 14.6% had no risk factors but were screened based on the NICE guidelines of that time (pre-2015).[79] A recent UK universal screening study found that 24% of GDM positive women were risk factor negative, and so would not have been identified using selective screening.[81]

In 2002, based on a secondary analysis of the Toronto Tri-hospital Gestational Diabetes Project data, a scoring system based on maternal age (> 30 years), BMI (> 22 kg/m^2) and ethnicity (non-Caucasian and non-black) was developed, in order to reduce the number of women requiring formal screening by means of an OGTT.[82] A more recent review by Farrar, et al. suggest that maternal age ≥ 25 years and/or a BMI ≥ 25 kg/m^2 would identify the majority of those affected by GDM.[78] The selection of traditional risk factors used to identify women at risk for GDM vary. An independent head-to-head comparison of 12 published GDM prognostic models applied in a single Dutch cohort found that only four models had a consistently positive net benefit. Risk factors common to these models were maternal age, maternal BMI, history of gestational diabetes mellitus, ethnicity, and family history of diabetes.[83]

Although selective risk-factor based screening is more likely to detect GDM than no screening at all, the poor efficacy of this screening strategy is described in sub-Saharan African countries.[36,71,84] Risk factor based selective screening for GDM is currently applied in South Africa.[72] On adopting the WHO 2013 GDM guidelines, the SEMDSA acknowledged

that universal screening for GDM may only be possible in well-resourced settings in South Africa.[59] Screening and treatment of GDM is largely restricted to secondary and tertiary care facilities in South Africa, and this is common in other LMICs.[85] Established services are at risk of being overwhelmed by an influx of GDM affected women in need of supportive care.

1.7.3 Fasting plasma glucose to screen for and diagnose GDM

The FIGO acknowledged that universal application of the OGTT to detect GDM may not be feasible in low resource settings and acceptable, feasible alternatives are critically needed.[4] According to the WHO 2013 diagnostic thresholds, a single abnormality of the OGTT, for example, an elevated fasting plasma glucose (FPG) of ≥ 5.1 mmol/l, is diagnostic of GDM.[47] The sensitivity of an elevated FPG varies between countries and ethnicities. In the HAPO study the frequency of an elevated FPG ranged from 24–74% and this varied between and within countries.[63] The HAPO authors suggest that a reliably measured FPG could be used as an initial screen in selected populations and this would reduce the number of women requiring a complete OGTT.[63]

The IADPSG recommendations include the use of the FPG to screen for GDM and undiagnosed DM in every pregnant women earlier in pregnancy, in populations with a high prevalence of disease.[3] The IADPSG has acknowledged that the HAPO study population had a low probability of GDM and a low risk of poor outcomes associated with an FPG ≤ 4.4 mmol/l.[73] A dual FPG threshold was previously suggested as a screening strategy, to reduce the number of women requiring an OGTT, specifically in low resource settings. An FPG ≥ 5.1 mmol/l is 100% specific for a positive diagnosis and an FPG ≤ 4.4 mmol/l indicates low risk, therefore, only those women with FPG of ≥ 4.5 mmol/l would require an OGTT, as this

indicates an intermediate to high risk for GDM.[73] This principle was retrospectively applied to a Brazilian cohort, which found that only 38.7% of women would need an OGTT, reducing the cost and inconvenience of screening.[86]

The use of the FPG for diagnostic purposes is not new. In 1997, the American National Diabetes Data Group recommended that the primary diagnostic test for DM should be the FPG because it is less costly, less time consuming for patients and the laboratory, easier to administer and is more reproducible than the OGTT.[87] The IDF recommends that each country should decide whether to implement screening for DM, and the FPG is the suggested screening procedure.[88] A review of 51 cohort studies by the US Preventative Services Task Force found that an FPG < 4.7 mmol/l had good sensitivity and specificity for excluding GDM (IADPSG criteria) while a GCT (50 g) was better at identifying GDM positive women. However, the GCT is not validated for the IADPSG diagnostic thresholds.[89] A recent retrospective South African study of the reproducibility of the FPG, found that this was better than the 2-hour plasma glucose of the 75 g OGTT in diagnosing GDM.[90]

There are reports of other clinical associations with the FPG result. An elevated FPG was an independent predictor of the need for insulin therapy in GDM, with a cut-off value of 5.8 mmol/l associated with a specificity 91.9% and a positive predictive value 80.6%. [91] In a retrospective analysis of French women universally screened at 24–28 weeks' gestation, fetal birth-weight and macrosomia risk were strongly correlated with an FPG ≥ 5.3 mmol/l.[92] The FPG is also described as the best predictor of GDM when applied in early pregnancy.[93] In a high-risk population of women screened in early pregnancy, FPG was added to a validated risk prediction tool and, the FPG was the strongest predictor for GDM.[94]

1.8 The Oral Glucose Tolerance Test

The 75 g OGTT is the gold standard test for diagnosing disorders of carbohydrate metabolism and this includes GDM, IFG, IGT and overt DM.[13,88] This one-step, two-hour procedure is widely accepted internationally and is used to determine the presence of dysglycaemia in children, adolescents, and in non-pregnant and pregnant adults. International recommendations of diagnostic thresholds are based on the results of this test. This allows epidemiological evaluations of disease burden between countries and over extended periods of time. Nevertheless, the OGTT attracts controversy. (Table 1.6)

Table 1.6. Controversies associated with the OGTT. [4,13,47,64,76,88,95–101]

1. There are multiple diagnostic thresholds, allowing for multiple interpretations, of the same test result.
2. The test must be done on patients in a fasted state.
3. There is a diurnal variation in the FPG with a higher concentration in the morning, meaning that afternoon FPG may miss GDM positive diagnoses.
4. GDM screening should occur at a specific time period in pregnancy.
5. The non-physiologic, hyperosmolar, 75 g glucose solution is unpleasant and may cause nausea and vomiting.
6. Poor venous access may limit completion of the test because multiple punctures are required.
7. This test is two hours long and this may not be convenient for patients or medical staff.
8. Delays in plasma separation of venous blood samples in a routine clinical setting cause a 5–7% per hour reduction in plasma glucose due to ongoing glycolysis ex-vivo, resulting in the underestimation of disease, specifically when sodium fluoride tubes are used.
9. The use of citrate rather than sodium fluoride blood sample collection tubes is associated with less pre-analytic glycolysis. However, existing diagnostic thresholds were established using sodium fluoride tubes.
10. Traditionally, a calibrated laboratory service is required to measure plasma glucose concentration, and this may be inaccessible.
11. Delays in laboratory turn-around-time and suboptimal laboratory analytic accuracy may cause errors in the clinical diagnosis.
12. The scarcity of test consumables and lack of equipment, especially in low resource settings, impact the feasibility of DM screening.
13. Intra-individual variations in patient characteristics, e.g. obesity, hydration, haematocrit and inflammatory response, affect the reproducibility of test results.
14. The test may need to be repeated.
15. Results may not be immediately available, necessitating a return visit, and this causes delays in initiating treatment.

1.9 Measurement of blood glucose concentrations in the OGTT

1.9.1 Laboratory measurement of plasma glucose

The range of the FPG diagnostic thresholds for GDM before 2013, based on the O'Sullivan, C&C, NDDG criteria is 5.0–5.8 mmol/l. The range of the FPG diagnostic threshold for GDM based on the post-2013 WHO, NICE and ADA criteria is 5.1–5.8 mmol/l. Except for the WHO de-escalation of the FPG threshold to ≥ 7.0 mmol/l between 1999–2013, there has been little change in absolute value of an abnormal FPG in GDM since 1964. (Table 1.2.) However, the laboratory methods of measuring blood glucose concentrations have changed substantially over this time. Changes in laboratory procedures have reduced bias, intra-laboratory and inter-laboratory variability, with improved repeatability of laboratory results.[88,89,102,103] Some of the changes include the following:

- Glucose is now measured in plasma rather than in whole blood.
- Enzymatic methods (e.g. glucose oxidase, hexokinase methods and infrequently, glucose dehydrogenase) have replaced chemical methods (e.g. ortho-toluidine method)
- Highly automated methods allow high volumes of measurements

Regulatory bodies like the American National Academy of Clinical Biochemistry (NACB) and the South African National Accreditation System (SANAS) determine the standards of acceptable laboratory quality controls, and this includes the coefficient of variation and bias in glucose measurement. In South Africa, the SANAS audits individual medical laboratories in both the private and state sector approximately once every two-years.

Based on the WHO 2013 GDM diagnostic criteria, only one abnormality is required to make a positive diagnosis of GDM. Laboratories are under pressure to minimize imprecision and

bias in glucose concentration measurements.[3,47] The most common enzymatic methods used by laboratories to determine plasma glucose concentrations are the glucose oxidase and hexokinase, with few laboratories using glucose dehydrogenase method.[104] There is no true gold standard method or higher order reference measurement system for the measurement of blood glucose concentration.[104]According to the NACB, there is no significant difference in mean measurements by the glucose oxidase and hexokinase methods, although, it is acknowledged that measurements near the diagnostic threshold may be misclassified using either method.[104]

The OGTT requires calibrated laboratory services to measure blood glucose concentrations and this may not be easily accessible to all health centres. For example, there is a shortage of calibrated laboratory services of international standard in sub-Saharan Africa.[105] A survey conducted in 2014 found that 91% (n = 345 of 380) of internationally accredited laboratories in Sub-Saharan Africa were in South Africa. (Table 1.7) The laboratory density per million people in South Africa is similar to many European countries, however, only 62 of the 345 laboratories provide services to the public health care sector.[105] Public health facilities provide services to an estimated 80% of South Africans.[29]

Table 1.7 Number and Type of Laboratories Accredited to Internationally Recognized Quality Standards in Sub-Saharan Africa. (amended from Source: Schroeder, et al. 2014)[105,106]

Country	Estimated total population	Type of Laboratory				N laboratories per 1 million people
		Private	Public	Research	Total	
South Africa	56 015 000	276	62	7	345	0.000006160
Kenya	48 462 000	4	0	4	8	0.000000165
Namibia	2 480 000	6	1	0	7	0.000002822
Botswana	2 250 000	2	1	3	6	0.000002667
Uganda	41 488 000	2	0	3	5	0.000000012
Ghana	28 207 000	2	0	0	2	0.000000071
Nigeria	185 990 000	2	0	0	2	<0.00000001
Ethiopia	102 403 000	1	0	0	1	<0.00000001
Mali	17 995 000	0	0	1	1	0.00000006
Mauritius	1 262 000	1	0	0	1	0.00000079
Tanzania	55 572 000	0	0	1	1	<0.00000001
Zimbabwe	16 1650 000	0	0	1	1	<0.00000001
Total	703 774 000	296	64	20	380	0.00000053

1.9.2 Glucometer measurement of plasma glucose

The NACB and the ADA recommend the use of glucometers for self-monitoring of blood glucose (SMBG) of those living with diabetes and this includes GDM.[107] Two studies conducted in different antenatal clinics compared the accuracy of the Accu-Chek Performa and Freestyle Lite glucometers with results from a laboratory which used a hexokinase method to measure glucose concentrations.[108,109] In both of these studies, venous blood

samples were centrifuged within 30 minutes of collection to minimize ongoing glycolysis ex-vivo and minimize underestimation of glucose concentration by the laboratory, in keeping with the NACB recommendations. Only one of these two studies concluded that this glucometer was sufficiently accurate for use in SMBG in pregnant women who had diabetes.[108,109] SMBG results inform clinical decisions such as adjustments to insulin doses required to maintain euglycaemia.

The American NACB's position is that there is insufficient published data to support the use of glucometers using finger-prick blood samples to diagnose DM or for population screening programs.[88] Imprecision of glucometer results and the differences between meters is the reason given for this stance.[88] In addition, there are no standards for the use of glucometers for diagnostic purposes. The current International Standardization Organization (ISO15197:2013) recommendations are a guideline for the performance of glucometers for SMBG when used by laypersons.[121]

In the 2006 WHO report on the Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia, the widespread use of glucometers for diagnosing DM was acknowledged.[13] In the 2016 Global Report on Diabetes, the WHO recommended that facilities for diagnosing and treating DM should be made available at primary health care settings.[6] The WHO endorsed the use of glucometers that meet current International Standardization Organization (ISO) standards as an acceptable alternative, if laboratory analysis of blood glucose concentrations is not feasible.[6] The WHO acknowledged that glucometers may not be available in all facilities in developing countries.[6]

In 2015, the FIGO has endorsed the use of plasma calibrated glucometers for the diagnosis of GDM in low resource settings.[4] Although results may be less accurate and precise, glucometers would allow screening for GDM in communities where laboratory services are unavailable or inaccessible. Other advantages of using glucometers to measure blood glucose concentrations identified by the FIGO include:[4]

- Women with a diagnostic elevated FPG need not continue with the OGTT and this avoids the need to ingest the glucose solution.
- Results may be communicated instantly, avoiding the need for the patient to return to obtain results on another day.
- Counselling and treatment may be initiated on the same day for those who are GDM positive.
- Glucometers that can be used by lay-community health workers and this could reduce the workload on health care professionals.

Recently, researchers in Ireland and the Netherlands evaluated the accuracy of glucometers relative to a routine clinical laboratory and a research laboratory service in diagnosing GDM.[95,110,111] Results indicate that glucometers may be more accurate than a routine laboratory service, but not a research laboratory service, in identifying GDM affected women.[95,110,111] Relative to the research laboratory, the routine laboratory service missed approximately a third of GDM positive cases, most likely due to underestimated glucose concentrations due to pre-analytic factors such as ongoing glycolysis.[88] This occurs when the separation of plasma is delayed or laboratory turn-around times are prolonged, both of which commonly occur in routine clinical practice.[95,96] The advantage of glucometers is blood sample handling is simple, blood glucose concentrations are measured instantly and results are available in five seconds.

It is known that there are differences in glucometer accuracy between commercial brands.[112] Consensus on glucometer selection will ensure uniformity in data collected on GDM prevalence. There are recent reports of GDM screening programs from Tanzania, Morocco and India where glucometers are used to measure blood glucose concentrations.[113–115] None of these studies describe the glucometer selection procedure, nor the glucometer compliance with latest ISO requirements. Only the study from India reported glucometer calibration with a laboratory service.[115] The Moroccan study did not name the glucometer brand used.[114] Interestingly, the Tanzanian study which evaluated GDM prevalence in urban and rural areas used the Haemocue glucometer, which is registered for diagnostic purposes in Germany.[113]

The HaemoCue glucometer (Angelholm, Sweden), commercially available since 1991, was intended for clinical use in hospitals and primary care centres.[116,117] It was the first glucometer to use a capillary-fill system and had either a battery or mains power source.[116,117] The system is simple to use, the finger-prick blood sample is drawn into special disposable microcuvette, which contains dried reagents including the enzyme glucose dehydrogenase. Previously, the reagent microcuvettes had to be stored in a refrigerator and brought to room temperature before analysis.[116,117] In 2003, a direct comparison of the HaemoCue, Accu-Chek, Glucotouch, One-Touch and Precision glucometers found that their accuracy was similar and all of these glucometers were suitable for GDM screening.[118] Diagnostic thresholds for GDM have since lowered and this data may no longer be valid.

The first glucometer, the Ames Reflectance glucometer was first commercially available in 1966, and glucometers' practical features and clinical accuracy have evolved since. (Table 1.8) Glucose measurements are based on interactions with one of three enzymes: hexokinase,

glucose oxidase (GOx) or glucose dehydrogenase (GDH) The majority of glucometers use the GOx method because it is cheap, has a relatively higher selectivity for glucose, and can withstand greater extremes of pH and temperature, thus allowing relatively relaxed storage norms.[119]

Table 1.8. Advances in glucometer functionality from 1966 to present.[119,120]

1. Improve portability with a more compact size.
2. Less expensive.
3. Less painful.
4. Easier to use with minimal operating steps.
5. Results available in 5 seconds (versus 240 seconds in the 1980s).
6. Smaller sample size (2–3 µl) with sample underfill detection.
7. Modified sampling procedure with no wiping and reduced operator variation
8. Plasma calibrated (correction ratio from capillary to plasma).
9. Haematocrit correction.
10. Autocalibration (no coding chips necessary).
11. A wide linear working range of 0.6–33.3 mmol/l.
12. Software memory to store and retrieve results.
13. Results from electrochemical sensors are reproducible, easily maintained and low cost.
14. Improved meter accuracy.

Standards for glucometer accuracy have become increasingly stringent and this is appropriate in the interest of patient safety. The American Food and Drug Administration (FDA), the ADA and the ISO have produced guidelines for glucometer accuracy.[121] ISO 15197:2013 revisions in the analytical performance requirements include the evaluation of influence quantities on glucometer results such as haematocrit.[121] For the first time, current ISO standards require that laypersons should be able to use glucometers with acceptable

accuracy.[121] Formal training is not required for the accurate use of these plasma calibrated glucometers, which provide results within 5 seconds.

Manufacturer compliance with these standards is voluntary and there is no ongoing independent surveillance of glucometers performance. Variation in accuracy between meter brands is reported, even if the glucometer is labelled as being compliant with current standards.[112,122]

1.10 GDM screening in low resource settings

Consideration of population specific problems, developmental index, and availability of infrastructure facilities may improve the reach of GDM screening in LMICs. Limitations to achieving universal screening for GDM in LMIC include constraints of resources and capacity, such as: [76,123,124]

- Lack of trained health care providers
- Low availability of consumables and equipment
- Lack of financing of health services and treatment
- Absence of standard protocols
- Poor referral systems
- Substantial change from long-established practices
- Integrating testing women in a fasted state with standard prenatal care
- Distance to health facilities

Currently in South Africa, the diagnosis and management of GDM occurs at secondary and tertiary level care.[72] This is not common in LMICs.[70] Typically, community health centres (CHCs) in South Africa deliver antenatal services to women with low to medium-risk

pregnancies, however, laboratory services are not available in primary level health care. To facilitate accessibility, system changes are needed to improve GDM screening and treatment at primary level care.[70,114] Valid alternatives to laboratory measurement of blood glucose concentrations in the OGTT, suitable for use in a low resource setting, may improve the accessibility of GDM screening procedures. This may include the use of glucometers to measure blood glucose concentrations.

1.11 Interventions for GDM

GDM is not yet recognised as a distinct clinical entity in South Africa and treatment is not available to affected women. According to the SADH guidelines for maternity care, GDM risk factor positive women must be referred to a hospital for an OGTT and, if necessary, treatment.[72] The effectiveness of this screening strategy is unknown. Treatment of diabetes in pregnancy varies between hospitals. For instance, at the Chris Hani Baragwanath Academic Hospital (CHBAH), diabetes in pregnancy patients are managed by both endocrinologists and obstetricians at one-two week intervals. At the Rahima Moosa Mother and Child Academic Hospital (RMMCAH), endocrinologists are not involved in the care of these patients. Both the CHBAH and the RMMCAH are tertiary level, teaching hospitals in Johannesburg, associated with the University of the Witwatersrand.

1.11.1 Benefits of treating GDM

A recent Cochrane review concluded that lifestyle interventions are a ‘beneficial primary therapeutic strategy for women with GDM’.[125] Lifestyle interventions commonly include

healthy eating, physical activity and SMBG. Typically, these are implemented from the time of diagnosis until the birth. Benefits of these interventions include:

- A reduced risk of having a large for gestational age infant and associated complications.
- Maternal postpartum weight goals were more likely to be achieved.
- A reduced risk of maternal postnatal depression.
- 90% of GDM affected women restored euglycaemia with lifestyle intervention, without the need for pharmacological therapy.[125]

The same review highlighted the need for data on longer-term benefits or harms of lifestyle interventions, long-term maternal and childhood outcomes of lifestyle interventions and the need to establish the value or benefits of GDM interventions in LMICs.[125]

Multiple clinical trials have provided good evidence that both lifestyle interventions and pharmacological therapies significantly reduce, by ≥ 50%, the progression from GDM to T2D.[14,60,126,127] There are socio-economic and public health benefits to reducing the morbidity and mortality associated with T2D and other NCDs.[60,126] The public health challenge is to identify asymptomatic individuals in a pre-diabetes phase with a reduced β-cell reserve who would most benefit from these interventions. Universal screening for GDM would allow the development of public health initiatives to identify vulnerable South Africans. The development and implementation of a culturally sensitive diabetes prevention program may help reduce the burden of DM on the public health system. Health promotion campaigns and interventions that begin with GDM may increase awareness and acceptance of the personal risk for the development of T2D.[128]

1.11.2 GDM Interventions

GDM treatment includes the transfer of diabetes health information on diet, exercise, SMBG and, in the minority, the use of pharmacological therapy.[125,129] Women are required to make the necessary lifestyle changes with immediate effect when diagnosed with GDM at 24–28 weeks' gestation and ideally, lifestyle changes should be retained lifelong.[14] Women are highly motivated to make these changes during their pregnancy for the wellbeing of their unborn child. However, postpartum follow-up and interventions have been less successful.[130–133] Reasons given why women decline to participate in post-partum follow-up include travel expense and distance travelled to the site where the intervention is delivered, childcare commitments, and not being concerned about personal risk for DM.[134,135] Effective diabetes prevention requires long term sustainable health behaviour change. A recent South African report of the management of GDM in the public sector concluded that health system interventions facilitating active long term follow-up of GDM affected women are needed to avert progression to T2D.[135]

1.11.3 Local adaptation of existing interventions

Intervention strategies proven effective in developed countries are not necessarily transferable to low resource settings. [136,137] For example, modified dietary interventions favourably influenced birth weight and maternal post-prandial glycemia, with a reduced need for pharmacological intervention.[138,139] However, a recent Cochrane review found there is no superior, universally applicable diet suitable for the treatment of GDM.[140] Culturally appropriate diabetes education programs are associated with sustained, improved glycaemic control.[137] Consideration of the resources, experiences, expectations and preferences of women with GDM will strengthen the development or adaptation of local interventions and help to appropriately frame implementation strategies.[136]

Culturally tailored diabetes interventions for socially disadvantaged populations may reduce health disparities in diabetes care.[136] Factors associated with effective culturally sensitive intervention for diabetes include:

- Lay health workers from the local community leading the intervention
- Individualized evaluation and reassessment with feedback
- Incorporation of treatment algorithms and referral systems
- Focus on health behaviour changes,
- High-intensity interventions with at least 10 sessions
- Interventions delivered over at least six months

Knowledge of the local community will allow adaptations to health literacy interventions and facilitate a high degree of responsiveness from individuals.[136]

Multiple diabetes education programs are available internationally. Diabetes education tools are used to transfer health information and typically, these programs include information on diet, exercise and SMBG. The Diabetes Conversation Map (DCM) is a highly interactive, group-based, patient-centred diabetes education tool. This International Diabetes Federation approved program promotes the understanding of diabetes and how to manage it, explores the emotional aspects of diabetes and promotes self-management of diabetes over a lifetime. The DCM was developed through extensive interviews and focus group discussions (FGD) with health care professions and patients. Theoretical underpinnings of the DCM include the Biopsychosocial Model of health and illness, Self-Efficacy Beliefs, the Health Belief Model, Common-Sense Model of Health and Illness Self-Regulation, the Transtheoretical Model and the Social Learning Theory.[141]

The DCM was extensively pilot tested in both high-income countries and LMICs which included Brazil, Egypt and India. It is equally effective in improving glycaemic control when compared to other programs with a more didactic educational style.[142] Didactic diabetes education programs are known to be less effective in disadvantaged communities.[136] The use of the DCM is currently under investigation for use in a state-sector, low-resource setting in South Africa.[143]

1.12 Thesis rationale

1.12.1 Problem statement

South African women are at high risk of GDM based on the prevalence of overweight and obesity, as well as the high morbidity and mortality associated with DM. Based on the recommendations of the IADPSG and the WHO, universal screening for GDM is indicated. This is important because identifying those affected by GDM will allow interventions to improve perinatal morbidity and initiate a DM prevention program in these high-risk individuals. The WHO and the SEMDSA acknowledge that GDM screening is costly and may not be feasible beyond well-resourced settings. In addition, not all health care centres in South Africa have laboratory services on site, making GDM screening less accessible with failure to identify affected women. Sustainable, standardized and scientifically valid, strategies, that are easily implemented in routine clinical care rather than in idealised research-based settings, are urgently needed. A potentially acceptable alternative to laboratory measurements of blood glucose is the use of plasma calibrated glucometers. These would reduce cost and improve the accessibility of screening. It is important to establish

whether glucometers used at the point of care are accurate in screening for GDM, particularly in vulnerable low-resource settings within South Africa.

1.12.2 Thesis Objectives

The purpose of this pragmatic study will be to investigate the feasibility of a modified universal screening program for GDM in urban African women, in a functioning urban low resource community health clinic (CHC). The accuracy of glucometers (index test) will be evaluated against a calibrated laboratory (reference test), in measuring plasma glucose concentrations of the OGTT. Because the current selective screening strategy may be difficult to implement and may miss GDM affected women, the use of a universally applied FPG as an alternative screening strategy will be investigated. In addition, as formative work for an intervention that may be applied in a low resource setting, the experiences of women previously affected by GDM will be evaluated in a series of focus group discussions (FGD).

Research questions:

1. What is the prevalence of GDM in an urban South African CHC?
2. Are glucometers a valid alternative to laboratory services in measuring plasma glucose concentrations of the OGTT?
3. Is the use of a universally applied FPG a valid GDM screening strategy in South African women?
4. Is risk-factor based selective screening adequately sensitive and specific in predicting GDM in African women?
5. What are the experiences of local women previously diagnosed with GDM?

Potential for impact:

1. Data will add to the local and global knowledge on GDM.
2. Research nested within the routine antenatal service of a low-resource CHC may provide evidence that decentralised screening is feasible, and if so, potentially reduce the burden on established hospital-based services and reduce screening inequity.
3. Glucometer use in the OGTT may simplify testing procedures, reduce costs, reduce turn-around-times to diagnosis and prevent delays in initiating clinical intervention.
4. The use of the FPG to screen for GDM may reduce the number of women requiring the resource-intensive OGTT.
5. Exploring the experiences of women previously affected by GDM may inform local adaptions of internationally established GDM interventions.

Chapter 2.

Validation of Glucometer Accuracy

Title

Accuracy of five plasma calibrated glucometers to screen for and diagnose gestational diabetes in a low resource setting

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2.1 Abstract

Aims

We investigated the clinical and analytic accuracy of five plasma calibrated glucometers, the use of which is advocated by the World Health Organisation and the International Federation of Gynaecology and Obstetrics, to screen for and diagnose gestational diabetes mellitus (GDM) in low resource settings.

Methods

592 consecutive black African women underwent a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks' gestation at an urban South African community health clinic. Capillary glucose was measured by one of five glucometer brands, each paired with a routine laboratory hexokinase method of plasma glucose measurement. The laboratory results served as the gold standard reference test for GDM diagnosis. World Health Organization GDM diagnostic thresholds were applied to glucometer and laboratory results.

Results

Glucometer and laboratory determined GDM prevalence was 75/592 (12.7%) and 30/592 (5.1%) with an elevated fasting glucose diagnostic in 64/75 (85%) and 24/30 (80%) of cases respectively. The proportion of glucometer results fulfilling ISO 15197:2013 recommended analytic accuracy at fasting, 60, and 120 minutes of the OGTT was 92.4%, 49.8% and 61.5%, with Bland Altman method revealing a positive glucometer bias of 0.22 mmol/l (-0.69–1.12 mmol/l), 0.96 mmol/l (-0.65–2.56 mmol/l) and 0.73 mmol/l (-0.73–2.19 mmol/l) respectively. Only three of the glucometer brands evaluated fulfilled ISO 15197:2013 analytic accuracy requirements and this was only achieved at fasting. All glucometers tested were inaccurate at one and two hours of the OGTT.

Conclusions

Not all glucometers may be suitable for GDM screening as only three were accurate compared to the reference test and then only at fasting of the OGTT. Importantly, laboratory fasting glucose was diagnostic of GDM in 80% of cases in this study population.

Research highlights

- An elevated fasting glucose defined 80% of laboratory GDM positive diagnoses.
- Selected glucometers fulfilled ISO 15197:2013 recommended accuracy at fasting of OGTT.
- All glucometers evaluated were inaccurate at one and two hours of OGTT.

Keywords

gestational diabetes; screening, primary care; fasting glucose; capillary glucose

2.2 Introduction

The prevalence of Gestational Diabetes Mellitus (GDM) is increasing in parallel with that of type 2 diabetes mellitus. Identifying this usually transient and asymptomatic condition will allow clinical interventions to reduce the perinatal morbidity associated with these high-risk pregnancies [3]. An estimated 16% of pregnancies are affected globally [12]. The World Health Organization (WHO) has adopted the diagnostic criteria for GDM advocated by the International Association of Diabetes in Pregnancy Study Group (IADPSG) [3,47]. Universal screening by means of a 75 g two-hour oral glucose tolerance test (OGTT) at 24–28 weeks' gestation is recommended [3,47]. Several low-middle income countries have adopted the WHO diagnostic criteria, including the recommendation for universal screening for GDM. In 2017, the Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) adopted these guidelines [59]. The South African National Department of Health's policy is guided by the WHO and SEMDSA recommendations, although universal screening for GDM has not yet been implemented in South Africa.

Potential barriers to implementing universal screening in low resourced clinic settings include the limitations of administering the OGTT which is expensive, labour intensive and dependent on calibrated laboratory services. Most Sub-Saharan African countries have minimal or no access to medical laboratory services that meet international quality standards [105]. The density of laboratories in South Africa is comparable with European countries, however, only 18% of these belong to the state- sponsored National Health Laboratory Service (NHLS) which provides services to more than 80% of the population [105]. The WHO has acknowledged that capillary blood glucose measurement by point of care glucometers is widely used in low resource settings to diagnose diabetes mellitus and that the use of glucometers meeting the current ISO standards (15197:2013) is an acceptable alternative to

laboratory glucose measurements [6]. The International Federation of Gynaecology and Obstetrics (FIGO) has endorsed the use of plasma calibrated glucometers to screen for and diagnose GDM in low resource settings [4]. There are no standards for the use of glucometers in the diagnosis of GDM which has lower diagnostic thresholds than dysglycaemia in a non-pregnant adult.

Our aims were to evaluate the measurement accuracy of ISO 15197:2013 compliant glucometers relative to a calibrated laboratory reference test and to assess the ability of the glucometers to correctly identify GDM affected women, relative to the laboratory, in the low resource setting of an urban South African community health clinic (CHC).

2.3 Study participants, materials and methods

Approvals and permissions

The University of the Witwatersrand Human Research Ethics committee granted approval for this study (M150365). The South African Johannesburg District Department of Health granted permission to conduct the study at a CHC in Soweto (Reference number 2015–16/031). All participants provided written informed consent.

Participants

We conducted this cross-sectional, prospective, pragmatic study between April 2016 and May 2017. Participants were recruited consecutively at their first prenatal visit. Women under

28 week's gestation and over the age of 18 years with no pre-existing type one or type two diabetes mellitus, attending the antenatal service of a single urban CHC were eligible to participate.

Gestational age was assessed by the clinic's obstetric nurse as part of usual care. Ultrasound and laboratory facilities were not available on site. Data collected from participants included maternal age, parity, gestation at their first prenatal visit and a risk factor assessment for GDM. Risk factors for GDM were those defined by the South African National Department of Health and these include repeated glycosuria, previous GDM, family history of diabetes (first degree relative), poor obstetric history (stillbirth of unknown origin), previous congenital abnormality, history of a high birth weight infant of >4.5 Kg, maternal obesity (body mass index >30 Kg/m^2) and women of South Asian descent. In keeping with this clinic's patient profile, all participants were indigenous African women who are historically considered to be at low risk of GDM. Indigenous Africans form 80% of the South African population. As participants were frequently unable to recall the birth weights from previous pregnancies, descriptions of "small, average or large" were used instead as this was the local standard practice. We recorded the presence of glycosuria (urine dipstick) from the clinic records and measured mid-upper arm circumference, body weight and height.

Materials and methods

Participants returned to the clinic on an appointed morning after an overnight fast for a modified 75 g OGTT at between 24–28 weeks' gestation. Study procedures were performed in an office within the usual functioning of the antenatal clinic. Modifications to the OGTT included the pairing of a glucometer test (finger-prick; capillary blood glucose concentration)

with a reference laboratory test (venous puncture; plasma glucose concentration) at fasting, 60 and 120 minutes. Finger-prick blood sampling procedures included: wiping the finger with an alcohol swab, allowing this to dry, puncturing the skin with a single use lancing device, the first blood drop was wiped off with dry cotton-wool and the second blood drop was used for measurement of glucose concentration per time point of the OGTT. Trained research staff operated independently from the community clinic staff. The first author and an experienced diabetes nurse educator supervised all study procedures.

Venous blood samples were collected in tubes containing the glycolytic inhibitor sodium fluoride and kept on ice from the time of phlebotomy until delivery to the laboratory at the end of the two-hour OGTT [13]. The time lapse between completion of the OGTT and delivery to the laboratory was approximately one hour. The American NACB (National Academy of Clinical Biochemistry) recommends immediate separation of plasma or alternatively, keeping samples in an ice slurry with the separation of plasma within 30 minutes [88]. Separation of plasma within 30 minutes was not possible, but this is not uncommon in a routine clinical setting. Indeed, the NACB and other researchers acknowledge that these procedures are neither widely used nor always practical in routine clinical settings [88,95,144].

ISO 15197:2013 compliant glucometers from five manufacturers which are commonly used in South Africa were selected for assessment. These included the Accu-Chek Active (Roche Diagnostics, Germany), used extensively in both the private and state sector; Freestyle Optium Neo (Abbott Diabetes Care Inc., USA), used in the private sector including in a large private hospital group and recently also in the state sector; Glucocheck Classic (TaiDoc Technology Corporation, Taiwan), the preferred glucometer of one of the largest South African medical insurers; One Touch Select Plus Flex (LifeScan Inc., Switzerland), used in

the private sector and is marketed as being gold standard ISO 15197:2013 compliant; and Contour Plus (Bayer, Czech Republic), used in the private sector and in the calibration of the Medtronic continuous glucose monitoring system (Medtronic, USA).

We followed the ISO 15197:2013 analytic procedures previously described for evaluating the glucometers performance and this included: finger-prick and venous blood sampling were less than five minutes apart; at least 100 participants were tested with each glucometer brand before changing to the next brand which was selected at random; at least three different lots of test strips were used per glucometer brand and at least 10 glucometers per brand were used over a period of at least 10 days [112,121]. A minimum of 100 paired blood glucose tests would be submitted at each of the time points of the OGTT per glucometer brand. We intended using one glucometer per participant per day, with the glucometer cleaned and reused on another testing day. All other glucometer testing procedures followed the manufacturer's instructions. All glucometers evaluated used 'non- coding technology' and so code chips were not necessary. Glucometer test strips were stored according to manufacturer's instructions. The ISO 15197:2013 minimum systems accuracy recommendations suggests that ≥95% of glucometer results fall within 0.83 mmol/l of the reference value at blood glucose concentrations <5.56 mmol/l and, that ≥95% of glucometer results fall within 15% of the reference value at blood glucose concentrations ≥5.56 mmol/l [121]. In this study, this was assumed as the total allowable error (TAE) between the paired glucometer and the reference laboratory values.

The accuracy of the glucometers was evaluated against results from a South African National Accreditation System verified private medical laboratory, which used a hexokinase method to measure plasma glucose concentration (Cobas 6000, Roche Diagnostics, Germany).*

This accreditation requires compliance with ISO 15189:2012 and this encompasses pre-examination, examination and post-examination processes of Medical Laboratory testing. As per, manufacturer calibration was performed after reagent lot change and as required, following quality control procedures. A two-point calibrations was performed including a H2O blank and Calibrator for Automated Systems (c.f.a.s). The assigned calibrator level in c.f.a.s. is standardized against Isotope Dilution Mass Spectrometry.

The hexokinase laboratory method, rather than the glucose oxidase method, is routinely used by both the NHLS and the two largest private sector medical laboratories in South Africa. Although manufacturers may specify a preferred reference test method to evaluate their glucometers performance, according to the ISO 15197:2013 recommendation, any method with verified metrological traceability may be used [121]. The laboratory was off-site and blinded to all but their own results.

The WHO 2013 GDM diagnostic thresholds were used to define the test positivity cut-offs for both the glucometers and the reference laboratory results [47]. The laboratory result served as the gold standard reference test and so these values were assumed to be the true result.

Analysis

Categorical variables are described as frequencies (n) and proportions (%), and continuous variables as means and standard deviations (SD). The TAE between paired glucometer and laboratory values at each time point was calculated. Bland Altman plots were used to evaluate the level of measurement agreement between the glucometer and laboratory results. Sensitivity, specificity and positive and negative predictive values were used to evaluate the ability of the glucometers to distinguish between GDM positive and negative states. The

positive likelihood ratios (PLR) and negative likelihood ratios (NLR) served as an overall indicator of the diagnostic accuracy of the glucometers against the reference laboratory test and a PLR ≥10 and an NLR ≤ 0.1 were assumed to be favourable associations. McNemar's test and the Kappa statistic was used to evaluate the clinical agreement between glucometers and the laboratory on GDM diagnoses. The kappa-statistic (k) values are graded as k = 0–0.19, poor; 0.20–0.39, fair; 0.40–0.59, moderate; 0.60– 0.79, good; 0.80–1.00, very good regarding the level of agreement between tests. Where appropriate, 95% confidence intervals (95% CI) are reported. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed on STATA software version 15 (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, USA).

2.4 Results

Participants

592 OGTTs, with paired glucometer and reference laboratory results, were submitted for analysis. The participants' mean age (SD) was 27.8 years (5.9 years), 173 (29.2%) were pregnant for the first time, 99 (16.8%) had a first-degree family member with diagnosed diabetes, 3 (0.5%) had previous GDM and 43 (7.3%) reported previous large birth weight infants. Participants mean body mass index was 26.8 Kg/m^2 (5.8 Kg/m^2) and their mid-upper arm circumference was 29.9 cm (4.4 cm). In this study population, 254 of 587 (43.3%) participants had ≥ one risk factor for GDM present. Note that the number of participants for each risk factor varied slightly due to missing values. (Table 1) The laboratory provided results within four hours of receiving samples. Glucometer results were available within five seconds. All glucometers were reused except for the Accu-Chek Active, which we considered

unsafe for multiple people use as it was easily visibly soiled with participants blood during testing procedures, creating a potential biohazard. Each Accu-Chek Active meter was used once and then discarded and fewer participants were tested with this glucometer brand. Participants were given their provisional glucometer results on the day of testing subject to confirmation by the gold standard reference laboratory results. Those who were confirmed as GDM positive were referred for clinical intervention.

GDM prevalence

The number of participants identified as GDM positive as determined by the glucometers and the laboratory were 74 (12.7%) and 30 (5.1%) respectively, being significantly different ($p < 0.0001$). Overt diabetes mellitus was consistently identified by both test methods in three participants (0.5%). Only one abnormality of the OGTT is necessary for a positive diagnosis of GDM and in this study population, an elevated fasting glucose was diagnostic in 64 of 75 (85%) glucometer positive diagnoses and in 24 of 30 (80%) laboratory positive diagnoses. The remaining GDM positives diagnosed by the glucometer and laboratory had normal fasting glucose but an elevated one and/or two-hour blood glucose in the OGTT. Of the glucometer GDM positive diagnoses, 27 of 75 (36%) were true positive relative to the gold standard reference laboratory test and of these true positives, 21 (77.8%) had an elevated fasting glucose.

Analytic accuracy of the glucometers

The mean (SD) blood glucose concentration for all glucometer and laboratory results at all time points of the OGTT (1776 observations) was 5.6 mmol/l (1.4 mmol/l) and 5.0 mmol/l (1.3 mmol/l) respectively. The glucometer results were consistently higher than the laboratory. The laboratory determined mean plasma glucose concentration at fasting, 60 and

120 minutes of the OGTT (592 observations at each time point) was 4.13 mmol/l (0.49 mmol/l), 5.62 mmol/l (1.39 mmol/l) and 5.27 mmol/l (1.21 mmol/l). Mean capillary glucose concentrations per glucometer brand at each time point of the OGTT is displayed in Figure 1. Only the Contour Plus, Accu-Chek Active and the One Touch Select Plus Flex fulfilled the ISO 15197:2013 recommended TAE compared to the reference laboratory results and this was only achieved at fasting of the OGTT. None of the glucometer brands accuracy were within the TAE at 60 minutes or at 120 minutes of the OGTT. Individual glucometer brands performance regarding accuracy at various timepoints of the OGTT is indicated in Table 2.

The overall proportion of glucometer results that fulfilled the TAE against the laboratory at fasting, 60 and 120 minutes of the OGTT were 92.4%, 49.8%, and 61.5% respectively. All glucometer results accuracy deviated the most from laboratory results at 60 minutes of the OGTT. Results between glucometer brands were also most widely spread at 60 minutes of the OGTT. Bland Altman plots confirmed that the glucometers results were consistently higher relative to those from the laboratory at all time points, except for the Freestyle Optium Neo which was neutral at fasting. The glucometers had an overall positive systematic bias relative to the laboratory. The overall average difference against the mean between glucometer and laboratory results indicated a glucometer positive bias at fasting, 60 and 120 minutes of the OGTT of 0.22 mmol/l (-0.69–1.12 mmol/l), 0.96 mmol/l (-0.65–2.56 mmol/l) and 0.73 mmol/l (-0.73–2.19 mmol/l) respectively. Individual glucometer Bland Altman plot results are indicated in Supplementary Figures 1–5.

Clinical accuracy of glucometers

Due to the low prevalence of laboratory identified GDM, this study was underpowered to truly evaluate the clinical accuracy, rather than the analytical accuracy, of the glucometers to identify GDM positive states. However, there are some clinically meaningful observations based on the data available. The One Touch Select Plus Flex failed to identify two participants who had GDM. Of all the glucometer false positive GDM diagnoses, 26/48 (54.2%) were associated with the Glucocheck Classic and one in four participants tested with this glucometer was falsely identified as being GDM positive. (Table 3) The Accu-Chek Active had strong positive and negative likelihood ratios in their ability to identify women affected by GDM relative to the reference laboratory results. However, the Accu-Chek Active failed to identify one woman who had GDM as defined by the reference laboratory. Fewer participants were tested with this meter for reasons indicated previously. Coincidentally, this glucometer was evaluated against results from reference laboratory equipment produced by the same manufacturer. The Kappa statistic was calculated to evaluate the glucometers clinical diagnostic accuracy (binary) relative to the reference laboratory GDM diagnosis (binary). The Kappa statistic (standard error) result for the Contour Plus, Accu-Chek Active, Glucocheck Classic, Freestyle Optium Neo and One Touch Select Plus Flex was 0.72 (0.08), 0.48 (0.13), 0.32 (0.07), 0.71 (0.08) and 0.22 (0.07) respectively. The exact McNemar's significance probability of agreement in GDM positive diagnoses between the glucometers and the reference laboratory were as follows: Contour Plus ($p = 0.0625$), Accu-Chek Active ($p = 1.0000$), Glucocheck Classic ($p < 0.0001$), Freestyle Optium Neo ($p = 0.0313$) and, One Touch Select Plus Flex ($p = 0.0386$).

2.5 **Discussion**

Prevalence of GDM

The reference laboratory identified a relatively low prevalence of GDM of 5.1% compared with the 12.7% determined by the glucometers. There is a paucity of data on the prevalence of GDM in Sub-Saharan Africa. A recent South African study by Macaulay et al. reported a 9.1% GDM prevalence in 1906 participants from a similar population but in a tertiary hospital setting and plasma glucose concentrations were determined by a research rather than a routine laboratory service (glucose oxidase method) [35]. Their study population were older (30 years vs 27.8 years), were more overweight (body mass index 29.5 vs 26.9 Kg/m^2), with fewer primiparous participants (12.1 vs 29.2%) and a higher proportion of positive laboratory GDM diagnoses based on an elevated fasting glucose (83.3% vs 80%) [35]. A study by Adam and Rheeder reported a GDM prevalence of 14.9% and 26.7% based on glucose concentrations measured by a Roche Accuchek Active glucometer and a routine laboratory service (hexokinase method) respectively [145]. Their laboratory results were 0.40 mmol/l higher than the glucometer results at fasting but 0.7 mmol/l and 0.4 mmol/l lower than the glucometer results at one and two hours of the OGTT respectively. An elevated fasting glucose was diagnostic of GDM in the majority of their laboratory defined positive cases. Their reported laboratory quality controls reflect a bias of 3.65% at a lower glucose concentration, which is not within the ≤2.2% recommended by the NACB [88,145]. This laboratory inaccuracy, specifically at lower glycaemic concentrations, may have contributed to the relatively higher GDM prevalence reported by Adam and Rheeder. In addition, the socio-demographics of their study sample of 529 women was not well described. This may be significant as South Africans of Asian descent are known to be at high risk of GDM.

In our study, a high proportion of GDM positive diagnoses were based on an elevated fasting glucose and this finding was unexpected as this is higher than that reported in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study population. When the

IADPSG diagnostic criteria was retrospectively applied to the HAPO study population, 55% (24–74%) of GDM diagnoses were based on an elevated fasting plasma glucose [63]. Sub-Saharan Africa was not included in the HAPO study. Sub-Saharan Africa has a historically undernourished population currently affected by a high prevalence of overweight and obesity and the effect of this on the GDM prevalence is unknown [21,22].

Clinical and analytical accuracy of glucometers in diagnosing GDM

In this study, the prevalence of GDM as determined by glucometers was significantly higher than the gold standard reference laboratory. Glucometers measured higher blood glucose concentrations than the laboratory at all time points of the OGTT. In a previous report comparing the diagnostic accuracy of a glucometer, routine analysis and an optimized laboratory, glucometer results approximated the optimized laboratory, however, the routine laboratory underdiagnosed GDM positive states [95]. It is known that blood glucose concentration drops by approximately 5–7% per hour ex vivo due to ongoing glycolysis, and sodium fluoride does not necessarily negate this effect within the first four hours [88]. The use of sodium fluoride tubes is included in the WHO recommended procedure for an OGTT [13]. Citrate may be a more effective plasma glucose stabilizer, although, the quality and availability of these tubes may vary and they are not routinely used in South Africa [88,95]. As glucometer measurements are unaffected by preanalytical factors such as ongoing glycolysis, they may be superior to routine laboratory services, but not to optimized laboratory conditions, in detecting those affected by GDM [95]. The Bland Altman method indicates the glucometer positive bias was within the ISO 15197:2013 recommended technical accuracy of ≤0.83 mmol/l at fasting [121]. All glucometers were inaccurate at one and two hours of the OGTT. It is known that differences between capillary and venous blood glucose are relatively minor at fasting, however, at 60 and 120 minutes of the OGTT capillary blood glucose concentrations may be 20–25% higher than venous glucose, due to oxygen consumption in tissues [88]. Also, laboratory analysed plasma glucose of the OGTT are known to have suboptimal reproducibility in diagnosing GDM, particularly at 60 and 120 minutes of the OGTT [146]. Selected glucometers fulfilled ISO accuracy requirements only at fasting of the OGTT and all were inaccurate at one and two hours of the OGTT. This

suggests that glucometers may be unsuitable for the diagnosis of GDM based on results of a complete OGTT.

Selection of glucometers suitable for GDM screening and diagnosis

Multiple glucometers were selected for assessment as we anticipated inconsistencies in performance between brands. There are independent reports of suboptimal glucometer fulfilment of ISO recommendations post-marketing [112]. Although the FIGO has endorsed the use of handheld plasma calibrated glucometers in low resource settings that are remote from laboratory services, they acknowledge there are no standards for their use in the screening and diagnosis of GDM [4]. This study was a calibration exercise between glucometers, the use of which is endorsed by the WHO and FIGO, and a local calibrated laboratory, in the setting of a low resource urban CHC rather than an optimal research setting. The ISO 1597:2013 recommendations for glucometer accuracy describe voluntary, manufacturer conducted, premarketing evaluation of the minimal accuracy requirements of over the counter glucometers [121]. The validation of glucometers level of compliance with ISO 15197:2013 recommendations would require a controlled research setting which was beyond the scope of this study. Independent ongoing surveillance of glucometer performance is necessary to ensure their safe use in screening for GDM.

Limitations

All our participants were indigenous African women and these results may not be generalizable beyond this population. This pragmatic study was conducted in the setting of a low resource community clinic, which may equate to routine care and it was not possible to process venous samples immediately. This may have resulted in a lower level of glucose

measured by the laboratory with a relative underestimation of GDM prevalence by this reference test. The low prevalence of GDM in this study population limits the generalisability of using glucometers for screening purposes.

2.6 Conclusion

The future use of plasma calibrated glucometers rather than laboratory services is inevitable and even desirable in low resource community clinic settings. However, only selected ISO 15197:2013 compliant glucometers may be suitable for the screening of GDM and then, only based on an elevated fasting blood glucose and not for a complete OGTT. This study provides evidence of a pragmatic and valid approach for the use of selected glucometers to determine fasting blood glucose concentration in pregnant women and may be essential to rolling out universal screening for GDM in low resource settings.

2.7 Acknowledgements

The Johannesburg District South African Department of Health granted us permission to conduct research at a CHC in Soweto. We are grateful for the support of the patients and community clinic staff. The sustained efforts of our research assistant Ms Nandi Mtshali were essential to the completion of the study on schedule.

Contributors

Methodology: LMD; EJB; SAN. Investigation: LMD. Formal analysis: LMD; EJB; CJVR; SAN. Writing: LMD. Reviewing and editing: EJB; CJVR; SAN. All authors have approved the final article.

Declarations of interest

None.

Role of the funding source

Neither the glucometer manufacturers nor the laboratory had any role in the study design, data analysis and interpretation of results, in the writing of the report or in the decision to submit the article for publication. The South African Medical Research Council supported LMD.

2.8 Tables and Figures

Table 2.1. Participant Characteristics

Participant characteristic	n total	Mean (SD) or, Frequency (%)
Age (years)	592	27.8 (5.9)
Family history of diabetes (first-degree)	588	99 (16.8%)
Glycosuria (urine dipstick) ≥ one event	592	6 (1%)
Mid-upper arm circumference (cm)	592	29.9 (4.4)
Body height (cm)	588	162.9 (7.2)
Body weight (Kg)	592	70.6 (15.8)
Body mass index (Kg/m2)	588	26.9 (5.8)
Obstetric history		
Parity at recruitment First pregnancy Second pregnancy Third pregnancy > Three pregnancies	592	 173 (29.2%) 196 (33.1%) 144 (24.3%) 79 (13.3%)
Gestational age at first visit (weeks)	592	19.1 (5.6)
Previous miscarriage	592	65 (11%)
Previous large for gestational age birth	591	43 (7.3%)
Previous stillbirth	592	32 (5.4%)
Previous congenital abnormalities	591	0 (0)
Previous GDM	592	3 (0.5%)

Note: Number (n) of participants for each characteristic varies slightly due to missing values.

Figure 2.1. Mean Glucose Concentrations as Measured by the Reference Laboratory and Each Glucometer Brand at Different Time Points of the OGTT.

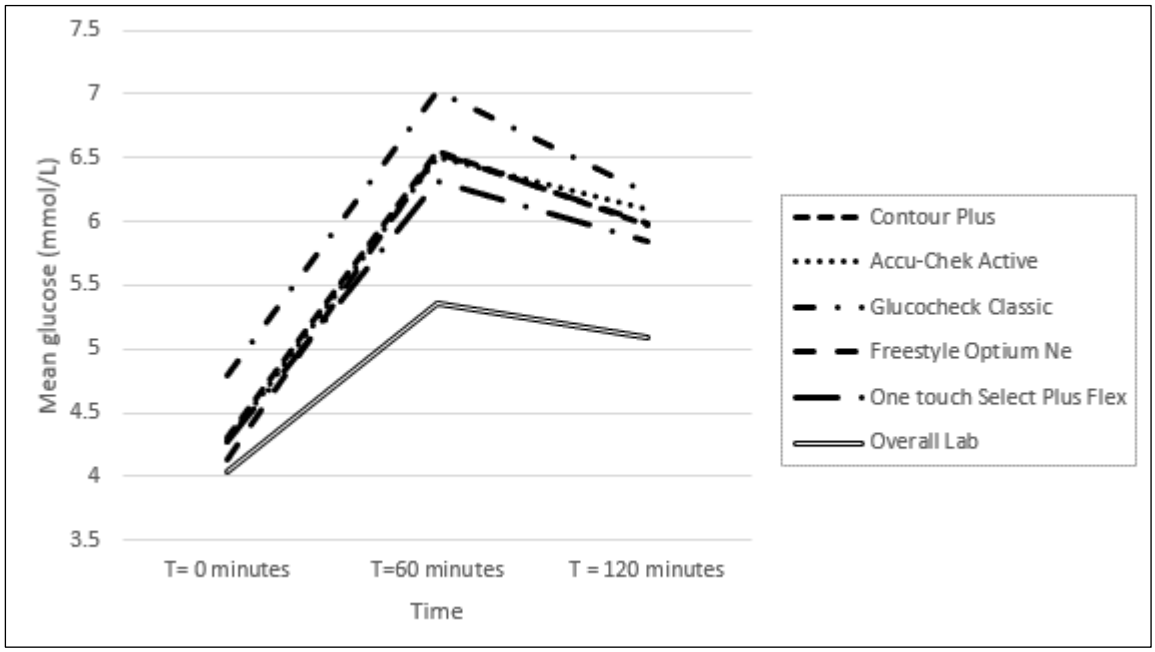

Table 2.2. Results of Statistical Analysis of Agreement Between the Glucometer Brands and the Reference Laboratory at OGTT Time Point.

Glucometer brands	T= 0 minutes	T=60 minutes	T = 120 minutes
Proportion of results within Total Allowable Error: (ISO 15197:2013 defined) between glucometers and the reference laboratory (%)			
Overall (n = 592)	92.4	49.8	61.5
Contour Plus (n = 143)	96.5	29.4	53.1
Accu-Chek Active (n = 56) *	100	58.9	67.9
Glucocheck Classic (n = 105)	76.2	30.5	35.2
Freestyle Optium Neo (n = 143)	94.4	63.6	77.6
One touch Select Plus Flex (n=145)	95.2	66.9	70.3
Bland Altman (95% LoA) mmol/l average difference against the mean between glucometers and the reference laboratory			
Overall (n=592)	0.22 (-0.69 – 1.12)	0.96 (-0.65 – 2.56)	0.73 (-0.73 – 2.19)
Contour Plus (n=143)	0.27 (-0.32 – 0.86)	1.20 (-0.04 – 2.44)	0.88 (-0.18 – 1.93)
Accu-Chek Active (n=58) *	0.12 (-0.49 – 0.72)	0.72 (-0.67 – 2.11)	0.59 (-0.54 – 1.71)
Glucocheck Classic (n=105)	0.57 (-0.52 – 1.65)	1.51 (-0.58 – 3.60)	1.16 (-0.96 – 3.29)
Freestyle Optium Neo (n=143)	0.00 (-0.81– 0.81)	0.70 (-0.57 – 1.96)	0.51 (-0.62 – 1.64)
One Touch Select Plus Flex (n=145)	0.17 (-0.74 – 1.07)	0.66 (-0.69 – 2.00)	0.54 (-0.74 – 1.82)

Note: Bland Altman difference against the mean: $p < 0.001$ for all values at all time points of the OGTT, except for the Freestyle Optium Neo which was neutral at fasting.

* Accu-Chek results may be spurious for reasons indicated in the text.

LoA = Limits of agreement.

Table 2.3. Statistical Analysis of Agreement in Gestational Diabetes Diagnosis Between the Glucometers Against the Hexokinase Method Laboratory Reference.

	All Glucometers (95% CI)	Contour Plus (Bayer) (95% CI)	Freestyle Optium Neo (Abbott) (95% CI)	Accu-Chek Active (Roche) (95% CI)	Glucocheck Classic (TaiDoc) (95% CI)	Plus Flex (Lifescan) (95% CI)
Number of participants	592	143	143	56	105	145
True Positive (n)	27	7	8	1	9	2
False Positive (n)	48	5	6	1	26	10
True Negative (n)	514	131	129	53	70	131
False Negative (n)	3	0	0	1	0	2
Sensitivity (%)	90 (74; 98)	100 (59; 100)	100 (63; 100)	50 (1; 99)	100 (66; 100)	50 (7; 93)
Specificity (%)	91 (89; 94)	96 (92; 99)	96 (91; 99)	98 (90; 100)	73 (63; 81)	93 (87; 97)
Positive Predictive Value (%)	36 (25; 48)	58 (28; 85)	57 (29; 82)	50 (1; 99)	26 (12; 43)	17 (2; 48)
Negative Predictive Value (%)	99 (98; 100)	100 (97; 100)	100 (97; 100)	98 (90; 100)	100 (95; 100)	98 (95; 100)
Positive Likelihood Ratio	10.54	27.20	22.50	27.00	3.69	7.05
Negative Likelihood ratios	0.11	0.00	0.00	0.51	0.00	

Chapter 3

Comparison of Results Between Laboratory Methods

Title

The impact of differences in plasma glucose between glucose oxidase and hexokinase methods on estimated gestational diabetes mellitus prevalence.

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3.1 Abstract

We evaluated the extent of measurement discordance between glucose oxidase and hexokinase laboratory methods and the effect of this on estimated gestational diabetes mellitus (GDM) prevalence in a routine clinical setting. 592 consecutive urban African women were screened for GDM. Paired venous specimens were submitted to two independent calibrated laboratories that used either method to measure plasma glucose concentrations. World Health Organisation diagnostic criteria were applied. GDM prevalence determined by the glucose oxidase and hexokinase methods was 6.9% and 5.1% respectively. The overall GDM prevalence was 9%. Only 34% of GDM positive diagnoses were common to both laboratory methods. Bland Altman plots identified a bias of 0.2 mmol/l between laboratory methods. Plasma glucose concentrations measured by the glucose oxidase method were more platykurtic in distribution. Low diagnostic agreement between laboratory methods was further indicated by a Cohen's kappa of 0.48 ($p < 0.001$). Reports of GDM prevalence using either the glucose oxidase or hexokinase laboratory methods may not be truly interchangeable or directly comparable.

Research highlights

GDM prevalence by glucose oxidase and hexokinase methods was 6.9% and 5.1% respectively.

Hexokinase and glucose oxidase methods agreed on 34% of GDM positive diagnoses.

Bias between hexokinase and glucose oxidase methods was 0.20 mmol/l.

Keywords

Gestational diabetes screening, Glucose-oxidase method, Hexokinase method

3.2 Introduction

Identifying usually asymptomatic gestational diabetes mellitus (GDM) will allow interventions to improve perinatal and long-term outcomes for both mother and her child. [3,47] In the Hyperglycaemia and Adverse Pregnancy Outcome study, which investigated the relationship between glycemia and birth outcomes, stringent research laboratory standards were applied across multiple research centres. [64] Evidence from controlled research laboratory settings, rather than routine clinical settings, informed the GDM clinical diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Group (IADPSG). [3] These recommendations were later adopted by the World Health Organisation (WHO). [47] The WHO recommended gold standard 75 g oral glucose tolerance test (OGTT), which is used in both research and routine clinical settings to identify dysglycaemia, describes blood sample collection and transport methods. [13] However, it does not indicate a standardized laboratory method of measurement of plasma glucose concentrations. [13]

Laboratory methods commonly used to measure plasma glucose concentrations include the enzymatic glucose oxidase (GOx) and hexokinase (HK) methods. [88] It has been reported that results of the HK method are negatively biased relative to the GOx method [147,148] but this does not affect the estimated prevalence of overt diabetes mellitus. [88] GDM has lower diagnostic thresholds than dysglycaemia in a non-pregnant adult. [13,47] Typically, GDM prevalence studies use either GOx [35,64,71,77,149] or HK laboratory methods [65,150,151] to measure plasma glucose concentrations. Meta-analyses on GDM prevalence often do not distinguish between laboratory methods used to measure plasma glucose concentrations. [80,84,152–155] The effect of measurement discordance between laboratory methods on the determined prevalence

of GDM remains unknown. The presence of significant discordance between laboratory methods may not only limit the interpretation of global surveillance on the prevalence of GDM but will also impact the public health and clinical management of pregnant women.

We evaluated the extent of discordance between the GOx and HK laboratory methods on measured plasma glucose concentrations and the effect of this on the estimated prevalence of GDM. This pragmatic study was conducted in a public sector community health clinic using accredited laboratory services to mimic actual routine clinical conditions rather than a research setting. The primary outcomes of this data analysis were the clinical accuracy regarding a positive diagnosis of GDM, as well as the analytical accuracy regarding the level of agreement between paired laboratory results.

3.3 Study subjects, methods, and materials

Approvals and permissions

The study protocols were reviewed and approved by the University of the Witwatersrand Human Research Ethics committee (M150365). This study was conducted in accordance with the principles of the Declaration of Helsinki. The South African Johannesburg District Department of Health granted permission to conduct this study at a community health clinic (CHC) in Soweto, Johannesburg (2015–16/031). All participants provided written informed consent.

Study design

This analysis is part of a study that investigated the utility of plasma-calibrated glucometers to universally screen for GDM in a low resource, routine clinical setting.[4,6,156] In this study both the HK and GOx laboratory methods were used as reference tests against the glucometers in all women tested. This prospective pragmatic cross-sectional study was conducted at a single CHC between April 2016 and May 2017. Consecutive women were recruited at their first antenatal clinic visit. Women aged 18 years and above and under 28 weeks of gestation were eligible for inclusion in the study. Women with type 1 or type 2 diabetes mellitus were excluded. All participants were urban African women, in keeping with this clinic's patient profile.

GDM screening procedures

Participants were recruited consecutively, and all completed an OGTT. In addition, all participants were evaluated for the presence of GDM risk factors which include maternal obesity (body mass index ≥ 30 kg/m^2), maternal age ≥ 40 years, previous history of GDM, first degree relative with diabetes mellitus, previous unexplained intrauterine foetal death, previous macrosomic baby or complications in the current pregnancy which include polyhydramnios, foetus large for gestational age or the presence of repeated glycosuria.[72] A modified two-hour 75 g OGTT was scheduled at the woman's convenience on a morning after an overnight fast at 24–28 weeks' gestation.[47] OGTT modifications included the collection of two venous blood samples at fasting, 60 and 120 minutes per participant. Venous blood samples were collected in tubes containing the glycolytic inhibitor sodium fluoride[13] (BD 454297) and kept on ice from the time of phlebotomy until delivery to the laboratories within an hour of completion of the OGTT. The immediate separation of plasma

or keeping samples on ice and separating plasma within 30 minutes was not feasible. Although these separation procedures are recommended by the American National Academy of Clinical Biochemistry (NACB), they and other researchers acknowledge that these procedures are uncommon in routine clinical settings.[88,95,96,144] Trained research staff operated independently from the CHC staff.

Laboratory services.

There is no laboratory on-site at CHCs in South Africa. The laboratories used in this study were 14 km (research medical laboratory) and 16 km (private medical laboratory) distant. A South African National Accreditation System (SANAS) verified private medical laboratory used the HK method (Cobas 6000, Roche Diagnostics International, Switzerland) and a medical research laboratory used the GOx method (Randox, Daytona Plus, USA) exclusively to determine plasma glucose concentrations. Study samples were processed within the usual functioning of these laboratories. Laboratories were not requested to adjust their routine standard operating procedures for this study. On request, laboratories provided us with their quality control results, namely, the analytic coefficient of variation (CV) and bias at two glucose quality control levels. For the HK method laboratory, at observed mean glucose concentrations of 3.32 mmol/l and 20.16 mmol/l, the CV was 1.79% and 1.74% and the bias was 0.36% and 0.13% respectively. For the GOx method laboratory, at observed mean glucose concentrations of 6.36 mmol/l and 15.80 mmol/l, the CV was 1.85% and 1.67% with a bias of 0.35% and 0.31% respectively.

* SANAS accreditation requires compliance with ISO 15189:2012 and this encompasses pre-examination, examination and post-examination processes of medical laboratory testing. The research laboratory is registered with the RIQAS (Randoxy International Quality Assessment Scheme) external quality control program to monitor performance of their analysers and to compare their results to that of other laboratories.

The NACB recommendation for total maximal allowable error in laboratory measurement of plasma glucose is ≤6.9% with an imprecision (CV) of ≤2.9% and a bias of ≤2.2%.[88]

Sample handling.

In this study, all venous blood samples were subject to similar preanalytical conditions. Paired venous blood samples were collected from a single venous draw, meaning that intra-individual biologic factors were unlikely to affect interlaboratory method comparisons.[101] It is known that blood glucose concentration drops by approximately 5–7% per hour ex-vivo due to ongoing glycolysis, and sodium fluoride does not necessarily negate this effect within the first four hours.[88,101] The use of sodium fluoride tubes is included in the WHO recommended OGTT procedure.[13] All samples were subject to similar transport conditions and ongoing glycolysis was unlikely to affect interlaboratory method comparisons. All venous blood samples were delivered to the off-site laboratories within an hour of completion of the OGTTs and within 15 minutes of each other. Meaning the blood samples for fasting, 60 and 120 minutes reached the laboratory after three, two and one-hour post phlebotomy respectively. Each laboratory processed samples within one hour of receipt and this includes centrifugation and measurement of plasma glucose concentration. For reasons of convenience, samples were delivered to the GOx laboratory before the HK laboratory. This study was conducted over a period of 14 months and so results were unlikely to be affected by a specific laboratory analytical run. The two laboratories operated independently and were blinded to all but their own results.

Clinical diagnostic criteria.

The WHO 2013 GDM clinical diagnostic criteria were used to define test positivity cut-offs for results from each laboratory method.[47]

Statistical analysis.

Categorical variables are described as frequencies (n) and proportions (%) and continuous variables as means and standard deviations (SD). The Bland Altman method was used to assess the level of agreement between HK and GOx methods and results are shown with 95% limits of agreement (95% LoA). McNemar's test, the kappa statistic, and Lin's concordance correlation coefficient were also used to evaluate the agreement between paired plasma glucose results. The kappa-statistic (κ) values were graded as <0.20 = poor, 0.20–0.39 = fair, 0.40–0.59 = moderate, 0.60– 0.79 = good and ≥0.80 = very good, regarding levels of agreement. The paired t-test was used to assess if the mean difference in glucose results between methods were different from zero. A p value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed using STATA software version 15 (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, USA).

Data availability.

Data will be made available on request.

3.4 Results

Participant characteristics

One or more risk factors for GDM was present in 257 (43.4%) of 592 participants. Clinical characteristics strongly associated with a GDM positive diagnosis include increased maternal

age ($p<0.001$), an increased body mass index ($p=0.001$) and a later presentation for their first antenatal clinic visit ($p=0.001$). (Table 1). Overall, participants were overweight with a mean body mass index (BMI) of 26.9 kg/m^2. In addition, 173 (29.2%) of 592 participants were pregnant for the first time.

Availability of results

The private laboratory provided results within four hours of receiving samples and the research laboratory provided results at the end of the week of testing. Participants were informed of their GDM status and those identified as being GDM positive, by either laboratory method, were referred for clinical intervention. Complete OGTTs for 592 women, in total 1776 paired plasma glucose results, were submitted for analysis. The mean (SD) glucose concentrations at fasting, 60 and 120 minutes of the OGTT for the GOx method were 4.01 mmol/l (3.95–4.07 mmol/l), 5.42 mmol/l (5.30–5.54 mmol/l) and 5.12 mmol/l (5.01–5.23 mmol/l) respectively. For the HK method, these were 4.13 mmol/l (4.09–4.17 mmol/l), 5.62 mmol/l (5.51–5.73 mmol/l) and 5.27 mmol/l (5.17–5.37 mmol/l) respectively. For all 1776 observations, the interquartile range for the GOx and HK methods was 1.70 mmol/l and 1.55 mmol/l respectively.

Clinical accuracy

The prevalence (95% Confidence Interval) of GDM as defined by the GOx method was 6.9% (5.0–9.3%) and for the HK method, 5.1% (3.4–7.2%). The composite laboratory GDM prevalence was 9.0%, meaning that 53 of 592 participants were GDM positive as defined by either or both laboratories. Regarding clinical agreement, 18 of the total 53 GDM positive diagnoses (34%) were common to both laboratory methods. The GOx method identified 23

additional participants as having GDM that were not identified by the HK method. The HK method identified 12 additional positive GDM cases not identified by the GOx method. An elevated fasting plasma glucose was diagnostic in 87.8% of GOx method and 80.0% of HK method GDM positive cases respectively. GDM positive diagnoses based on abnormalities at various time points of the OGTT as determined by the GOx and HK methods are displayed as Venn diagrams in Figure 1. The overall observed clinical agreement in GDM status between the GOx and HK laboratory methods was high (94.1%) because of the high proportion of GDM negative cases. The overall Cohen's kappa statistic was calculated as 0.48 ($p<0.001$), which suggests a moderate agreement between the two laboratory methods in terms of clinical accuracy in diagnosing GDM. Using a significance level of 5%, McNemar's test indicates no significant disagreement in GDM diagnoses between laboratory methods ($\chi^2 = 3.46$; $p = 0.0895$).

Laboratory analytical accuracy

Of the paired laboratory results at fasting, 60 and 120 minutes of the OGTT, the average difference against the mean (95% LoA) were -0.12 mmol/l (-1.31–1.07 mmol/l), -0.20 mmol/l (-1.80–1.39 mmol/l) and -0.15 mmol/l (-1.70–1.40 mmol/l) respectively. On average, the HK laboratory method results were positively biased (higher) relative to the GOx method results at all time points of the OGTT. Bland Altman plots for paired results for each time points of the OGTT are presented in Figure 2. The overall average difference against the mean between the two methods for all 1776 observations was -0.20 mmol/l (-1.6–1.3 mmol/l). The systematic bias between methods is indicated by the 95% Confidence Interval for the mean difference (-0.2 to -0.1 mmol/l), which does not cross a zero baseline. This is confirmed by the mean difference between methods being statistically different from zero at

each time point of the OGTT ($p < 0.001$). The concordance correlation coefficients (95% Confidence Interval) between the GOx and HK methods at fasting, 60 and 120 minutes of the OGTT were 0.53 (0.48–0.58), 0.83 (0.81–0.86) and 0.81 (0.78–0.84) respectively.

3.5 Discussion

Although each laboratory fulfilled the NACB recommended analytic accuracy standard, there was a low agreement regarding GDM positive status. Possible reasons for this clinical difference are the systematic bias of 0.20 mmol/l revealed by the Bland Altman analysis as well as the difference in the distribution of plasma glucose results, the kurtosis, between methods. The mean plasma glucose concentration measured by the HK method was higher than that of the GOx method at each time point of the OGTT, but the HK method identified a lower prevalence of GDM. The interquartile range of measures from the HK method was relatively lower by 0.15 mmol/l and this suggests that the HK method produced a narrower distribution of measures contained within the distribution of measures from the GOx method. This, in turn, indicates that measures from the GOx method are both lower in the lower range and higher in the higher range relative to the HK method. The HK method is known to be more specific than the GOx method.[117] Substances such as uric acid, ascorbic acid, bilirubin, haemoglobin, tetracycline, and glutathione may cause falsely low glucose results measured by the glucose oxidase method.[117]

Internationally, inconsistent laboratory methods are used to measure plasma glucose concentrations and there is no recognized gold standard reference test.[104] The American Centre for Disease Control has previously suggested isotope dilution gas chromatography-mass spectrometry as the gold standard reference test, but this was not adopted by the NACB.[88,104] Laboratories measure glucose almost exclusively by the enzymatic HK or GOx

methods with few laboratories using the glucose dehydrogenase method.[88] However, the IADPSG recommendations, which were largely based on the clinical outcomes results of the HAPO study, are based on plasma glucose concentrations measured by the GOx method.[64] In South Africa, the HK laboratory method is used in the state-sponsored National Health Laboratory Service as well as the two largest private medical laboratories. It is possible that the HK method may underestimate the prevalence of GDM and fail to identify women at high risk of poor perinatal outcomes as identified in the HAPO study population.

This pragmatic study was conducted in a low resource urban African CHC which had the advantage of access to off-site accredited laboratory services. The availability of these services should not be assumed as it is known that Sub-Saharan Africa has minimal or no access to internationally accredited medical laboratory services.[105] This translational research study, applied in a routine clinical setting, serves to raise awareness of discordance between laboratory methods as a further limitation to the global comparison on GDM prevalence estimates. The analytic accuracy of routine but varying laboratory methods of measuring glucose may be unable to support the clinical accuracy required by the WHO GDM evidence-based diagnostic guidelines. Implementation of universal screening programs for GDM with medical decisions based on poorly reproducible laboratory results may adversely affect both the women affected and the optimal utilization of public health systems resources.

Limitations

The low prevalence of GDM and the small proportion of GDM positive diagnoses common to both methods, limits the precision of the reported estimates. The potential clinical

diagnostic uncertainty between laboratory methods should be explored in larger groups of patients and in more diverse clinical settings.

Acknowledgments.
The Johannesburg District South African Department of Health granted permission to conduct this study at the community health clinic in Soweto. We are grateful to the patients and community health clinic staff for their support of the project. The sustained efforts of our research assistant Ms. Nandi Mtshali were essential to the completion of the study on schedule.

Competing interests

None.

Funding

The work reported herein was made possible through funding by the South African Medical Research Council through its Division of Research Capacity Development under the SAMRC CLINICIAN RESEARCHER (M.D. PHD) SCHOLARSHIP PROGRAMME from funding received from the South African National Treasury. The contents hereof are the sole responsibility of the authors and do not necessarily represent the official views of the SAMRC or the funders. SAN is supported by the Department of Science and Technology and National Research Foundation Centre of Excellence in Human Development at the University of the Witwatersrand, Johannesburg, South Africa. A World Diabetes Foundation (Denmark) grant supported the oral glucose tolerance tests analysed by the research laboratory (GOx method).

3.6 Tables and Figures

Table 3.1. Participant Clinical Characteristics.

Clinical Characteristic	All participants		Composite laboratory (HK and GOx) GDM Positive		p-value
	n	Value n (%) or Mean (SD)	n	n (%) or Mean (SD)	
Age, (Years)	592	27.8 (5.9)	53	31.4 (6.8)	<0.001
Family history of diabetes	588	99 (16.8)	53	13 (25.0)	0.099
Glycosuria (urine dipstick)	592	6 (1.0)	53	4 (7.6)	-
Mid upper arm circumference (cm)	592	29.9 (4.2)	53	31.9 (4.3)	<0.001
Body height (cm)	588	162.9 (7.2)	53	160.7 (6.6)	0.103
Body weight (Kg)	592	70.6 (15.8)	53	76.8 (15.1)	0.003
BMI (Kg/m²)	588	26.9 (5.8)	53	29.5 (5.6)	0.001
Obstetric Characteristics			53		
Gestational age at first visit (weeks)	592	19.1 (5.6)	53	20.8 (5.7)	0.001
Number of pregnancies including current	592				
1		172 (29.2)		7 (13.2)	0.007 (1 vs 2+)
2		197 (33.1)		12 (22.6)	<0.001 (≤2 vs 3+)
3		223 (37.6)		34 (64.2)	0.415 (≤3 vs 4+)
Previous large for gestational age birth	591	43 (7.3)	53	8 (15.1)	0.045
Previous stillbirth	592	32 (5.4)	53	3 (5.7)	1.000
Previous congenital abnormalities	591	0 (0)	53	0 (0)	-
Previous GDM	592	3 (0.5)	53	1 (1.9)	-

Note: Number (n) of participants for each characteristic varies

Figure 3.1. Venn diagrams illustrating the number of GDM positive cases identified at various time points of the OGTT by the GOx (Glucose Oxidase) and HK (Hexokinase) laboratory methods. (WHO 2013 test positivity cut-offs).**

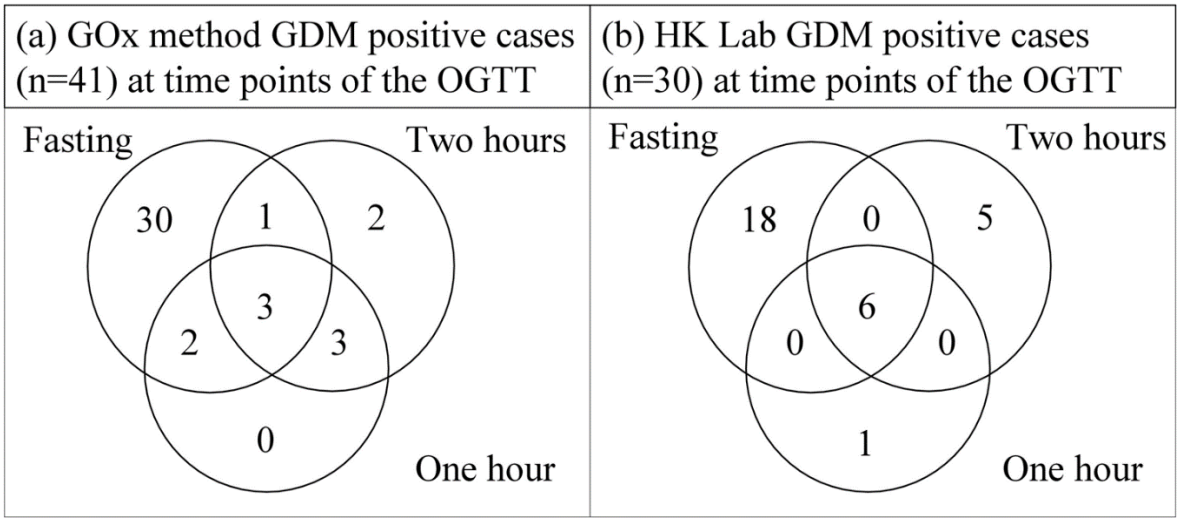
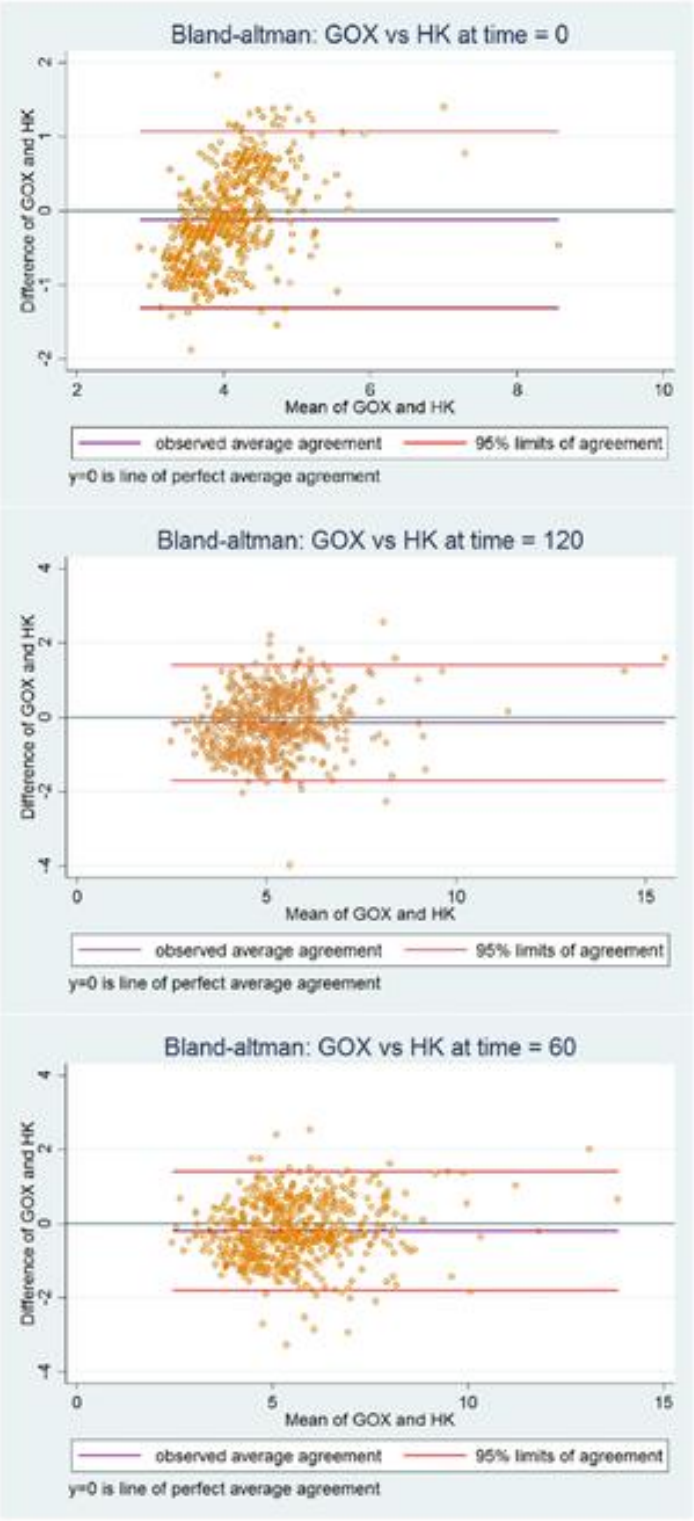


Figure 3.2. Bland Altman plots of the paired plasma glucose results (mmol/l) measured by the GOX (Glucose Oxidase) and HK (Hexokinase) methods at 120 minutes of the 75 g oral glucose tolerance tests for 592 women screened for gestational diabetes.



Chapter 4.

Fasting Plasma Glucose to Screen for GDM

Title:

Fasting plasma glucose and risk factor assessment: comparing sensitivity and specificity in identifying gestational diabetes in urban African women

Authors

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4.1 Abstract

Background

Identifying gestational diabetes mellitus (GDM) affected women allows interventions to reduce associated poor perinatal outcomes. A fasting plasma glucose (FPG) ≥ 5.1 mmol/L is 100% specific for a diagnosis of GDM and the International Association of Diabetes in Pregnancy Study Group acknowledges that an FPG < 4.5 mmol/L has a low probability of GDM.

Objective

The validity of selective screening for GDM based on the presence of risk factors was compared with the universal application of FPG ≥ 4.5 mmol/L, indicating intermediate-high risk for GDM and the need for a diagnostic OGTT, in an urban low resource setting.

Methods

589 consecutive South African women were recruited to a two-hour 75 g OGTT at 24 – 28 weeks' gestation in an urban community health clinic. Venous blood samples were analysed using a glucose oxidase laboratory method. The World Health Organization GDM diagnostic criteria were applied. All participants underwent a risk factor assessment.

Results

The prevalence of overt diabetes mellitus and GDM were 0.5% and 7.0% respectively and 87.8% of GDM positive diagnoses were based on an elevated FPG of ≥ 5.1 mmol/L. Risk factor-based selective screening indicated 204 (34.6%) of women needed an OGTT but 18 of 41 (43.9%) of GDM positive cases would have been missed. Universal screening using the FPG threshold of ≥ 4.5 mmol/L indicated 152 (25.8%) of women needed an OGTT and one of 41 (2.4%) of GDM positive cases were missed. The sensitivity/specificity of the presence

of ≥ one risk factor and for the FPG of ≥ 4.5 mmol/L, were 56%/67% and 98%/80% respectively.

Conclusion

Universal screening using FPG ≥ 4.5 mmol/L had greater sensitivity and specificity and required fewer women undergo a resource-intensive diagnostic OGTT and this strategy may be more efficient and cost-effective than risk-factor based selective screening for GDM in South African women.

Research highlights

The prevalence of overt diabetes and gestational diabetes were 0.5% and 7.0% respectively.

FPG ≥ 5.1 mmol/L identified 87.8% of glucose oxidase laboratory defined GDM.

Selective risk factor screening indicated 34.6% needed an OGTT but missed 43.9% of GDM.

Universal screening using FPG ≥ 4.5 mmol/L indicated 25.8% needed an OGTT but missed 2.4% of GDM.

Keywords

Gestational diabetes mellitus, Screening strategies, Fasting plasma glucose, Primary care

4.2 Introduction

The World Health Organization (WHO) estimates that 16% of pregnancies are affected by gestational diabetes mellitus (GDM) globally.[6] Identifying affected women may allow interventions to improve perinatal outcomes.[47] Both screening strategies and diagnostic thresholds for GDM attract controversy.[100] The International Association of Diabetes in Pregnancy Study Group (IADPSG) advocates universal screening for GDM, however, the WHO recommends that screening strategies should be based on disease burden and the availability of resources.[3,47] Risk factor based selective screening for GDM is currently applied in South Africa.[72] A selective screening strategy may fail to identify a high proportion of women affected by GDM.[71,84,157] In addition, this strategy may be inadequate and difficult to implement and women at risk may not be offered screening, even in well-resourced settings.[79,80]

An alternative to selective or universal application of the OGTT is universal screening using the fasting plasma glucose (FPG). According to the WHO diagnostic criteria, an elevated FPG of ≥ 5.1 mmol/L is by definition 100% specific for a diagnosis of GDM, but the sensitivity of this diagnostic threshold varies between countries and ethnicities.[63] The HAPO study group has suggested that 'in populations in which FPG is diagnostic in more than half of those with GDM, it may be reasonable to perform an accurately measured FPG as an initial step, reserving a full OGTT for those with a non-diagnostic FPG'.[63] The IADPSG acknowledges the low probability of GDM and the low risk of adverse outcomes in the HAPO study cohort associated with an FPG < 4.5 mmol/L.[73] Regarding the need for an OGTT, an FPG ≥ 5.1 mmol/L is 100% specific and an FPG < 4.5 mmol/L indicates low risk. Therefore, only those women with FPG of ≥ 4.5 mmol/L would require an OGTT, as this

indicates an intermediate to high risk for GDM. This dual FPG threshold has been suggested for use in low resource settings, as this reduces the number of women requiring an OGTT, but also avoids missed diagnoses in populations where the sensitivity of the FPG may be suboptimal or unknown.[73,86,158]

We compared the utility of this universally applied dual FPG threshold, namely ≥ 4.5 mmol/L indicates formal screening is required and < 4.5 mmol/L rules out GDM. The sensitivity and specificity were compared with the current standard practice of risk factor based selective screening in identifying urban African women affected by GDM.

4.3 Study methods

Approvals and permissions.

The University of the Witwatersrand Human Research Ethics committee reviewed and approved the study protocols (M150365). The South African Johannesburg District Department of Health granted permission to conduct this study in Soweto, Johannesburg (2015–16/031). All participants gave written informed consent.

Study design.

This cross-sectional, pragmatic, prospective study took place at a single urban community health clinic (CHC) between April 2016 and May 2017. This analysis is part of a research study to assess the feasibility of implementing a universal screening, diagnosis and GDM lifestyle intervention program in an urban low resource setting.[156,159] Consecutive women were recruited at their first antenatal clinic visit. Women under 28 weeks' gestation were eligible for inclusion and we excluded those below the age of 18 years and those known to have type 1 or type 2 diabetes mellitus. Gestational age was determined by the clinic nurse as

part of usual care. There were no ultrasound facilities on site. Study procedures were conducted within the usual functioning of the antenatal service of the CHC.

Participants.

Data gathered from all participants included risk factors for GDM as defined by the South African Department of Health (SADH).[72] These include maternal obesity (body mass index ≥ 35 kg/m^2, which is the WHO obesity class ≥ II), maternal age ≥ 40 years, previous history of GDM, first degree relative with diabetes mellitus, previous unexplained intrauterine fetal death, previous macrosomic baby or complications in the current pregnancy which include polyhydramnios, fetus large for gestational age or the presence of repeated glycosuria.[72] All participants in this study were of indigenous African ethnicity, in keeping with this clinics patient profile, and so the risk factor of being of South Asian descent did not apply. Additional data collected included gestation at the first antenatal visit, parity, cigarette smoking, history of chronic hypertension, and blood pressure and mid-upper arm circumference measurements.[83,160] Participants were frequently unable to recall exact infant birth weights from previous births and so the terms 'small, average or large' were used instead and this was standard practice at this clinic.

Oral glucose tolerance test.

All participants underwent a two-hour 75 g glucose OGTT in the morning after an overnight fast at 24–28 weeks' gestation. Venous blood samples were collected in tubes containing the glycolytic inhibitor sodium fluoride (BD 454297) and samples were kept on ice ex-vivo. The use of sodium fluoride tubes is included in the WHO recommended OGTT procedure.[13] Typically, there are no on-site laboratories at CHCs in South Africa. All venous blood samples were delivered to the off-site laboratory, which was 14 km distant, within an hour of completion of the OGTTs. This research laboratory used the glucose oxidase method

(Randox, Daytona Plus, USA) to determine plasma glucose concentrations. On request, the laboratory provided us with their quality control results. At mean glucose concentrations of 6.36 mmol/L and 15.80 mmol/L, the analytic coefficients of variation (CV) were 1.85% and 1.67% with a bias of 0.35% and 0.31% respectively. These quality control results are within the recommendation of the American National Academy of Clinical Biochemistry (NACB) for laboratory measures of plasma glucose (a CV of ≤ 2.9% and a bias of ≤ 2.2%).[88] Trained research staff operated independently from the CHC staff.

Clinical diagnostic criteria.

The WHO 2013 diagnostic criteria, which was endorsed by the Society of Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) in 2017, were used to define OGTT cut-offs for a positive GDM diagnosis.[47,59] Only one plasma glucose abnormality of the two-hour OGTT is necessary for a positive diagnosis of GDM. GDM is defined as a plasma glucose concentration of 5.1–6.9 mmol/L at fasting, ≥ 10.0 mmol/L at one-hour or 8.5–10.9 mmol/L at two-hours of the OGTT. Diagnostic thresholds for overt diabetes in pregnancy, which indicates probable preconception diabetes, are a plasma glucose concentration of ≥ 7.0 mmol/L or ≥ 11.0 mmol/L at fasting and 120 minutes of the OGTT respectively. Participants diagnosed with overt diabetes or GDM were referred for clinical intervention.

Analysis.

Categorical variables were described as frequencies and proportions (%) and continuous variables as means and standard deviations (SD). The Chi-squared test was used to determine associations between categorical variables, especially between known risk factors and a positive GDM diagnosis. Fisher's exact test was used in the cases where expected frequencies were lower than five. In this analysis, FPG thresholds were retrospectively used to indicate

the need for an OGTT and the categories were: low risk (< 4.5 mmol/L) meaning no need for an OGTT and intermediate to high risk (≥ 4.5 mmol/L) indicating the need for a formal diagnostic OGTT to determine the presence and extent of dysglycaemia. The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratios (PLR) and negative likelihood ratios (NLR) for a positive GDM diagnosis were calculated for the FPG ≥ 4.5 mmol/L, FPG ≥ 5.1 mmol/L as well as for the presence of ≥ one risk factors for GDM (SADH). We also evaluated the utility of a modified SADH recommended risk score to include a BMI ≥ 30 kg/m^2 (Obesity class I), as a comparison to the standard BMI ≥ 35 kg/m^2 (Obesity ≥ class II).[161][21] A p value of < 0.05 was assumed to be statistically significant and 95% confidence intervals (95% CIs) are presented where appropriate. Statistical analyses were performed on STATA software version 15. (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, USA). The SAS (v9.4) software (SAS Institute Inc., Cary, NC, USA) macro NLEstimate was used to compute model-based 95% CIs for the likelihood ratios.

4.4 Results

Participants.

Of the 1270 women who attended the antenatal clinic over the twelve-month recruitment period of the study, 969 (76.3%) were willing and eligible to participate. The number of women recruited and the reasons for the attrition of participant numbers before data analysis are presented in Figure 1. Overt diabetes mellitus was identified in three (0.5%) and GDM was present in 41 (7.0%) of 589 participants (95% CI: 4.9–9.2%). The mean BMI of 26.9 kg/m^2 (SD 5.8 kg/m^2) indicates that, overall, participants in this study were overweight. A BMI of ≥ 35 and ≥ 40 kg/m^2 were present in 57 (9.7%) and 16 (2.7%) of all participants

respectively. Six participants were glycosuria positive on one occasion with no opportunity for repeat glycosuria testing prior to the elective OGTT. Participant characteristics are presented in Table 1.

Characteristics of GDM positive women.

GDM positive women were significantly more overweight with a 6.1 kg (95% CI: 1.1–11.1 kg) heavier body weight and a mid-upper arm circumference that was 2.1 cm (95% CI: 0.7 – 3.4 cm) greater than their non-GDM counterparts. GDM positive participants were of older maternal age ($p<0.001$), presented later in their pregnancy for their first antenatal visit ($p=0.001$) and had higher diastolic blood pressure ($p=0.004$). Five (12.2%) and 27 (63.4%) of 41 GDM positive participants were pregnant for the first or ≥ third time respectively. A higher parity was associated with an increased risk of GDM where for instance the group who was pregnant for at least the third time had a 30.1% higher risk of GDM ($p < 0.001$). Unexpectedly, in this study population, a positive family history of diabetes mellitus was not associated with a positive GDM diagnosis ($p=0.520$). (Table 1)

Assessment of risk factors.

Based on the current SADH guidelines (includes a BMI ≥ 35 kg/ m^2) 204 (34.6%) of 589 participants had ≥ one risk factor for GDM and would have required an elective OGTT, however, 18 (43.9%) of 41 GDM positive cases would have been missed. At a BMI ≥ 30 kg/m^2, the number of participants requiring the OGTT would have been 262 (44.5%) of 589 participants and the number of missed GDM positive cases would have been reduced to 12 (29.3%). (Table 2) A selective screening strategy based on the presence of ≥ two SADH risk factors (including a BMI ≥35 kg/m^2) had a sensitivity, specificity, PPV, NPV, PLR and NLR

(95% CIs) of 23% (11–38%), 88% (86–91%), 13% (6–22%), 94% (92–96%), 1.95 (1.05–3.63) and 0.88 (0.74–1.04) respectively. The use of ≥ two risk factors (including a BMI ≥ 35 kg/m^2) would have resulted in 33 (80.5%) of 41 GDM positive cases being missed.

Assessment of laboratory results.

The mean (95%CI) plasma glucose concentrations at fasting, 60 and 120 minutes of the OGTT were 4.01 mmol/L (3.95–4.07 mmol/L), 5.42 mmol/L (5.30–5.54 mmol/L) and 5.12 mmol/L (5.01–5.23 mmol/L) respectively. The number of abnormalities per time point of the OGTT is presented in a Venn diagram (Figure 2). The use of an FPG ≥ 5.1 mmol/L as a universal screening strategy for GDM would have required 36 (6.1%) of 589 participants undergo an OGTT, however, five (12.2%) of the 41 GDM positive participants would have been missed. Based on the dual threshold screening strategy, if those participants with an FPG of < 4.5 mmol/L were assumed to be at low risk and so were not formally screened, 152 (25.8%) of 589 participants would have required an OGTT and 40 (97.6%) of the 41 GDM positive diagnosis would have been identified. (Table 2)

4.5 Discussion

The prevalence of GDM as determined by the glucose oxidase laboratory method in a routine clinical setting was 7.0% in this population of urban African women attending a single CHC. Our results have similarities and differences to recent South African reports of GDM prevalence. A study by Macauley, et al. reported a 9.1% GDM prevalence in a tertiary hospital setting, using a research laboratory (glucose oxidase method) and participants had a higher risk profile for GDM.[35] A study by Adam & Rheeder possibly overestimated the GDM prevalence at 25.8% and one reason for this is the laboratory bias of 3.65%, which is not

within the ≤ 2.2% recommended by the NACB, would adversely affect the quality of plasma glucose measures.[88,145]

Importantly, 87.8% of GDM positive diagnoses in this study population were based on an elevated FPG. This confirms the findings of Macauley, et al and Adam & Rheeder that the majority of GDM diagnoses in South African women screened were based on an elevated FPG. The use of the FPG alone to screen for GDM is attractive as this is less expensive, avoids the need for multiple punctures, reduces laboratory workload and avoids exposing pregnant women to the sometimes emesis inducing oral glucose load.[76,98] There is outcomes-based evidence that an elevated FPG alone is comparable to a complete OGTT in predicting large for gestational age infants, as well as indicating the need for insulin treatment of GDM.[91,150,162] Although an FPG ≥ 5.1 mmol/L is 100% specific for a diagnosis of GDM, the sensitivity of this diagnostic threshold varies between countries and ethnicities, in both low and high-risk populations.[48,63,86,163,164] When retrospectively applied to the HAPO study cohort, the proportion of GDM positive diagnoses based on an elevated FPG was 55% (24–74%) and this varied between and within countries.[63] The underlying mechanism responsible for this variability is unknown. Sub-Saharan Africa was not included in the HAPO study. The prevalence of an elevated FPG in a multi-ethnic South Africa, affected by historical undernutrition and a current high burden of obesity, is unknown and the use of a single value of the OGTT may miss GDM affected women. The low-cost algorithm of a dual threshold FPG, with ≥ 5.1 mmol/L (specificity 100%) used to rule in GDM and < 4.5 mmol/L to rule out a GDM is associated with a reduction in the need for a complete OGTT when applied to the HAPO, United Arab Emirates, and Brazilian cohorts.[73,86] In order to improve accessibility to screening, it may be possible to screen women for GDM with point of care testing, thus reducing the need for more expensive and sometimes inaccessible laboratory services. The

use of glucometers to screen for and diagnose DM and GDM is endorsed by the WHO and the Federation of International Gynaecology and Obstetrics.[4,6] The reliable use of selected plasma calibrated glucometers to measure the FPG, in a universal GDM screening program in a low resource South African setting, was recently reported.[156]

Maternal obesity was strongly associated with a GDM positive diagnosis in this study. South Africa has a high prevalence of obesity, which is associated with increased risk of insulin resistance and dysglycaemia.[16,20] Epidemiologically, the prevalence of GDM increases by 0.9% per one point increase in BMI.[33] In this study, the use of a BMI ≥30 kg/m^2 was associated with an increased sensitivity compared to a BMI ≥35 kg/m^2.[165] Based on the current screening strategy of risk factor based selective screening, a high proportion of South African women may require an OGTT, posing a potentially overwhelming burden to existing health care and laboratory services. The low sensitivity and specificity of a risk factor assessment to identify GDM affected South African women in this study confirms the findings of Adam and Rheeder.[3,36,113] This is aligned with international findings that almost half of GDM affected women will be missed by selective screening based on conventional risk factors. In 2017, the SEMDSA adopted the WHO 2013 diagnostic thresholds for GDM, with a suggestion that a universal screening strategy could be implemented only in well-resourced settings within South Africa.[59] A previous report suggests that rural dwelling South African women may be at high risk for diabetes in pregnancy.[166] Ideally, equal access to GDM screening should be available to all pregnant women, whether in a private or state health care setting, whether urban or rural dwelling and regardless of ethnicity.

Prior to the WHO revision of GDM diagnostic thresholds in 2013, there was evidence that plasma glucose concentration abnormalities at all time points of the OGTT could predict the need for insulin therapy.[91] There are no prediction models for which GDM affected women

are likely to need oral hypoglycaemic agents or insulin treatment to restore euglycaemia during pregnancy. In addition, increases in fasting and the two-hour plasma glucose concentrations are associated with an increased risk of developing overt diabetes in later years.[15] For this reason, in the event that a GDM diagnosis is made based on an elevated FPG, it may be necessary to perform a complete OGTT

Strengths and limitations.

This translational research project was conducted within the usual functioning of a CHC, which equates to routine care rather than a research clinical setting. Our participants were urban indigenous African women attending the antenatal service of a single urban CHC and so our results may not be generalizable beyond this population profile. The sample size and the low GDM prevalence of 7.0% (95% CI 4.9–9.2%) were insufficient to provide robust estimates of the sensitivity of the FPG screening threshold of ≥4.5 mmol/L. Further studies are needed in a more diverse patient population and clinical settings to confirm these results.

4.6 Conclusion

A universally applied FPG threshold of ≥ 4.5 mmol/L, as an indicator of intermediate-high risk for GDM, has improved sensitivity and reduces the number of women needing to undergo the unpleasant, poorly reproducible and resource intensive OGTT compared to the current practice of risk factor based selective screening.

Acknowledgments.

The Johannesburg District South African Department of Health granted permission to conduct this study at the community health clinic in Soweto. We are grateful to the participants and the community health clinic staff for their support of the project. The sustained efforts of our research assistant Ms. Nandi Mtshali were essential to the completion of the study on schedule.

Contributors.

LMD, EJB, SAN: Methodology. LMD: Data collection and had full access to all data during the study. LMD, EJB, CJVR, SAN: data analysis. LMD: wrote the manuscript. EJB, CJVR, SAN: Reviewed and edited the manuscript.

Competing interests.

None.

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4.7 Tables

Table 4.1. Participant characteristics, with comparison of GDM positive and with GDM negative women.

Clinical Characteristic	All Participants		GDM Positive n=41		GDM Negative n=548		p-value
	n	n (%) or Mean (SD)	n	n (%) or Mean (SD)	n	n (%) or Mean (SD)	
Age, (Years)	589	27.8 (5.9)	41	31.1 (6.9)	548	27.5 (5.7)	<0.001t
History of chronic hypertension*	588	19 (3.2%)	41	1 (2.5)	547	18 (3.3)	1.000 F
Active smoker (cigarettes)	589	21 (3.6%)	41	4 (10.0%)	548	17 (3.1%)	0.051 F
Family history of diabetes *	585	99 (16.9%)	40	8 (20.0%)	545	91 (16.6%)	0.591χ
Glycosuria (urine dipstick)	589	6 (1.0%)	41	2 (4.9%)	548	4 (0.7%)	-
Mid upper arm circumference (cm)	589	29.9 (4.4)	41	31.8 (4.3)	548	29.7 (4.4)	0.004 t
Body height (cm) *	588	162.1 (6.6)	40	160.7 |(6.2)	548	162.2 (6.6)	0.152 t
Body weight (kg)	589	70.7 (15.7)	41	76.4 (15.3)	548	70.3 (15.7)	0.017 t
BMI (kg/m²) *	588	26.9 (5.8)	40	29.2 (5.3)	548	26.7 (5.8)	0.009 t
Systolic blood pressure (mmHg) *	588	122.3 (14.9)	41	122.8 (19.9)	547	122.2 (14.5)	0.200 U
Diastolic blood pressure (mmHg) *	588	72.6 (11.0)	41	77.4 (9.6)	547	72.2 (11.0)	0.004 t
Gestational age at first visit (weeks)	589	19.1 (5.6)	41	22.0 (4.2)	548	18.9 (5.6)	<0.001t
Number of pregnancies including current							
≥2	589	417 (70.8%)	41	35 (85.4 %)	548	383 (69.7%)	0,033 χ
≥3	589	223 (37.9%)	41	27 (65.9%)	548	196 (35.8%)	<0.001χ
>3	589	79 (13.4%)	41	9 (22.0%)	548	70 (12.8%)	0,096χ
Previous large for gestational age birth *	588	43 (7.3%)	41	6 (14.6%)	547	37 (6.8%)	0.108 F
Previous stillbirth	589	32 (5.4%)	41	3 (7.5%)	548	29 (5.3%)	0.481 F
Previous congenital abnormalities	588	0 (0)	41	0 (0)	548	0	-
Previous GDM	589	3 (0.5%)	41	1 (2.4%)	548	2 (0.4%)	-

* Number of participants for each characteristic varies slightly due to missing values.
Abbreviations: GDM, gestational diabetes mellitus; t, t-test; F, Fisher's exact test; χ, Chi-square test; U, Mann-Whitney U test.

Table 4.2. Validity measures of FPG and Risk Factors as a GDM screening Strategy

	Universal screening based on dual threshold FPG verses universal OGTT		Selective screening strategy based on risk factors verses universal OGTT	
	FPG ≥5.1 mmol/L	FPG ≥4.5 mmol/L	≥ 1Risk factor(s) including BMI ≥30 kg/m^2	≥ 1Risk factor(s) including BMI ≥35 kg/m^2
Number of participants	589	589	589	589
True Positive (n)	36	40	29	23
False Positive (n)	0	112	233	181
True Negative (n)	548	436	315	367
False Negative (n)	5	1	12	18
Sensitivity (%)	88 (74–96)	98 (87–100)	71 (54 - 84)	56 (40 - 72)
Specificity (%)	100	80 (76–83)	57 (53 - 61)	67 (63 - 71)
Positive Predictive Value (%)	100	26 (20–34)	11 (8 - 16)	11 (7 - 16)
Negative Predictive Value (%)	99 (98–100)	99 (99–100)	96 (94 - 98)	95 (93 - 97)
Positive Likelihood Ratio	Undefined	4.77 (3.95–5.60)	1.66 (1.30 - 2.03)	1.70 (1.19 - 2.20)
Negative Likelihood Ratio	0.12*	0.03 (-0.03–0.09)	0.51 (0.26 - 0.75)	0.66 (0.43 - 0.89)

Abbreviations. OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; BMI, body mass index; GDM, gestational diabetes mellitus.

*Model did not converge to yield 95% CIs.

Chapter 5.

Women's experience of GDM

Title:

Women's accounts of the gestational diabetes experience – a South African perspective.

Authors

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5.1 Abstract

Background

Consideration of the perspectives of African women affected by gestational diabetes mellitus (GDM) may facilitate the development of culturally sensitive interventions to address this public health concern.

Methods

The experiences of urban African women (n=10) previously affected by GDM were documented through a series of focus group discussions. The Diabetes Conversation Map education instrument was used to facilitate discussions. Sessions were audio-recorded, transcribed and thematically analyzed.

Results

Participants experienced shock and fear on diagnosis of GDM, but family support and sharing their experiences with their peers provided relief from anxiety. They were aware of the inconsistent implementation of GDM diagnostic procedures at tertiary hospitals and community health clinics, and this exacerbated their confusion. Despite their initial difficulty adjusting to a diet perceived as unpalatable, adopting a healthier lifestyle was considered a positive consequence of a GDM diagnosis. Healthy lifestyle changes were partially retained postpartum and were reported to have a positive effect on other family members. The participants had low awareness of their long-term risk of diabetes mellitus and the need for

regular ongoing screening. Unexpectedly, participants thought that being positive for human immunodeficiency virus (HIV) was less stressful than living with diabetes.

Interpretation

Participants viewed being HIV positive as preferable to having GDM, and this may reflect their distress caused by inadequate pre-test counselling, inconsistent health information, inconsistent screening practices and suboptimal support from health care professionals.

Research highlights

Adopting a healthy lifestyle was considered as a positive consequence of diagnosis.
Lifestyle changes were partially maintained and positively affected the family.
Participants valued peer and family support, which provided relief from anxiety.
Inconsistent GDM diagnostic procedures caused confusion.

Keywords

Gestational diabetes, Qualitative study, Diabetes Conversation Maps

5.2 Introduction

The WHO estimates that, globally, 16% of pregnancies are affected by gestational diabetes mellitus (GDM).[6] Women diagnosed as having GDM are at high risk of poor perinatal outcomes, and both mother and child are at high risk of developing type 2 diabetes in later years.[3,14] Lifestyle intervention alone is an effective treatment for GDM in as many as 90% of those affected.[125] These are complex interventions that include dietary advice, exercise, diabetes education and self-monitoring of blood glucose. Diabetes education and sustained healthy lifestyle choices are also important components of long-term diabetes prevention programs.[167–170] However, intervention strategies proven effective in developed countries are not necessarily directly transferable to low resource settings.[171] Culturally appropriate dietary advice and diabetes education are associated with improved blood glucose control which is sustained over time.[137,172,173] Locally available skills, local resources and pre-existing circumstances and attitudes may also affect GDM interventions and implementation strategies.[174,175] Locally acceptable interventions that can be applied in low resource settings are urgently needed to support women affected by GDM.[6]

Consideration of the experiences and expectations of local women may strengthen the development or adaptation of existing GDM interventions, and help appropriately frame implementation strategies.[175–178] It is known that there are cultural differences in women's experience of GDM.[179] Shock, anxiety, uncertainty, feelings of abandonment and a need for support in adapting to GDM are reported.[129,179,180] African women are reported to have increased pregnancy associated anxiety, with greater difficulty adjusting to GDM treatment delivered within health care services of developed countries.[181,182] To our knowledge, this is the first qualitative research report of the GDM experiences of indigenous African women in

an urban African setting. The purpose of our study was to identify the personal experiences, challenges, coping strategies and health decisions made by urban indigenous South African women affected by GDM.

5.3 Methods

Setting and study participants

We conducted this study at the CHBAH (Chris Hani Baragwanath Academic Hospital) in Soweto, Johannesburg, from December 2015 to February 2016. Participants were recruited from the S1000 cohort (Soweto First 1000 Days Cohort). This cohort of women is followed up intensively during pregnancy, at birth and after pregnancy. All are screened for GDM at 26-29 weeks' gestation using a 75 g oral glucose tolerance test. Women with pre-existing type 1 or type 2 diabetes mellitus and those below the age of 18 years are excluded from this cohort. Once diagnosed as having GDM, women are referred to the CHBAH Diabetes in Pregnancy Clinic for treatment. A purposive sample of S1000 participants known to have had GDM in the previous 24 months was selected using telephonic recruitment (n=15). Approval to conduct this study was granted by the University of the Witwatersrand Human Research Ethics Committee (M150365). Participants provided written informed consent.

Study design and protocol

This study is part of a larger study concerned with the development of a GDM screening and lifestyle intervention suitable for use in a low resource setting.[156,159] The International Diabetes Federation approved educational instrument, the 'Healthy eating and keeping

active' DCM (Diabetes Conversation Map), was used both as a conceptual framework and to facilitate semi-structured FGDs (Focus Group Discussions). The DCM is a verbal, visual and a highly interactive program designed for delivery to groups of patients. It promotes the understanding of diabetes and how to manage it, explores the emotional aspects of diabetes and promotes self-management of diabetes over a lifetime. It is equally effective as other programs with a more didactic educational style.[142] The first author, who was trained in the use of the DCM instrument by a certified master facilitator, served as the FGD moderator. Each participant attended a single FGD and the purpose of the FGD, as well as the role of the moderator, was explained at the outset. Discussions were conducted in English, but women were encouraged to speak in their own language. Two research assistants acted as interpreters when language was a barrier to participation. Each FGD lasted 60-75 minutes. A structured script was developed to establish consistency in the data collection process.

Data collection and analysis

Clinical data were collected from participants' records and these included age, parity, body mass index, family history of diabetes and their past obstetric history. FGDs were audio recorded, transcribed and analyzed manually on a thematic basis for commonalities and differences between participants' responses. Qualitative software was not used in this analysis. Themes and subthemes were derived from the data and unexpected themes were identified and noted. The context, frequency and intensity of the participants' comments guided the selection of quotations that were reflective of the group experience. This thematic analysis was validated by a second researcher. After preliminary analysis of the data, participants were invited to a single, formal member checking session. Results were presented and the participants were invited to make further comments. Their level of

agreement with the preliminary findings was noted but no additional information was provided.

5.4 Results

Participants

Of the 15 GDM women who were invited, 10 agreed to participate. To accommodate the participants, multiple FGDs (n=3 per FGD) took place and the number of participants per FGD varied between two and six. Several weeks later, eight of the ten participants attended the member checking session. All participants were urban black African women, in keeping with this hospital's patient profile. Their mean age was 35 years, body-mass index was 26.8 Kg/m^2 and half of them had a positive family history of diabetes mellitus. Adverse previous pregnancy outcomes were frequent. Five participants had at least one previous miscarriage and one had a stillbirth before her most recent pregnancy.

Qualitative data presented as themes and sub–themes

Theme 1: Participants' responses to their diagnosis of GDM

Participants were aware of inconsistencies in applying GDM diagnostic procedures and criteria at the research unit, the CHBAH antenatal clinic and the CHC (Community Health Clinic). Some witnessed disagreement between doctors on which diagnostic criteria to apply and this left them unconvinced that they had GDM. Participants expressed feelings of shock and fear because their diagnosis was unexpected. They associated their previous miscarriage

or stillbirth with the possibility of undiagnosed GDM. They were reminded of and felt responsible for their previous pregnancy losses because they were "not eating right". This exacerbated their anxiety, which often persisted throughout their pregnancy.

At the member checking session, all participants agreed that there should be more awareness of GDM in the community, with increased availability of screening. However, some women were ambivalent on awareness and thought they would have preferred not to know their diagnosis.

Table 5.1. Quotes of participant's responses to their diagnosis of GDM.

Subtheme: confusion, disbelief Group 2: "The research unit said I am diabetic, but doctors at Bara (CHBAH) also said I am not diabetic, but the professor said I am diabetic. So, I don't know which was, but they gave me some tablets for diabetes." "This doctor said, 'No, this is for the fourth time now you have got positive results for glucose in your urine test, you must do this OGTT test'. Already I had tested at the research unit and it was positive. When I was supposed to start my diabetic treatment that's when I went to theatre for an emergency Caesar because the baby was in distress"
Subtheme: shock, fear, anxiety Group 1: "The worse fear was losing the baby because I didn't know what made me lose the first baby. They told me that diabetes could make me lose this baby" Group 2: "It was stressful because father has diabetes and didn't want to inject myself like my father and have diabetes my whole life." "If I was attending a local clinic maybe I could have died, I might have lost the baby because I wouldn't have known I had diabetes." Group 3:

"My mother has diabetes, so I knew what to expect"
Subtheme: self–blame, guilt Group 2: "I maybe made mistakes with the baby I lost. Maybe I didn't eat right. Maybe I didn't try my best. Maybe I got gestational diabetes that time. I don't know."

Theme 2. Participants' experiences of the health care service

Most participants were admitted to the obstetric ward for initiation of treatment on diagnosis of GDM. Participants were highly vocal and emotive in expressing dislike of their in-patient experience. Suboptimal communication between the research unit and the CHBAH staff on the purpose of the GDM research project caused frustration. Patients bore the brunt of the nurses' frustration, who complained that women were being admitted for treatment, despite the shortage of hospital beds.

Although participants were aware of resource shortages and the inequity in distribution of health care services between the CHC and hospital, they would have preferred attending antenatal services at the CHC because this was closer to their homes and so incurred less transport costs and was less crowded. At the member checking session, all participants agreed that the CHC should improve the quality of regular check-ups. Most were of the opinion the diagnosis of GDM could be missed at the CHC. Also, the inconsistency of health information provided in their GDM affected pregnancies left them confused and insecure.

Table 5.2. Quotes of participant's experience of the health care service

Subtheme: Experience of hospital admission Group 2:

"When we were admitted, our motivation was that we didn't want to stay longer so we drank a lot of water and ate their food and then we would be discharged."
Subtheme: Interactions with health care professionals Group 1: "The nurses shouted at me because they believed that I am not diabetic, and they were also complaining about this study…"
Subtheme: Awareness of resource shortages Group 2: "It is full, it is full, the patients are sitting on benches the whole day, taking medication from the bench, even those who have blood pressure, but if you are diabetic, they make amends for you to get a bed quickly." Group 3: "they sent me home to test myself because the hospital was full"
Subtheme: Inconsistent health information Group 1: "I did not receive education while admitted to hospital and did not receive special treatment" Group 2: "I was told that my baby would be big, but my baby was small, and the nurses shouted at me in the labour ward asking me why was I taking medicine for diabetes because now my baby was too small and premature."

Theme 3. Lifestyle adjustments in pregnancy

Adjusting to the prescribed diet was the most challenging aspect of treatment. Some participants felt that the diet was unpalatable. Some tolerated a temporary loss of dietary autonomy because changes were presumed necessary only for the duration of their pregnancy. Those who were given the opportunity to consult a dietician felt better able to cope. Overall, changing to a healthy eating plan was considered a positive consequence of their GDM diagnosis. They learned that exercise helps control blood sugar and they

incorporated exercise into their daily activities. Participants who had a family member living with diabetes felt better able to cope. The wellbeing of their baby strongly motivated all participants to adopt and maintain healthy choices during pregnancy.

At the member checking session, participants agreed that eating unhealthy food 'makes you tired'. Although small meals and the inclusion of fruit and vegetables in their diet would be ideal during pregnancy, these choices were generally considered to be more expensive.

Table 5.3. Quotes of participant's lifestyle adjustments in pregnancy

Subtheme: Diet was unpalatable Group 1: "The food you have to eat is like eating cardboard, a piece of paper that is only placed in water. There is no taste."
Subtheme: Loss of autonomy Group 1: "It was a hardship for me having to eat that food because I was forced." Group 3: "I had to adjust because there was nothing I could do"
Subtheme: Dietary adjustment difficulties Group 1: "I attended sessions with the dietician and went home relieved and empowered that you know what, I can actually manage this." Group 2: "I am eating spinach and trying by all means. I have a little garden now where I planted a bit of greens." "First I was so stubborn I didn't want to change"
Subtheme: What is healthy eating Group 1 "… lots of vegetables, low fat milk, low fat cooking techniques like boiling and roasting, reducing spices, no sauces, diluting fruit juice" Group 2

"The diabetic diet is not much different from my usual diet in that I eat vegetables and fruits although I never stopped eating fatty foods" Group 3: "When I am finished eating unhealthy food, I feel tired"
Subtheme: Healthy eating is expensive Group 3: "Diabetes food is more expensive as you can no longer eat pap (maize meal) which makes diabetes complicated especially with food prices going up and, if you don't eat in a proper manner you become sick."
Subtheme: Benefits of exercise Group 1: "I would recommend exercise to another pregnant woman with gestational diabetes although I did not exercise myself Group 2: "When I go to work, I walk to the station. Sometimes when I am late, I have to run because the train is there and if you are not at the station it will leave. So, for me I don't have to go to gym."

Theme 4. Women's need for support during pregnancy

Most said they had additional family support after being diagnosed, which made it easier to cope with the challenges of treatment. A minority said they had to cope with everything on their own. Participants acknowledged they had benefitted from informal peer support, both when they were admitted to hospital and during their clinic visits. In the waiting area of the clinic they became accustomed to each other and had started sharing "tips". Sharing experiences with others who were "in the same boat" helped ease their anxiety. "Talking heals" was a common sentiment.

It was unanimous at the member checking session that while support from family, friends and peers was important, ultimately, the individual was responsible for her own health and the changes she had made.

Table 5.4. Quotes of participant's need for support during pregnancy

Subtheme: Support from partner and family Group 1: "My mother in law was diabetic so she helped me to eat correctly which made it easier." Group 2: "When your partner or family does not want the same as you it makes following the diet more difficult especially when they eat takeaways in front of you." Group 3: "My brother who has diabetes said it is not a life sentence. Then he told me that he will help me, and I was okay."
Subtheme: Support from peers Group 1: "I believe that talking heals. Sitting with a group of women who are going through the same experiences eases your anxiety levels. Knowing that you are not alone helps." Group 2: "Sharing experiences and things that work for you with others and hearing their ideas and experiences helps."
Subtheme: Self-reliance Group 2: "I think it has to come out from you, it is a decision that you have to make to take care of yourself."

Theme 5. Women's understanding of diabetes

Participants who had a family member with diabetes had a better understanding of the disease, the different types and its underlying causes. A minority were fatalistic regarding

their future risk of developing diabetes mellitus and although they were aware of the importance of healthy eating, they did not sustain the changes postpartum because the diet was not aligned with their personal preferences. Not all participants had undergone an oral glucose tolerance test at six weeks post-partum, even though this is clinically indicated. One of the participants did have the test but had not been informed of the results six months later. Those who were aware of their future risk of developing diabetes mellitus were unsure where they should go for continued care.

Table 5.5 Quotes of participant's understanding of diabetes

Subtheme: Diabetes knowledge Group 1: "I think that is the reason why you have it is because your family members have it. Not everybody from the family will get it, like from my family it is only me and we are four right, it chose me." Group 2: "I was pregnant, and I was telling people I am diabetic they said, 'Maybe they made a mistake, how can you be diabetic when you are so thin?' because they think diabetes is only for big people."
Subtheme: Sustainability of healthy choices Group 1: "So, I was eating healthy and I said I think I am doing well so why change and go back. It is like I have been eating like this forever." "My husband liked eating pap (maize meal) and meat, I was only doing vegetables for myself, but I managed to change him as well." Group 2: "After the pregnancy I am back to my usual diet but less sugar intake." Group 3: "I will start eating the diet again once I have diabetes. I don't want to lie. I can't live with those kinds of foods every day of my life forever."

Subtheme: Awareness of diabetes risk Group 1: "I thought about my mother … I used to see her taking these pills every day and stuff and I said I don't want to go to that stage." Group 3: "… having family members who have passed away from diabetes makes me realise I want to be around for the people I love."

Theme 6. Unexpected theme

In two of the three FGD, participants said that it would be less stressful to be infected with HIV than to have diabetes.

At the member checking session, all but one of the participants agreed that living with HIV would be less stressful than living with diabetes.

Table 5.6. Quotes of unexpected themes

Subtheme: Being HIV positive is preferable to having diabetes Group 1: "I would rather be HIV positive than being diabetic, the stress." Group 2: "Having HIV is better than having diabetes because diabetes is stressful"

5.5 Discussion

To the authors knowledge, this is the first qualitative study of indigenous African women's experience of GDM conducted in a LMIC setting. There are commonalities and differences to the experiences of their international counterparts.

Health care professionals' interaction with participants.

Patient confusion and disbelief regarding their GDM status was exacerbated by witnessing the professional discourse on the local implications to the change in GDM diagnostic criteria on clinical ward rounds. They were also aware of inconsistent screening practices, namely urine testing or the OGTT. Our participants' GDM affected pregnancies occurred soon after the WHO (World Health Organization) revised the GDM diagnostic thresholds in 2013.[47] The current South African National Department of Health's policy on GDM still reflects the WHO 1999 diagnostic criteria. External shapers such as Government policy and the training and experience of health care professionals may affect the doctor-patient relationship. Doctors' beliefs about the seriousness of GDM affects women's beliefs and health related behaviour, as well as their understanding of the long term consequences for the mother and her offspring.[182,183] Uniformity in screening practices with access to screening at all health care centres may improve the safety of pregnancy.

Although it would have been more convenient to attend the antenatal service of the local community health clinic, participants were not confident that their GDM would have been identified there. In South Africa, diagnostic testing and treatment for GDM is carried out only at hospitals and this is not uncommon in low-middle income countries.[70,72] In addition, GDM is still not recognized as a distinct clinical entity and so treatment is not consistently offered

in a non-research setting. Treatment of overt diabetes in pregnancy varies between hospitals. For instance, at the CHBAH diabetes in pregnancy clinic, patients are managed by both endocrinologists and obstetricians at each visit. At the Rahima Moosa Mother and Child Academic Hospital which is also a teaching hospital in Johannesburg associated with the University of the Witwatersrand, endocrinologists are not involved in the care of these patients. Availability of GDM screening and treatment in low resource settings and less affluent communities is essential to reduce the morbidity associated with these high-risk pregnancies.

GDM from the perspective of women affected

Standard care at CHBAH includes the admission of all newly diagnosed GDM patients. This is not uncommon in LMIC.[70] This serves to rapidly restore euglycaemia by optimizing medication doses and this includes the use of insulin. Participants were strongly against hospital admission, exacerbated by abrasive nursing staff, shortage of beds and unpalatable hospital food. In addition to their awareness of the shortage of health care resources, they were uncertain of the benefits of this experience. It is possible that admission for the intermediate hyperglycaemia of GDM could be avoided because as many as 90% of those affected do not require medication.[125] Based on an increase in disease prevalence and lower diagnostic thresholds, an increasing number of women will be diagnosed with GDM with the likelihood that existing services will be overwhelmed. The need for routine hospital admission should be re-evaluated when local guidelines for GDM diagnosis and management are reviewed.

Dietary advice is a core component of GDM interventions and diabetes prevention programs. Participants found the prescribed diet as unpalatable, not aligned with their personal preferences and unsustainable long term. There are reports describing the GDM prescribed diet as contrary to women's personal preferences, culturally insensitive and difficult to follow.[179,180,183–186] The wellbeing of the unborn child and a history of pregnancy loss compelled women toward dietary adherence until the birth. However, clinicians' disregard for individual preferences and circumstances may not facilitate the sustained, lifelong change necessary to prevent GDM recurrence or the development of overt diabetes. A recent Cochrane review found no superiority between ten different diets in the primary outcome of the development of macrosomia in GDM affected pregnancies, nor in the prevention of GDM development.[187,188] There is no ideal, universally applicable diet for the treatment of GDM. Rather than adherence to a specific diet, avoiding excess maternal weight gain and lifestyle change to restore euglycaemia is associated with a reduction in the perinatal morbidity of GDM.[189–191]

Participants experienced anxiety, self-blame and guilt secondary to unresolved distress from previous pregnancy losses, and this has been previously described. [192,193] Unresolved distress from their previous experiences affected their response to the GDM diagnosis. Some were ambivalent regarding knowing their GDM status. Inconsistent health care messages between the research unit, doctors and nurses may have contributed to this. Pretest counselling prior to screening may reduce patients' anxiety. GDM awareness and skills training of doctors, midwives and lay-health workers at all health care centres will allow consistent delivery of health care messages.

Fear of diabetes and HIV

An unexpected finding was the perception by participants that having diabetes is worse than living with HIV. This may have contributed to the ambivalence some participants experienced on whether they would have preferred to know their GDM status. DM2 was reported to be something hidden, a dangerous medical condition that was difficult to diagnose and treat, with potentially catastrophic consequences. Even if one was formally screened, the diagnosis may still be missed. The underlying cause of DM was poorly understood by participants, particularly by those who did not have a positive family history. In South Africa HIV is the fifth leading cause of death, but the trend for this and other infectious diseases is decreasing. Diabetes is the leading cause of death of South African women and second leading cause of all deaths, with an increasing trend for DM and other non-communicable diseases. Women may benefit from consistent health care information to reduce GDM associated distress.

Limitations

Participants directed the flow of discussions and subthemes were not consistently generated within each group. Findings which emerge from FGDs are not equal to the opinions or ideas of any individual member, nor are they capable of being inferred to any population beyond the group. This is a known limitation of FGDs as some participants may be more inclined to dominate the group.[194] The composition of the focus groups was restricted to a single state sector sample from Soweto. Diverse social, economic and cultural differences are therefore unlikely. The combined experience of this group may adequately reflect that of an urban Black South African population with poor obstetric history attending a tertiary health facility.

Implications for clinical research and practice

Women diagnosed with GDM are at high risk of recurrence in subsequent pregnancies as well as the development of overt diabetes in both mother and child in later years.[4] Women were aware of the association between diabetes and genetic predisposition, obesity and unhealthy lifestyle choices. There was low awareness that the development of diabetes is preventable. Perception of risk post-GDM is known to affect lifestyle choices postpartum.[195] There is evidence that sustained lifestyle changes of healthy eating, weight loss and exercise prevent the onset of type 2 diabetes mellitus.[196,131] A WHO review of evidence-based diet and exercise education programs that are effective even in low resource settings discussed community development campaigns (e.g. diabetes prevention) and targeting high risk groups (e.g. pre-diabetic women) with group-based activities for homogenous groups of individuals (e.g. urban black African women).[197] Intercultural variations in perception of ideal weight gain and nutrition in pregnancy have been described.[198] Failure to clarify and address these issues may sabotage the success of GDM interventions in a local population. It may be necessary to culturally tailor gestational weight gain interventions to optimise health outcomes and the local acceptability of interventions.

Conflict of Interests

None

Contributors

Methodology: LMD; EJB; SAN. Investigation: LMD. Formal analysis: LMD; EJB; TM; SAN. Writing: LMD. Reviewing and editing: EJB; SAN.

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Chapter 6.

Integrated Discussion

6.1 Summary of results

The purpose of this research was to investigate the feasibility of a universal screening and diagnosis program for GDM, using glucometers rather than the laboratory service to measure glucose, in a low resource CHC in South Africa. Also, qualitative research techniques were used to examine women's experience of GDM, for the purpose of informing the development of a GDM intervention. The specific research objectives and the study findings were presented as individual manuscripts in Chapters 2–5. A summary of the major findings is presented in Table 6.1.

Table 6.1. Summary of research questions and major aligned empiric findings.

Research Objective	Chapter	Summary of findings
Evaluation of the measurement accuracy of selected plasma calibrated glucometers, relative to a laboratory, in screening for and diagnosing GDM.	2 & 3	Overall GDM prevalence as defined by all methods of measurement was 16.1%. * GOx and HK methods: GDM prevalence was 5.1% and 6.9% respectively and laboratories agreed on 34% of positive diagnoses. [Unexpected finding] Of the five glucometers evaluated, only three were accurate and then only at fasting of the OGTT. ** All glucometers were inaccurate at one and two-hour of the OGTT. **
Evaluation of the validity of a universally applied dual threshold FPG against a selectively applied risk factor-based screening program to screen for GDM.	4	Sensitivity of FPG ≥ 5.1 mmol/l, FPG ≥ 4.5 mmol/l and ≥ one risk factor *** to identify GDM were 88%, 98%, and 71% respectively. Specificities of FPG ≥ 5.1 mmol/l, FPG ≥ 4.5 mmol/l and ≥ one risk factor *** to identify GDM were 100%, 80%, and 57% respectively. The number needed to screen based on FPG ≥ 5.1

(GOx method = reference)		mmol/l, FPG > 4.5 mmol/l and ≥ one risk factor *** were 36 (6.1%), 152 (25.8%) and 262 (44.5%) of 589 participants respectively and the number of missed GDM would have been five, one and 12 respectively.
Identify the personal experiences of GDM affected women.	5	Sharing experiences with their peers provided relief from GDM associated anxiety. Inconsistency in health care information exacerbated their confusion. Dietary requirements were associated with a subjective loss of autonomy and choices were perceived to be unpalatable and expensive. Lifestyle choices were partially retained postpartum and partially adopted by other family members. There was low awareness of long-term risk as well as when, where and how to screen for DM. Women reported that living with HIV was preferable and evoked less stress than having DM. [Unexpected finding]

* Composite laboratory and glucometer results are presented as supplementary information.

** The glucometer accuracy results were reported with an HK method as the reference test because this is used by the NHLS and major private medical laboratories.

*** BMI ≥ 30kg/m^2

6.2 Reflection on challenges encountered to universal GDM screening

The initial research site setup involved more than accessing material resources and developing optimal flow for the daily routine of the project. At the beginning, it was necessary to establish a working relationship with the local clinic staff. The researcher met

with the clinic manager and the head of the antenatal unit and established that all necessary permissions were granted. A room within the area of the antenatal clinic was provided for the project and this ensured that patients and CHC staff had easy access to research staff and procedures. The researcher was made familiar with the basic functioning of the antenatal service, the staff structure and the referral system for patients in need of additional services. Later, all staff of the antenatal unit were invited to a briefing session, where the purpose of the study and the daily procedures of the project were discussed.

It was also necessary to develop a basic understanding of the women attending the antenatal service of the CHC, and the researcher had multiple opportunities for this. Women were recruited from the waiting room of the clinic and at this stage, their basic demographic information, employment status, level of formal education and past medical and obstetric history were documented. On the days of the OGTT, between two and twelve women were in the research room for at least two hours, and usually they chatted with the researcher and each other between procedures. Themes which emerged from these encounters are discussed below.

There are public and personal perspectives of pregnancy, and both influence the antenatal care experience.[3] There was a wide spectrum of socioeconomic circumstances among the women attending this clinic. It was not uncommon, for instance, to have a college student living with her parents who was pregnant for the first time, a woman with five children living in informal housing and a married office administrator with complex demands on her time, all chatting about their current pregnancy, between research-related activities. Pregnancy planning, adapting to the pregnancy, support from their partner and family, awareness of the

importance of antenatal care and the direct and indirect costs of attending the clinic, all affected the timing of their first and subsequent antenatal visits.[199,200]

6.2.1 Barriers to women participating in GDM screening

Women are usually healthy when they voluntarily present themselves to the medical profession in the antenatal period. This is an opportunity to screen for multiple health risks as well as offer health education messages.[72] The consort diagram for participants recruited to this study (Chapter 4, Figure 4.1) indicated that the majority of women (76.3%) attending this CHC, were willing and eligible to participate in the GDM screening program. Of those who were recruited, 68.7% completed an OGTT, meaning that 52.4% of women who attended this antenatal clinic between April 2016 and May 2017 were formally screened for GDM.
The CHBAH in Soweto, the world's third biggest hospital, provides services to low, moderate and high-risk pregnant women.[201] A GDM prevalence study conducted at the CHBAH between June 2013 and April 2017 recruited 3656 eligible participants and 1906 (55%) of those recruited completed the OGTT.[35] An estimated 17000 births occur annually at this facility according to the CHBAH website.[201] This implies that an estimated 2.8% of women who gave birth at this hospital were formally screened for GDM over the duration of the study. Adam and Rheeder's GDM prevalence study, which was conducted at an undisclosed primary health clinic in Johannesburg over 33 months from September 2013 to June 2016, recruited 1000 participants and 554 (55.4%) of these underwent an OGTT.[145] Insight into barriers to participation are important in order to improve the uptake of GDM screening.

At Zola CHC in Soweto, where this study was based, possible reasons emerged as to why women were not screened. A common reason given for not attending their OGTT appointments was that women had returned to their family home, usually in a rural town. Gauteng, the smallest but most populous province of South Africa, generates a third of South Africa's gross domestic product.[29] Of all nine provinces, Gauteng receives the highest number of migrant workers annually because of better job opportunities.[29] In South Africa, it is not uncommon for women to work in a province away from their family home and this is a known reason for late antenatal booking.[200] Women booked at this antenatal clinic to confirm their pregnancy, but they returned home because they preferred to have the birth within the supportive environment of their family. Families are the main providers of material and emotional support for women during their pregnancy in South Africa.[202]

Women's personal and social responsibilities often prevented them from keeping their appointments. When the OGTT appointment day did not coincide with their routine antenatal visits, women were more likely to miss their appointments. Those who were employed or enrolled in tertiary education were reluctant to take extra days off to attend the clinic. There was also poor attendance when OGTT appointments coincided with the day of collection of the South African Social Services Agency grant. Due to limited resources within the study, OGTTs were scheduled for either a Wednesday or Thursday of each week and this was not always convenient to participants. Where possible, appointments were rescheduled.

High drop-out rates are known to occur when women are required to return for an OGTT on another day.[157] Solutions may include incorporating GDM screening into routine antenatal care, rather than as a separate and isolated event that requires an additional visit. This may improve the effectiveness of a GDM screening program. The use of glucometers to measure

blood glucose concentrations would allow the immediate availability of results and there would be no need for an additional visit. Ease of test administration (finger-prick rather than venous puncture) and the reduced cost of testing (ZAR 12.00 rather than ZAR 220.00 for a complete OGTT) will make screening more cost effective and easier to implement, even in large and busy health care facilities. GDM screening would therefore be more accessible.

6.2.2 Technical challenges encountered in implementing GDM screening

The diagnostic accuracy of glucometers in screening for and diagnosing GDM were evaluated according to the STARD guidelines. A reference test (laboratory) was paired with an index test (glucometer) in each woman screened and the reference test result was used to determine participants GDM status. Initially, in the pilot phase of the study, there were delays in obtaining results from the research laboratory (reference test) and so a private medical laboratory was used as a temporary solution. When the research laboratory results were made available, dissimilarities between the laboratories results became apparent. The researcher decided to continue the study, at significantly increased cost, using both laboratories as a composite reference test. This decision was made in the interest of patient safety, in order to avoid missing GDM positive women. The protocol was then amended to include the use of both laboratories as a composite reference test and participants with a positive GDM diagnosis by either or both laboratories would be offered clinical intervention.

On further review of the literature, the researcher became aware of the absence of a gold standard for the measurement of plasma glucose, as well as the challenges and controversies associated with glucose measurement. Explaining the difference between laboratories results required the examination of laboratory procedures and equipment used, and variations in

methods of measurement used by the two laboratories were discovered. Subsequent analysis at the end of the study confirmed the tentative findings of the pilot phase, namely, the poor intra-individual reproducibility in identifying GDM between the HK and GOx laboratory methods.

Adam and Rheeder evaluated the accuracy of the Accu-Chek glucometer against a laboratory for the purpose of diagnosing GDM. The laboratory quality control results were reported but not necessarily interpreted against recommended standards. Rather than acknowledge the invalidity of the laboratory glucose measures due to poor quality control results, the authors concluded that the glucometer was unreliable. The clinicians understandably but incorrectly assumed that laboratory results were a reliable gold standard. This assumption may negatively affect patient diagnosis and management.

6.3 Conceptual framework revisited

6.3.1 Government Policy: GDM Screening Procedures

The patient centred conceptual framework was selected for use in this study (Chapter 1.1). Professional norms, professional training and clinical experience as well as government policy are external shapers that affect the patient's health care experience.[1] The SADH guidelines for GDM will be updated following the WHO and SEMDSA recommendations. Clear and consistent recommendations should ensure the success of GDM programs. The continuation of conventional clinical practice of relying on laboratory services to measure glucose concentrations may be inappropriate and possibly unjustifiable.

The widespread use of plasma calibrated glucometers for diagnostic purposes is inevitable following the endorsement from the WHO and the FIGO.[4,6] In this study, glucometers missed fewer diagnoses than either laboratory. (Chapter 2; Appendix III Supplementary data) It is possible that they were more effective than the laboratory in identifying GDM positive women. Glucometers were also easy to use, inexpensive and had a turn-around time of a few seconds. However, because of the limitations of laboratory methods of measuring glucose concentrations, there is no reliable system in place to evaluate glucometer accuracy.

This study adds to international evidence of uncertainty in plasma glucose measurements in diagnosing GDM in routine clinical settings.[95,96] The two calibrated laboratories with acceptable quality control measures had low agreement on the presence of GDM. The HK method, which is known to be more specific, is widely used by state-sponsored and private medical laboratories in South Africa, and this is unlikely to change. Evidence from the Adam and Rheeder study suggests that maintaining acceptable quality controls is more important than differences in the selection of enzymatic method of measurement used, to avoid misdiagnosis of GDM.[145] Direct comparisons of clinical outcomes of HK and GOx defined GDM are unlikely. It would be unethical to withhold treatment from GDM positive women diagnosed by a calibrated laboratory, regardless of the method of measurement used.

The use of a local, routine medical laboratory to calibrate glucometers at regular intervals has been previously described.[203] This may not be ideal based on the limitations of a routine laboratory reported in this study (Chapter 3). Preapproval of glucometers' precision and system accuracy, by an independent party supervised by government agencies, may improve the safe use of glucometer for diagnostic purposes.[120] Evaluation processes, reference methods used and legal and funding issues should be clearly defined and transparent.

Glucometer quality and accuracy, rather than price, should inform glucometer approval.[120] Both pre-marketing and ongoing post-marketing glucometer evaluations are necessary.

6.3.2 Patient centred care

The high recruitment rate in this study indicates that women at this CHC were willing to participate in this voluntary GDM screening program. However, in the FGD (Chapter 5) women's account of their experiences suggests they were not adequately prepared for the consequences of being diagnosed with GDM. For example, they reported being emotionally distressed on diagnosis and they remained anxious throughout the pregnancy. They also assumed that health behaviour changes were necessary only for the duration of the pregnancy. However, GDM is an index event that heralds a lifetime risk for T2D. Women would likely benefit from pre-test and post-test counselling before screening for GDM. This may reduce the risk of emotional distress associated with a GDM diagnosis, facilitate acceptance of the long-term risk associated with this diagnosis, and improve the likelihood of retention of health behaviour changes initiated in pregnancy.

The ADA, NICE and SEMDSA recommendations include preconception counselling for women known to have overt pre-conception DM, but no guidelines are given for pretest counselling for GDM screening. The NICE guidelines suggest that informed consent, rather than counselling, is obtained prior to GDM screening and the information that should be disclosed is prespecified (Table 6.2). The tone of the information disclosed may be interpreted as dissuasive and possibly untrue. For example, most women with GDM do not need pharmacological intervention. Education on the need for lifelong health behaviour

change is unfortunately not included in the recommendations of the ADA, NICE or SEMDSA.

Table 6.2. NICE recommended disclosures for informed consent prior to GDM screening.[58]

1. In some women, gestational diabetes will respond to changes in diet and exercise
2. The majority of women will need oral blood glucose-lowering agents or insulin therapy if changes in diet and exercise do not control gestational diabetes effectively
3. If gestational diabetes is not detected and controlled, there is a small increased risk of serious adverse birth complications such as shoulder dystocia
4. A diagnosis of gestational diabetes will lead to increased monitoring, and may lead to increased interventions, during both pregnancy and labour.

In the SADH guidelines for maternity care, essential screening investigations for pregnant women include syphilis serology, human immunodeficiency virus (HIV) serology, urine dipstick for protein and glucose, haemoglobin level and Rhesus (D) blood group. Point of care testing is used for all these investigations and so results are available on the day of testing.[72] Only HIV testing, a chronic disease which requires ongoing treatment postpartum, attracts routine pre-test and post-test counselling. In South Africa, the Prevention of Mother-To-Child HIV Transmission (PMTCT) program reduced the rate of infection of HIV exposed infants to 2.6% nationally.[204] This approximates the transmission rate under clinical trial conditions.[204]

Developers of GDM screening programs should consider applying strategies successfully used in the PMTCT program in a South African setting.[72,205,206] These include:

- Testing and counselling initiated by the health care worker rather than the patient.
- Patients may refuse testing and should be offered ‘post-refusal’ counselling.
- Group-based pretest counselling.

- Rapid testing with same day results using glucometers.
- Use of lay counsellors for testing and counselling for optimal use of human resources.
- Ongoing training of staff to ensure the delivery of consistent health care information.
- Male partner involvement and couples counselling.
- Extension of testing and counselling into all health care centres.
- Developing community involvement by:
    - creating social spaces for dialogue within communities,
    - promoting a local sense of ownership of the problem,
    - identifying and emphasizing community strengths and resources,
    - building knowledge and basic skills,
    - mobilizing existing local formal and informal networks,
    - building partnerships between local, national and international agencies.

6.4 Recommendations based on research results

"This study adds to existing published research that plasma glucose concentrations measured by a routine clinical laboratory should be interpreted with caution by clinicains."[95,96,145,207] (Chapter 2 and 3) Based on the endorsement of the WHO and the FIGO, previous reports of under-diagnosis of GDM by routine laboratory services and our research findings, the roll out of GDM screening using glucometers is possible.[95,96] In addition, a dual threshold FPG has greater sensitivity and specificity than a risk factor based selective screening strategy in identifying GDM positive urban indigenous South African women. Applying a dual FPG threshold would reduce the number of women requiring a resource intensive complete OGTT.

Traditional components included in GDM screening and treatment guidelines are diagnostic thresholds, screening strategies and treatment algorithms. The SEMDSA recommendation of

2017 includes the comment that “universal screening for gestational diabetes may be adopted in well-resourced settings”. A systemic inequity of GDM screening in South African maternity care would be inevitable if this was applied to clinical practice. This should serve as an urgent stimulus for action in order to reduce GDM related morbidity and mortality in less affluent communities.

The following measures may address the gaps in GDM screening procedures that currently exist in South African antenatal services:

- Women should be offered pre-test and post-test counselling.
- Using glucometers to measure plasma glucose concentrations would enable screening for GDM at the CHC, with the immediate availability of results.
- A dual threshold FPG should be applied at 24-28 weeks' gestation, using glucometers to measure blood glucose concentrations before proceeding to a complete OGTT.
- Women with overt DM (WHO 2013) should be referred for specialist care.
- Antenatal visits should occur at two-week intervals from the diagnosis of GDM until the birth.
- Women who fail to maintain euglycaemia as the pregnancy progresses should be referred for specialist care.

An increased number of women with GDM will need health care support and so efficient systems are necessary across all levels of health care. Engagement with multidisciplinary health care professionals is necessary to establish diagnostic and treatment priorities, clinical guidelines and an optimal referral system for women in need of more advanced care. Interdisciplinary collaboration is essential for patient safety. Avoidance of excessive delays in initiating treatment should be emphasised. Once consensus is established, guidelines and

training should be made available in all institutions and to both midwives and doctors. Robust medium to long term surveillance systems are necessary to track and manage progress and obstacles in the implementation of these guidelines.

Changing from selective to universal screening for GDM, and from hospital-based to the availability of GDM services at all health care centres, should be carefully managed. Pilot programs are necessary to inform policy formation, planning and implementation of a universal GDM screening and treatment program. GDM guidelines should be standardized, with reasonable flexibility, across provinces, in all health care facilities and in both urban and rural areas. GDM screening should be integrated into basic antenatal care in low resource settings which should include CHCs.

The responsibility of the laboratory regarding acknowledging the level of accuracy of results generated is unclear. Chemical pathologists and/or laboratory technicians should be compelled to disclose the limitations of glucose results based on current laboratory quality controls. The effect of prolonged laboratory turn-around times should also be disclosed. This would allow clinicians to make informed decisions, with optimal interpretation of laboratory results, reducing the likelihood of misdiagnosis and patient mismanagement.

6.5 Strengths and limitations of this research

In this cross-sectional study, participants were recruited consecutively and not preselected based on prior testing, thus minimizing the risk of bias. In the pilot phase, either rather than both laboratories were used as the reference test. The pilot phase data were excluded from the analysis, meaning that all participants were evaluated with a similar, composite reference test

and this reduced the risk of bias. Diagnostic thresholds were prespecified and identical for both the index and reference test. Bias was unlikely to affect the diagnostic process of determining women's GDM status.

Glucometers are cost effective with a fast turn-around time to results availability and the finger-prick blood sampling is less invasive than the multiple venous punctures required for laboratory testing. However, a higher proportion of women were identified as being GDM positive with the glucometers. It is important to note that one glucometer brand, the Glucocheck Classic was responsible for 26 of the 48 (54.2%) glucometer false positive GDM diagnoses. (Chapter 2; Appendix III Supplementary data) Appropriate selection of glucometers may reduce the frequency of misdiagnosis of GDM.

This pragmatic study investigated testing procedures that are simple, economical and feasible on a large scale. Selected glucometers to measure glucose in the OGTT and screen for GDM is possible, but caution is indicated. Glucometer results were higher than both laboratories at all time points of the OGTT. However, this increase was above the ISO 15197:2013 recommended TAE at one and two hours of the OGTT for all glucometers evaluated. There was variation in the extent of this error between glucometer brands, and it was most pronounced with the One Touch Select Plus Flex. (Figure 2.1)

In women of South Asian descent, an elevated one and two-hour OGTT result may be more likely to identify GDM than the FPG.[63] Based on glucometers tendency to overestimate glucose concentrations at one and two hours of the OGTT, false positives may be more likely in this subgroup of women. For example, it is possible that South African women of South Asian descent may be more likely to identify as GDM positive based on an elevated level one and two hours of the OGTT. There were no participants of Asian descent in this study

because of the patient profile of this CHC. The use of glucometers for diagnostic purposes should be examined in a more diverse sample of South Africans.

6.6 Future research

6.6.1 Measurement of glucose

The WHO 2013 diagnostic criteria for GDM requires a single abnormality of the OGTT to establish a positive diagnosis. Routine clinical laboratories may not be suited for this demand for accuracy. Due to preanalytical, inter-laboratory variability and inter-method variability, laboratory methods may not be the ideally suited to measure plasma glucose concentrations in low resource settings concerned with identifying GDM affected women Future research should be directed toward glucometer use for diagnostic purposes. Identifying a suitable reference test for evaluation of glucometers remains a concern. Expert opinion suggests radiometer arterial blood gas analysers may be used as a reference test against glucometers.[120]

6.6.2 Assumption of false positive results

In the absence of a true gold standard, all methods of measurement of blood glucose in a routine clinical setting are flawed. The limitations of the method of measurement selected for screening should be taken into consideration. The glucometers, GOx method and HK method identified a GDM prevalence of 12.7%, 6.9%, and 5.1% respectively. However, the composite prevalence of GDM using all methods of measurement was 16.1%, and this is not different from global estimates of GDM. The composite test in the study, which includes all

glucometers and laboratories, may be more reflective of the true prevalence of GDM in South Africa.

The laboratory results defined participants' GDM status in this study, and participants identified as GDM positive by either or both laboratories were offered clinical intervention. Participants with a positive GDM diagnosis uniquely identified by glucometers were not offered clinical intervention. The WHO endorsement of the IADPSG recommendation included the observation that there is an absence of data on the consequence of false positive or false negative test results.[47] Based on this study's results, the definition of a laboratory false positive and negative test for GDM is unknown. In rolling out GDM screening programs, clear guidelines on the preferred method of measuring glucose concentration in a routine clinical setting are necessary. In future studies, all positive cases, whether determined by glucometer or laboratory, should be offered clinical intervention, until such time as the definition of a negative GDM test is clarified.

6.6.3 Intervention development

Once identified as having GDM, women should be offered an intervention to restore euglycaemia in pregnancy. In the FGD sessions (Chapter 5), women reported that informal peer support provided relief from anxiety and this was also a source of health information. Women identified as GDM positive in this study were given an intervention which was delivered at the CHC at two-week intervals by research staff. GDM is currently not a defined clinical entity and so support was not otherwise available. The intervention delivered included dietary advice, an exercise program, daily self-monitoring of blood glucose and FGD of 20–30 minutes duration. The Diabetes Conversation Map was used to deliver health

information to groups of women. These sessions were well received, and women often extended their discussions beyond the time allocated. With participant consent, these sessions were recorded and will be analysed with the intention of refining the intervention. It is possible that in future, lay-health care workers could be trained to facilitate these peer support, group based, diabetes education sessions.

6.6.4 Multicentre GDM screening

This pilot study has demonstrated that a GDM screening, diagnosis and lifestyle intervention program is feasible in a CHC. Recommendations arising from this study should inform a scaled-up version of this study. A stepped wedge study design would suit this purpose because it will allow a randomized sequential roll-out of the intervention to a cluster of CHCs.[208] At the end of the random allocation, all CHCs in a district would have participated in the active arm of the intervention. Because the intervention is assumed to be beneficial rather than causing harm, withholding the intervention from a proportion of participants would be unethical but unavoidable in a traditional parallel study design. Potential challenges in a roll-out of the intervention may include logistical, practical and financial constraints, and a stepped wedge study design will allow the intervention to be implemented in stages. This study design is also used for cost-effective analysis of interventions that are previously demonstrated to be effective.[208]

6.7 Conclusion statement

Universal screening for GDM based on a dual threshold FPG in a low resource setting and this has greater sensitivity and specificity than a risk factor based selective screening strategy. The use of selected glucometers to measure plasma glucose concentrations is inexpensive, with reduced turn-around time and possibly less ambiguity than a routine laboratory service.

6.8 Executive Summary

A South African GDM Screening Strategy

What is the issue?

Revision in current diagnostic thresholds is necessary

Following revised international diagnostic thresholds, the development of a feasible, efficient and accessible universal GDM screening program is urgently required. The WHO adopted the stringent diagnostic thresholds for GDM recommended by the IADPSG in 2013. The SEMDSA adopted the WHO GDM recommendations in 2017. Historically, the South African National Department of Health guidelines for diabetes care are based on the WHO and the SEMDSA recommendations.

Disease burden

DM is the second leading cause of death of all South Africans. T2D is preventable and if identified in the early stages of the disease, may be reversible. GDM is a T2D precursor. The WHO estimates that 16% of pregnancies are affected by GDM globally.

Two recent South African reports of GDM prevalence are 9.1% and 26.7%.

<u>Screening strategies</u>

South Africa currently has a risk factor based selective screening program for GDM. Universal screening for GDM is recommended by the IADPSG and the FIGO. GDM screening is usually done at 24–28 weeks' gestation with an OGTT. Traditionally, the two-hour OGTT is dependent on a calibrated laboratory service. The WHO (2016) and the FIGO

(2015) have endorsed the use of plasma calibrated glucometers for diagnostic purposes, as an alternative to a laboratory service. The accuracy of these inexpensive devices is not yet established.

Why is it important?

- There is an urgent need to develop a local, sustainable, feasible, cost-effective and accessible GDM screening program.
- Effective screening will allow an opportunity to reduce GDM associated morbidity and mortality.
- Identifying these high-risk individuals will allow early implementation of effective interventions such as the Diabetes Prevention Program.

What did we do?

- This pilot study was concerned with the feasibility of screening for, diagnosing and offering a lifestyle intervention for GDM within the usual functioning of an urban CHC.
- 592 consecutive urban black South African women had a modified OGTT to evaluate the accuracy of five glucometer brands against two calibrated laboratories.
- Retrospectively, strategies to reduce the number of women requiring a complete OGTT were compared, namely, risk-factor based selective screening and a universally applied FPG.
- The experiences of women previously affected by diabetes were examined in a series of focus group discussions.

What evidence did we find?

- GDM Prevalence
  - The prevalence of GDM by all methods of measuring plasma glucose concentration was 16%, and this is identical to the estimated global prevalence of GDM.
  - The glucometer determined prevalence of GDM was 12.7%

    Glucometers were most accurate at fasting of the OGTT.
  - Composite laboratory determined prevalence of GDM: 9.0%

    Only 34% of GDM positive diagnoses were common to both laboratories.
  - An elevated FPG identified ≥80% of GDM positive diagnoses by all methods.

- OGTT: measuring plasma glucose concentrations
  - Glucometers
    - Glucometers were inexpensive, easy to use, and results were available in five seconds.
    - Glucometers missed fewer diagnoses than either laboratory. They were effective in ruling out GDM.
  - Laboratory method
    - A medical research laboratory used a GOx method and a private medical laboratory used a hexokinase method to measure plasma glucose.
    - A negative systematic bias of the HK method contributed to a low agreement between laboratories on GDM positive status.
    - The HK laboratory missed 23 of the GOx laboratory GDM positive results

The GOx laboratory missed 12 of the HK laboratory GDM positive results.

- Glucometers missed 3 of the HK and18 of the GOx laboratory GDM positive results.

This suggests that the glucometers were more accurate than either laboratory.

❖ Screening strategy

- Risk factor-based selective screening indicated:
  - 204 of 592 (34.6%) participants needed an OGTT, however, 18 of 41 (43.9%) of GDM positive cases would have been missed.
  - The sensitivity and specificity of ≥ one risk factor was 56% and 67% respectively.
- Universal screening using the FPG indicated:
  - 152 of 592 (25.8%) participants needed an OGTT, however, one of 41 (2.4%) of GDM positive cases were missed.
  - The sensitivity and specificity of an elevated FPG was 98% and 80% respectively.
  - This suggests that the universal application of the FPG is superior to a risk factor based selective screening strategy, which is the current South African standard practice, in identifying GDM affected women.

❖ Women's perspective of GDM

Women previously affected by GDM viewed being HIV positive as preferable to having diabetes, and this may reflect their distress caused by inadequate pre-test counselling, inconsistent health information, inconsistent screening practices and suboptimal support from health care professionals.

Adopting a healthy lifestyle was considered as a positive consequence of diagnosis.

Lifestyle changes were partially maintained and positively affected the family.

What does this mean?

- Universal screening for GDM is feasible in a low resource setting in South Africa, thus allowing equity in access, regardless of whether women reside in urban or rural area of South Africa.

- The use of glucometers to screen for GDM
  - reduced the number of missed diagnoses; the glucometers were more accurate than either laboratory in identifying GDM affected women
  - results were available within five seconds, thus
    - avoiding the need for an additional antenatal visit
    - reducing the demands on the time of health care professionals
    - allowing the immediate initiation of treatment
    - reducing the inconvenience to women
  - By avoiding the need for laboratories in universal screening,
    - the need for additional laboratory services is avoided
    - the transport of samples in those centers without an on-site laboratory is avoided
    - the additional demands on skilled health care professionals is avoided.
  - The glucometers required a finger prick rather than the invasive venous punctures required by a conventional, laboratory requiring OGTT, thus reducing pain and discomfort to women

- The use of the FPG to screen for GDM
  - improved the efficiency and effectiveness of screening by increased the probability of identifying those affected,

- reduces the demands of time spent by health care professionals
- reduces the cost of material resources,
- reduces the number of women required to ingest for the unpalatable and nausea inducing oral glucose solution

CONCLUSION

This pilot study has demonstrated that a universal GDM screening program is feasible in a low resource CHC. Universal screening for GDM using the FPG and glucometers is feasible has greater sensitivity and specificity than a risk factor based selective screening strategy, requires fewer women to undergo a resource-intensive diagnostic OGTT, with reduced turn-around time and possibly less ambiguity than the costly laboratory measurements of plasma glucose.

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APPENDICES

I. Human Research Ethics Committee Clearance Certificate

Letter of approval from the University of the Witwatersrand Human Research Ethics Committee (Medical) to conduct this research.

R14/49 Dr Lynnsay Marcia Dickson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150365

NAME: (Principal Investigator)	Dr Lynnsay Marcia Dickson
DEPARTMENT:	MRC Developmental Pathways for Health Research Unit Zola Primary Health Care Antenatal Clinic, Soweto
PROJECT TITLE:	Screening, Diagnosis and Lifestyle Intervention Program for Gestational Diabetes Mellitus in an Urban Primary Health Clinic in South Africa
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Shane Norris and Prof Eckhart Buchmann
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/06/2015

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

DECLARATION OF INVESTIGATORS

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

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date 22/06/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

II. **Johannesburg District Department of Health**

Letter of approval from the Johannesburg District Department of Health of South Africa to conduct this study at the Zola Community Health Clinic.

III. Supplementary data

A. Bland Altman Plots of Glucose concentrations (mmol/l) measured by specific glucometer brands against the HK method at t=0, t=60 and t=120 of the OGTT.

Figure S1. Bland Altman Plots of Glucose concentrations (mmol/l) measured by Contour Plus glucometer s against the HK method at t=0, t=60 and t=120 of the OGTT.

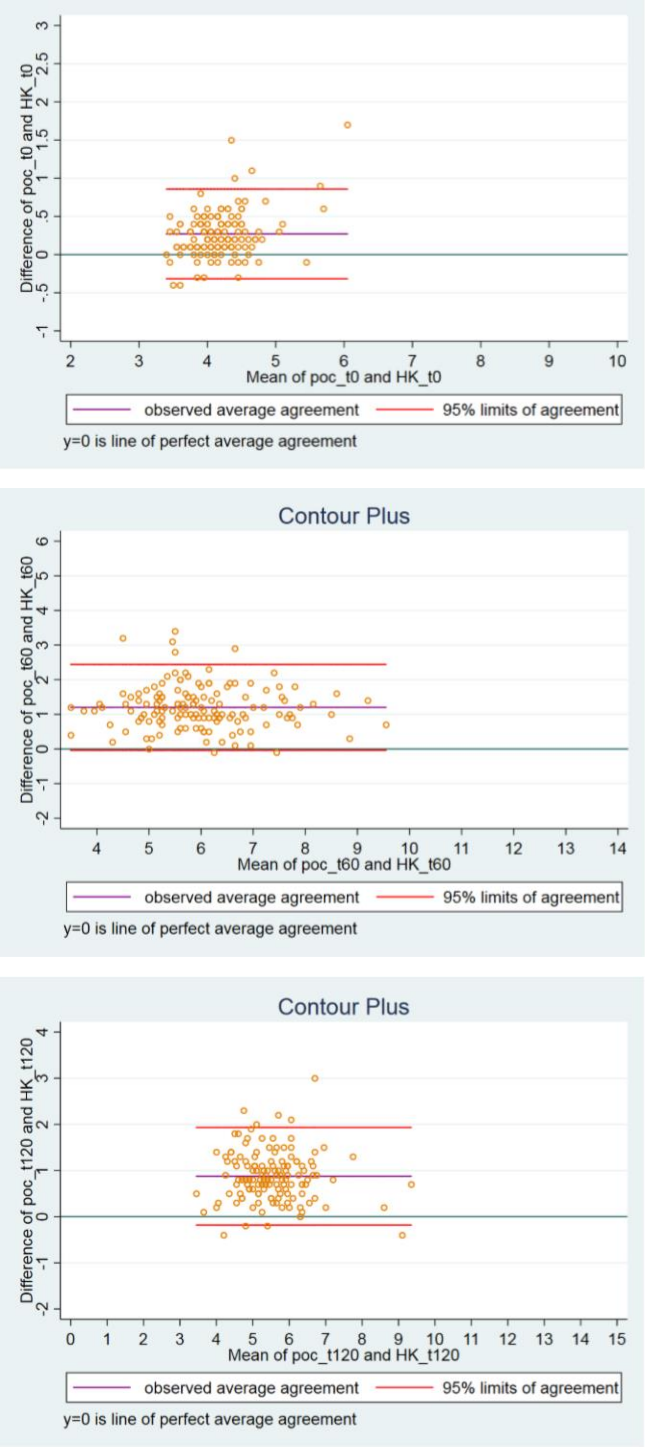


Figure S2. Bland Altman Plots of Glucose concentrations (mmol/l) measured by Accu-Chek glucometer s against the HK method at t=0, t=60 and t=120 of the OGTT.

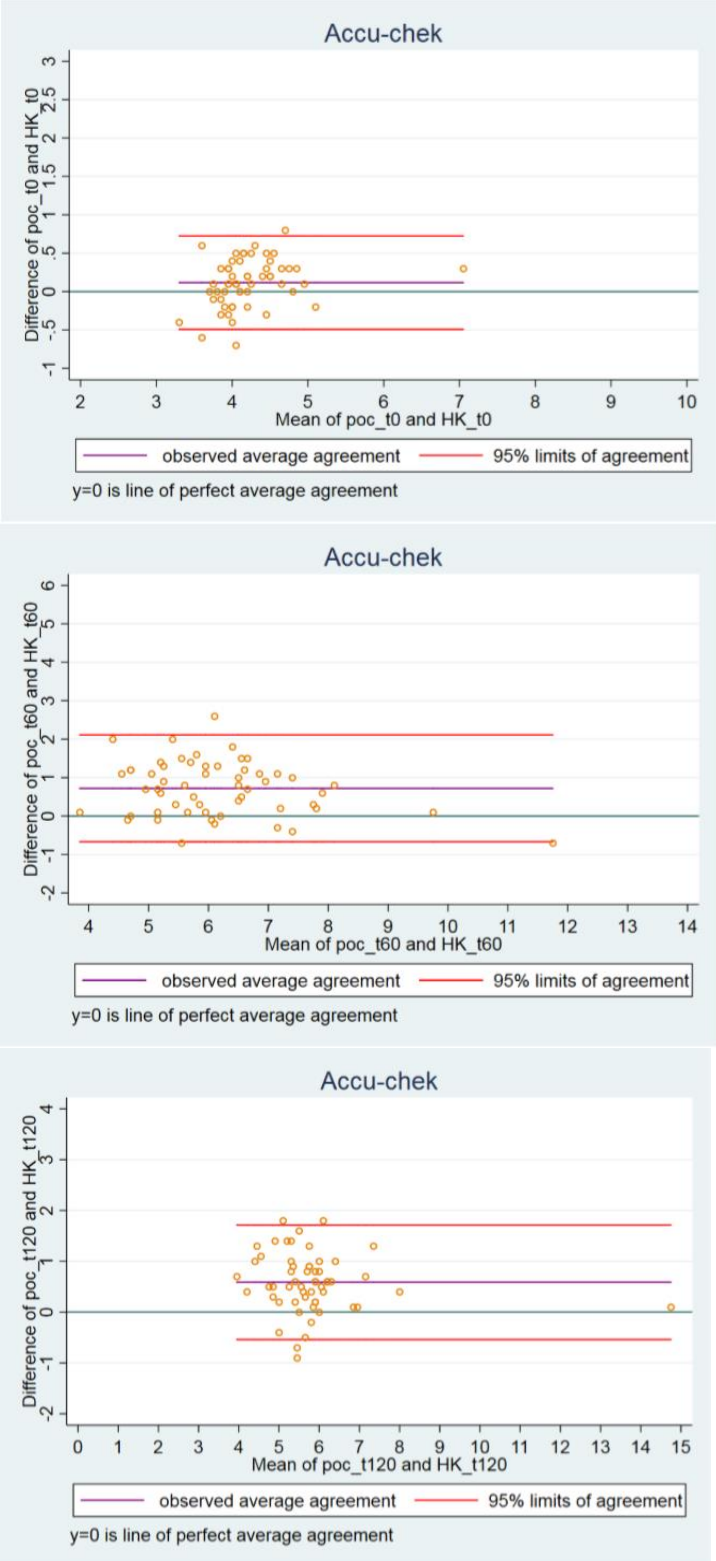


Figure S3. Bland Altman Plots of Glucose concentrations (mmol/l) measured by Glucocheck glucometer against the HK method at t=0, t=60 and t=120 of the OGTT.

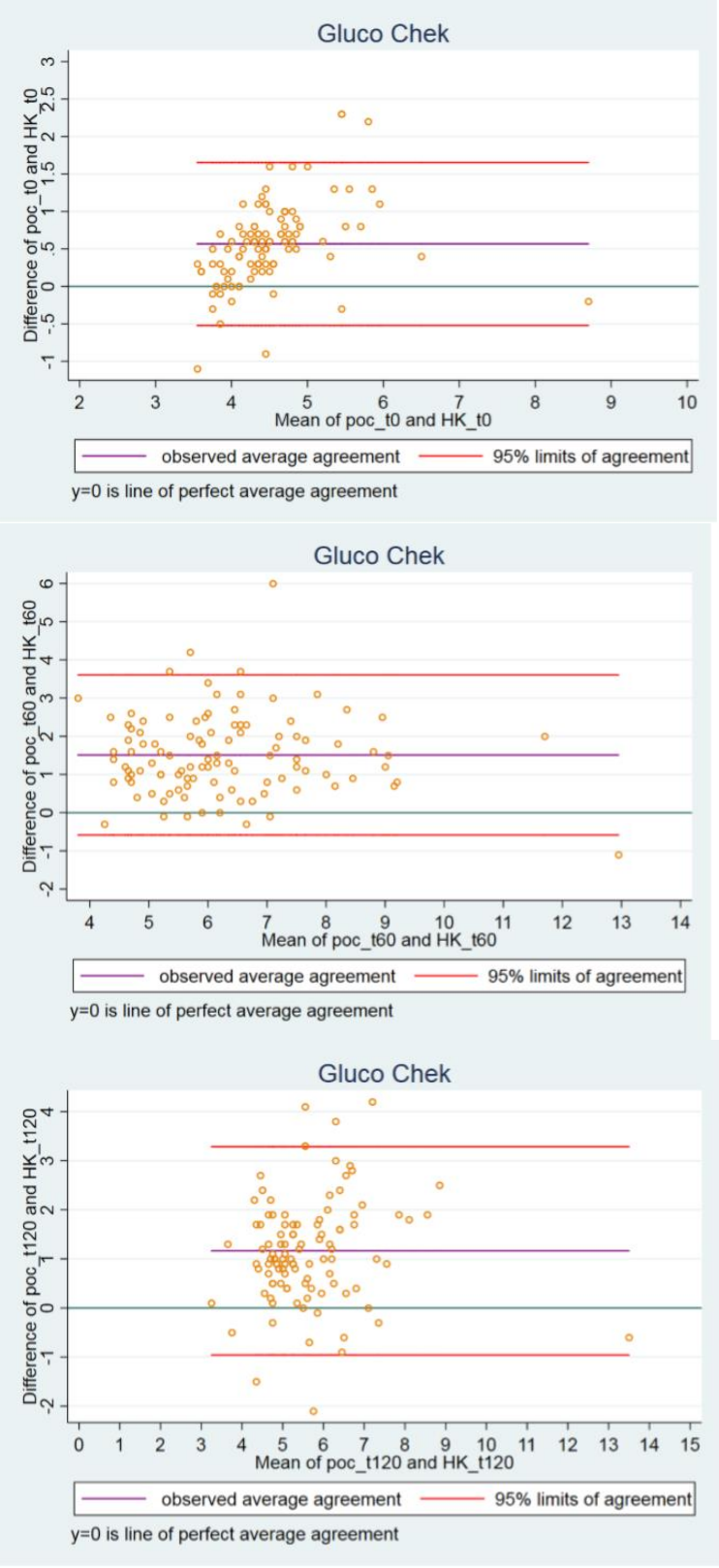


Figure S4. Bland Altman Plots of Glucose concentrations (mmol/l) measured by Freestyle glucometers against the HK method at t=0, t=60 and t=120 of the OGTT

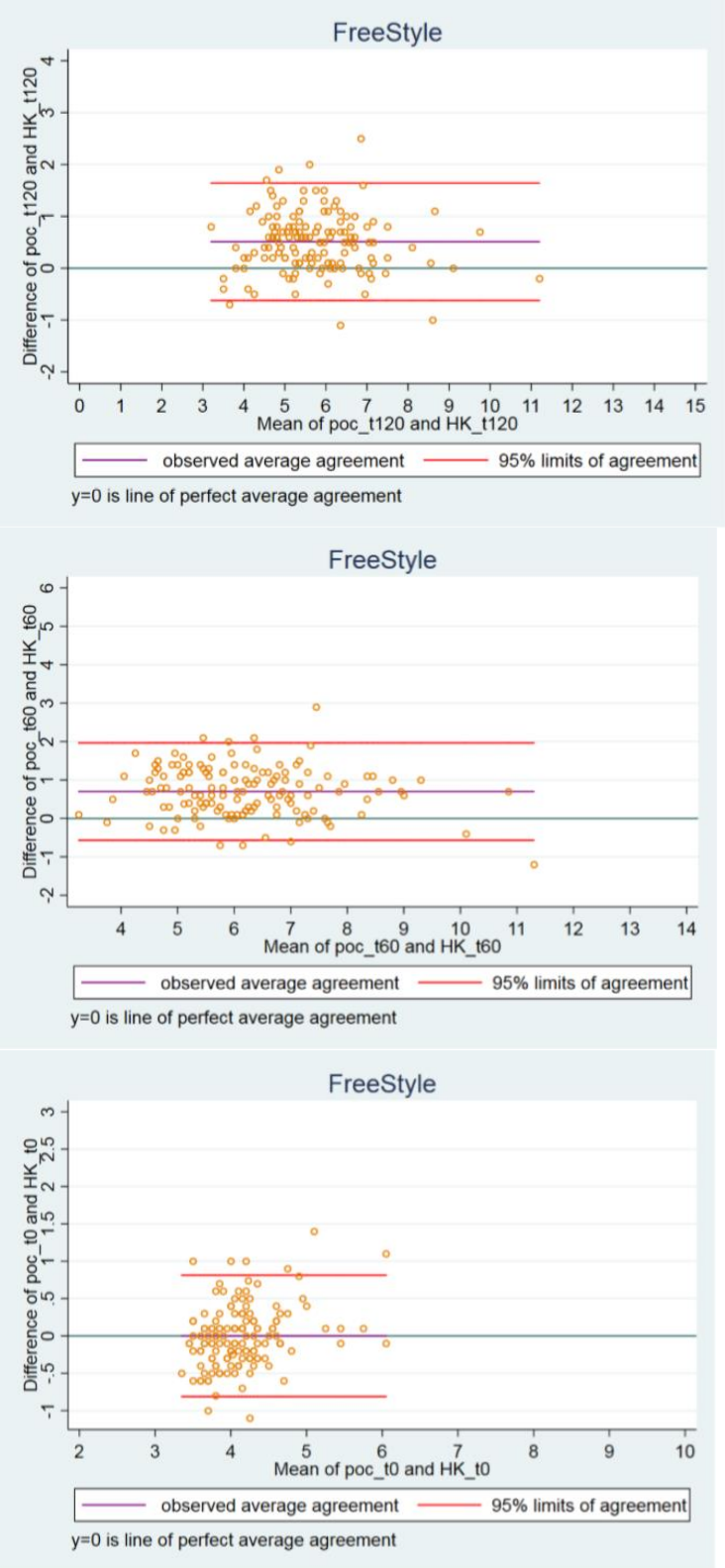
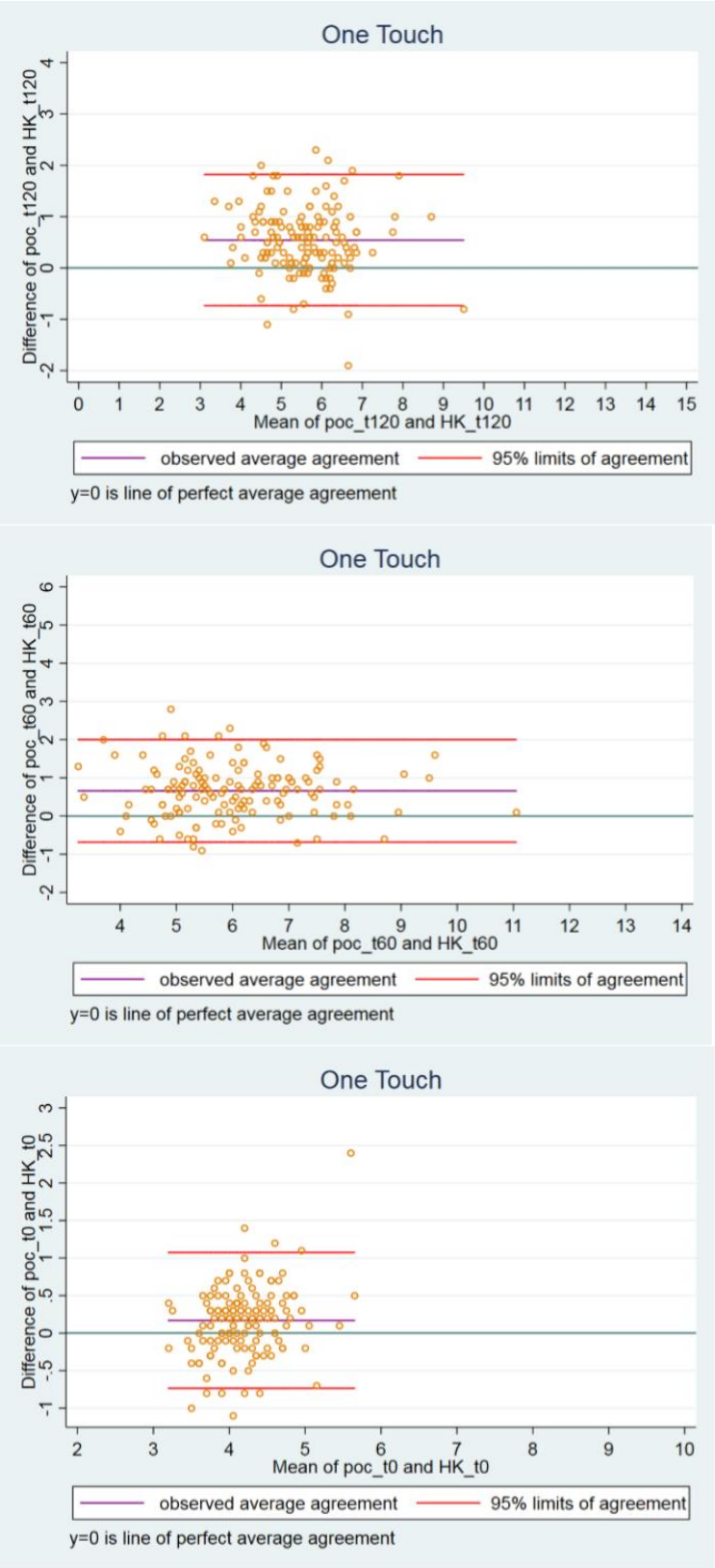


Figure S5. Bland Altman Plots of Glucose concentrations (mmol/l) measured by One touch Select Plus glucometer s against the HK method at t=0, t=60 and t=120 of the OGTT.



ABBREVIATIONS

POC = Point of care glucometer

HK = Hexokinase laboratory method

OGTT = Oral glucose tolerance

B. The HK method and composite laboratory results serve as the reference test o evaluate the accuracy of the glucometers.

Prevalence of GDM

GDM prevalence determined by all test methods (all glucometers and all laboratories) was 16%. The prevalence of GDM as determined by the POCs (all brands) and the composite reference test was 12·7%, and 9·0% respectively. Overt DM was consistently identified by all test methods in three participants (0·5%). Within the reference test, 34% of positive GDM diagnoses (18 of 53 participants) were common to both laboratories. The GOx laboratory identified 23 participants as having GDM that were not identified by the HK laboratory. The HK laboratory had 12 GDM positive results not identified by the GOx laboratory. The POCs identified 42 unique positive GDM cases not detected by the reference test (Supplementary Figure 1.).

Agreement between test methods

The mean blood glucose for all OGTT results at all time points (1776 observations) for the POCs, the GOx and the HK laboratories were 5·6 (1·4) mmol/L, 4·8 (1·4) mmol/L and 5·0 (1·3) mmol/L respectively. The POCs mean glucose was higher than that of the laboratories and the HK result was higher than the GOx laboratory. The laboratory range of plasma glucose concentrations at the time points of zero, 60 and 120 minutes were 2·5–8·3mmol/L, 2·2–14·2mmol/L, and 2·2–16·3mmol/L for the GOx and 3·0–8·8mmol/L, 2·3–13·5mmol/L, and 2·7–14·7mmol/L for the HK laboratory.

Accuracy of POCs against the composite reference test (GOx and HK methods)

The sensitivity and specificity of the POCs varied between glucometer brands. Both the Contour Plus and Freestyle Optium Neo correctly classified eight of the nine (89%) positive GDM participants and both failed to identify one positive participant each compared to the composite reference test. The One Touch Select performed poorly with a sensitivity of 20% and failed to identify eight of the ten participants who had GDM. One in five participants tested with the Glucocheck Classic were falsely identified as having GDM. The Accu-Check Active had the lowest sensitivity (13%), highest specificity (98%) and a high false negative rate compared to the composite reference test. (Supplementary Table 1.)

The positive likelihood ratios (PLR) and negative likelihood ratios (NLR) served as an overall indicator of the diagnostic accuracy of the POCs against the composite reference test. A PLR ≥10 and a NLR ≤0·1 were assumed to be favourable associations.[23] The ability of the Contour Plus and Freestyle Optium Neo to diagnose GDM was superior to that of the other POCs with a PLR of 29·78 and 19·85 respectively as compared to the One Touch Select which had the lowest PLR of 2·7. Both the Contour Plus and the Freestyle Optium Neo had favourable NLRs of 0·11 and 0·12 respectively. The Accu-Chek Active had the poorest NLR of 0·86. (Supplementary Table 1)

We used the area under the ROC curve (AUC) to establish the ability of the POCs to discriminate between a GDM positive and negative state compared to the individual laboratory methods. All the POCs performed less well against the GOx laboratory. The AUC for the Contour Plus, Freestyle Optium Neo, Accu-Chek Active, Glucocheck Classic and One Touch Select against the GOx laboratory were 78·3%; 77·3%; 81%; 80·3% and 63·3%. Against the HK laboratory these were 91·3%; 86·3%; 99·3%; 87·3% and 72%

respectively. The AUC was mostly optimal at zero minutes of the OGTT, but this varied slightly between POC brands. (Supplementary Table 2)

Figure S 6. Venn Diagram Illustrating the Distribution of GDM Positive Participants as Defined by the Different Test Methods.

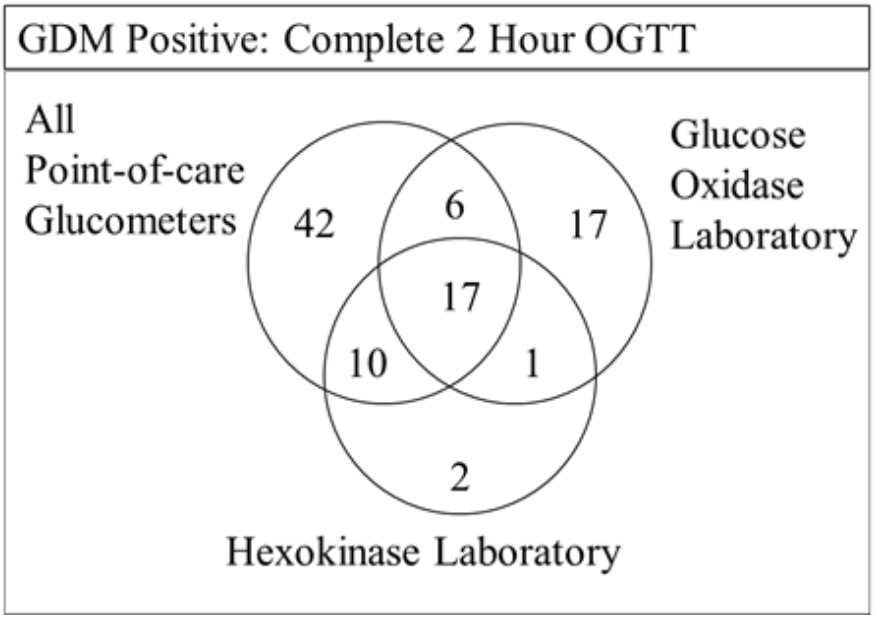


Table S1. Number of GDM positive diagnoses missed by the glucometers, GOx and HK laboratories methods compared with composite of GDM positive results (n=95).

	N.
Number of positive GDM diagnoses missed by the glucometers against all methods	20
Number of positive GDM diagnoses missed by the GOx laboratory against all methods	54
Number of positive GDM diagnoses missed by the HK laboratory against all methods	65

Table S 2. Statistical Analysis Results of the Plasma Calibrated Glucometers Against the Composite Laboratory Reference Test.

	All POCs	Contour Plus (Bayer)	Freestyle Optium Neo (Abbott)	Accu-Chek Active (Roche)	Glucocheck Classic (TaiDoc)	One touch Select (Lifescan)
Number of participants	592	143	143	56	105	145
Number of glucometers used	165	18	32	56	28	31
True Positive	33	8	8	1	14	2
False Positive	42	4	6	1	21	10
True Negative	497	130	128	47	67	125
False Negative	20	1	1	7	3	8
Sensitivity	0·62	0·89	0·89	0·13	0·82	0·20
Specificity	0·92	0·97	0·96	0·98	0·76	0·93
Positive Predictive Value	0·44	0·67	0·57	0·50	0·40	0·17
Negative Predictive Value	0·96	0·99	0·99	0·87	0·96	0·94
Positive Likelihood Ratio	7·99	29·78	19·85	6·00	3·45	2·7
Negative Likelihood ratios	0·41	0·11	0·12	0·89	0·23	0·86

Table S 3. Area Under ROC values by Glucometer Brand Against the Composite and Individual Reference Test at Different Time Points in the OGTT.

Laboratory(s)	POC Glucometers	Time=0min AUC (95% CI)	Time=60min AUC (95% CI)	Time=120min AUC (95% CI)
Composite Reference test	Contour Plus	90% (79; 100)	77% (57; 97)	83% (64; 1.00)
	Accu-Chek Active	92% (83;100)	83% (69; 97)	68% (48; 0.89)
	Glucocheck Classic	80% (66; 94)	82% (71; 92)	81% (72; 0.91)
	Freestyle Optium Neo	82% (64; 100)	75% (48; 100)	81% (60; 1.00)
	One Touch Select	82% (71; 92)	60% (39; 82)	60% (42; 0.78)
Glucose Oxidase Method	Contour Plus	86% (70; 100)	70% (42; 98)	79% (51; 1.00)
	Accu-Chek Active	92% (84; 100)	83% (69; 97)	68% (48; 0.89)
	Glucocheck Classic	78% (63; 93)	81% (69; 92)	82% (72; 0.91)
	Freestyle Optium Neo	77% (50; 100)	79% (44; 100)	76% (38; 1.00)
	One Touch Select	72% (59; 85)	58% (35; 81)	60% (42; 0.78)
Hexokinase Method	Contour Plus	91% (79; 84)	88% (75; 100)	95% (87; 100)
	Accu-Chek Active	98% (94; 100)	100% (100;100)	100% (100; 100)
	Glucocheck Classic	87% (69; 100)	91% (83; 99)	84% (75; 94)
	Freestyle Optium Neo	84% (64; 100)	83% (60; 100)	92% (83; 100)
	One Touch Select	94% (88; 100)	63% (18; 100)	59% (20; 99)

Table S4. Summary statistics of glucose values measured by POC, GOx and HK at fasting, 1hr, and 2hr of the OGTT

Variable	POC t0	GOx t0	HK t0	POC t60	GOx t60	HK t60	POC t120	GOx t120	HK t120
mean	4.35	4.01	4.13	6.58	5.42	5.62	6.00	5.12	5.27
Sd	0.65	0.75	0.49	1.34	1.51	1.39	1.18	1.37	1.21
variance	0.42	0.56	0.24	1.79	2.27	1.93	1.38	1.88	1.46
cv	0.15	0.19	0.12	0.20	0.28	0.25	0.20	0.27	0.23

C. Passing Bablok analysis of comparison between methods

Figure S6. Passing Bablok Fit: Glucometers against the GOx laboratory results

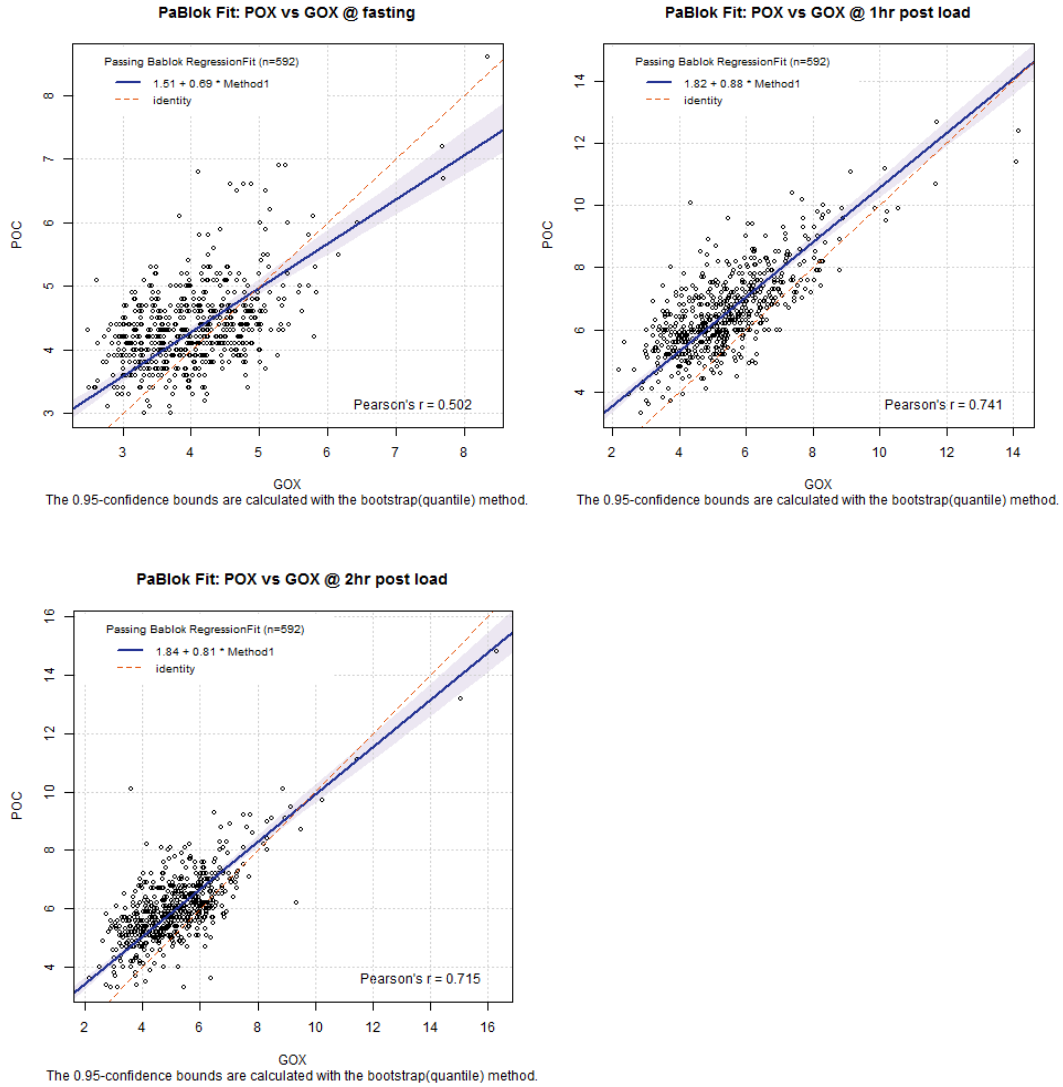


Figure S7. Passing Bablok Fit: Glucometers against the HK laboratory results

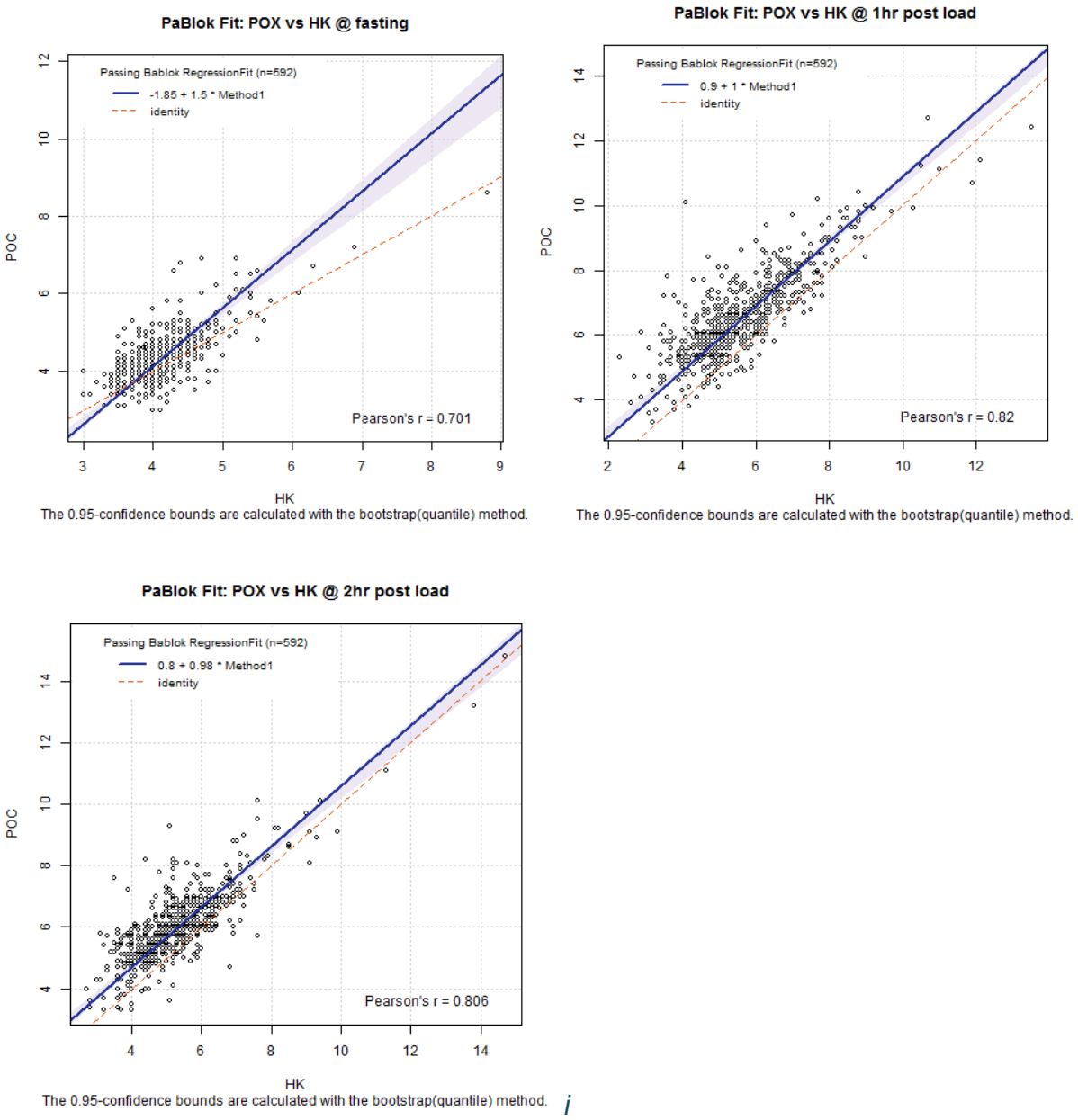


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*Figure S8. P*assing Bablok Fit: HK against the GOx laboratory method results

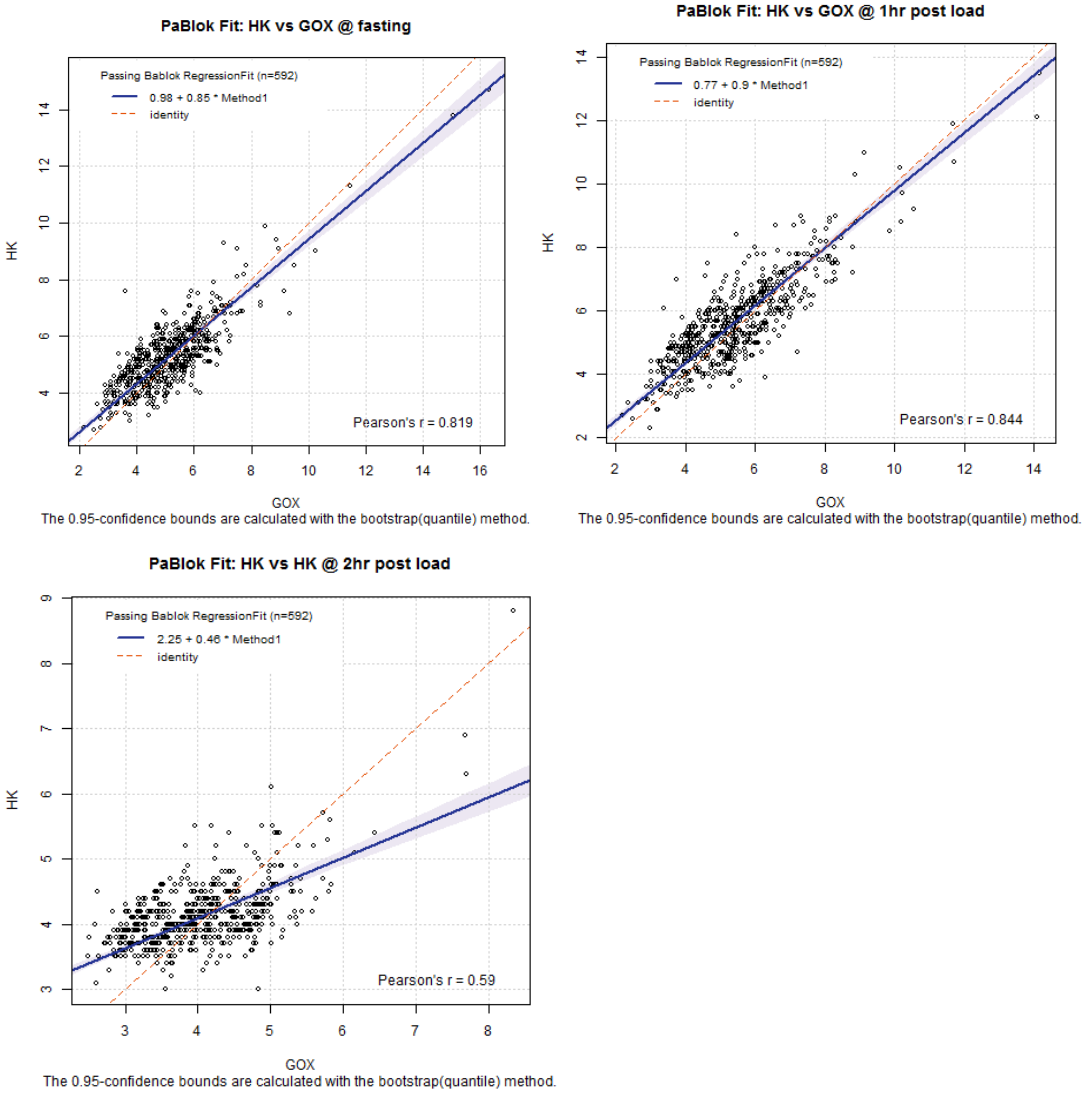
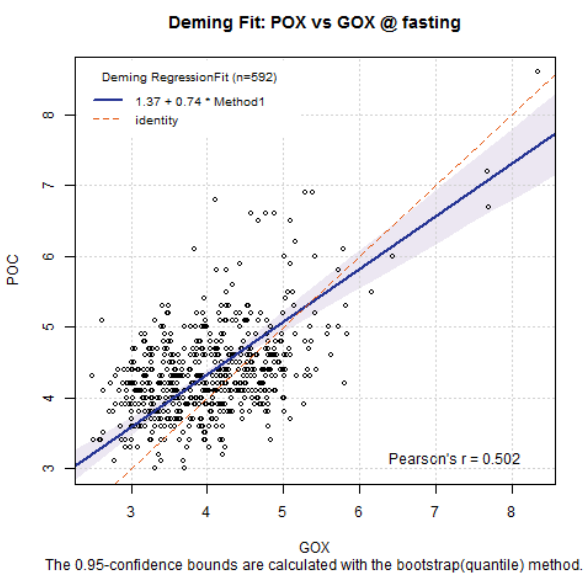


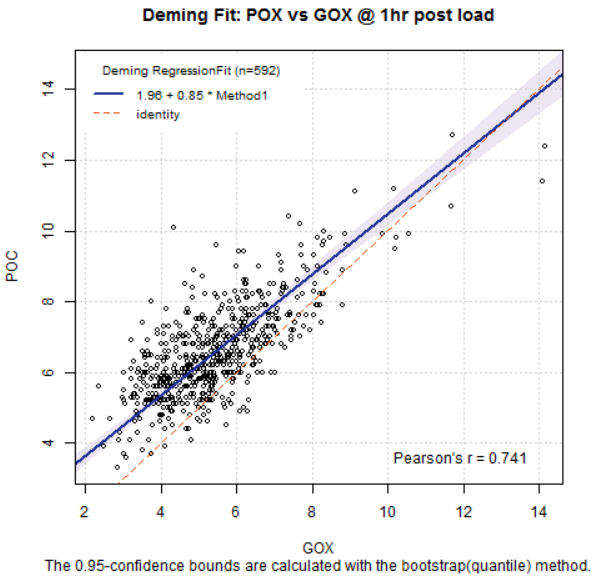
Table S5. Passing Bablok Summary Statistics of Glucose values Measured by POC, GOx anf HK at Fasting, 1hr and 2hr of the OGTT

						95% CI	
Regression method	New methods	Old method	Time point	effect	int/slope estimate	LCI	UCI
passing bablok	poc	hk	0	Intercept.9	-1.85	-2.24	-1.17
passing bablok	poc	hk	0	Slope.9	1.50	1.33	1.60
passing bablok	poc	hk	60	Intercept.10	0.90	0.90	1.36
passing bablok	poc	hk	60	Slope.10	1.00	0.93	1.00
passing bablok	poc	hk	120	Intercept.11	0.80	0.60	1.20
passing bablok	poc	hk	120	Slope.11	0.98	0.90	1.00
passing bablok	poc	gox	0	Intercept.12	1.51	1.18	1.80
passing bablok	poc	gox	0	Slope.12	0.69	0.62	0.78
passing bablok	poc	gox	60	Intercept.13	1.82	1.49	2.10
passing bablok	poc	gox	60	Slope.13	0.88	0.82	0.94
passing bablok	poc	gox	120	Intercept.14	1.84	1.50	2.11
passing bablok	poc	gox	120	Slope.14	0.81	0.75	0.87
passing bablok	hk	gox	120	Intercept.15	0.98	0.73	1.21
passing bablok	hk	gox	120	Slope.15	0.85	0.80	0.90
passing bablok	hk	gox	60	Intercept.16	0.77	0.53	1.01
passing bablok	hk	gox	60	Slope.16	0.90	0.86	0.95
passing bablok	hk	gox	0	Intercept.17	2.25	2.07	2.44
passing bablok	hk	gox	0	Slope.17	0.46	0.41	0.51

D. Deming regression analysis of comparison between methods

Figure S9. Deming Regression Plots For Glucometers against GOx Laboratory method results





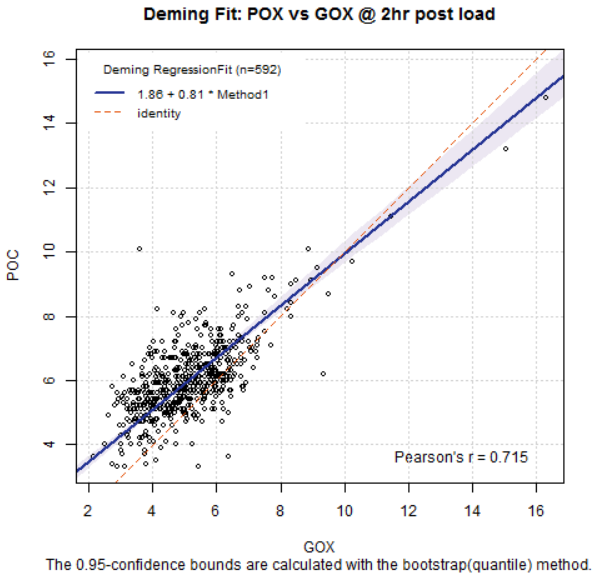


Figure S10. Deming regression plots for Glucometers against the HK laboratory method results

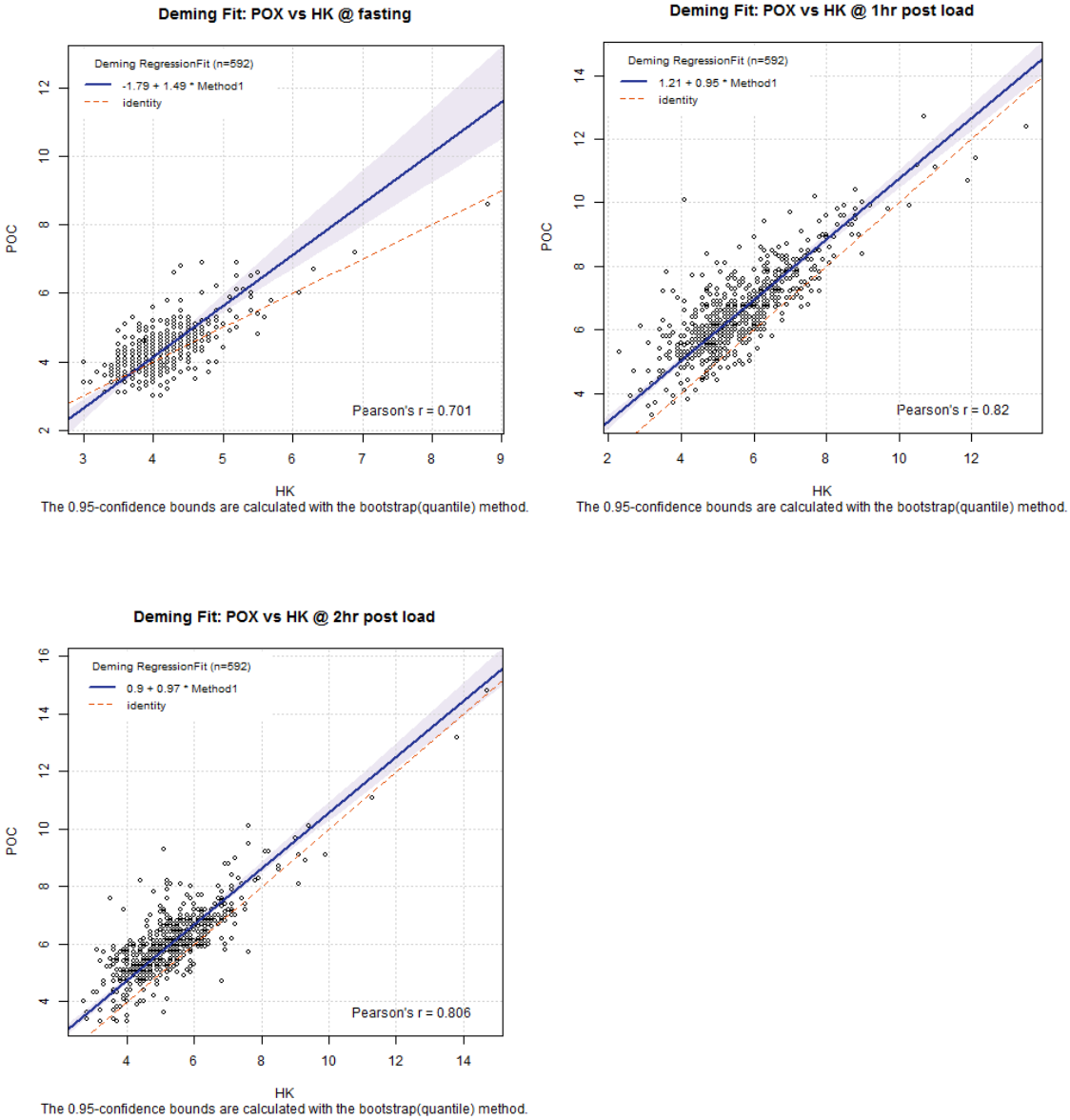
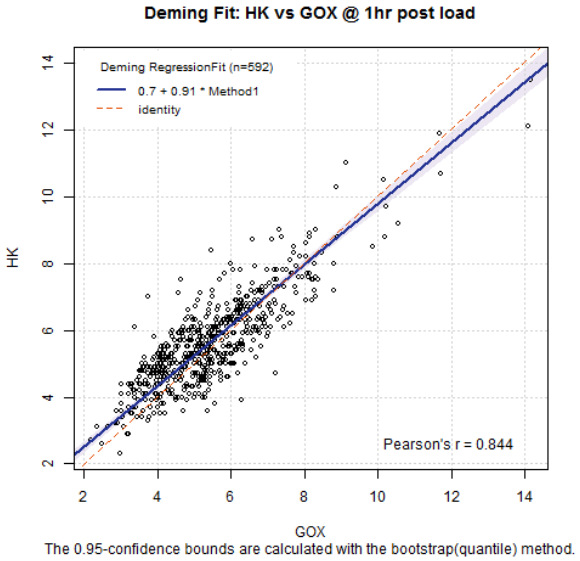
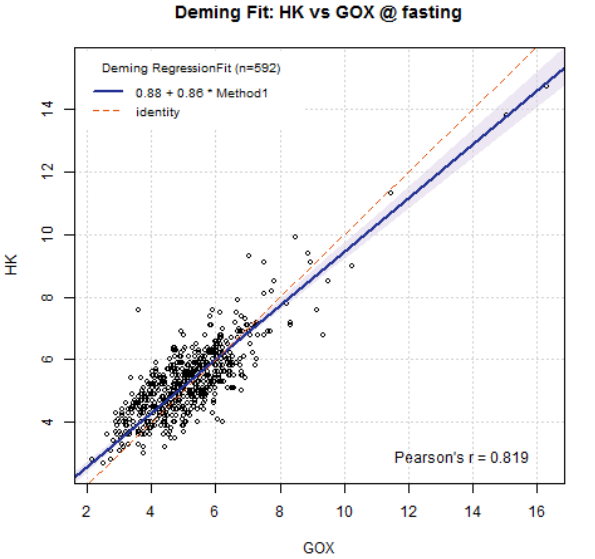


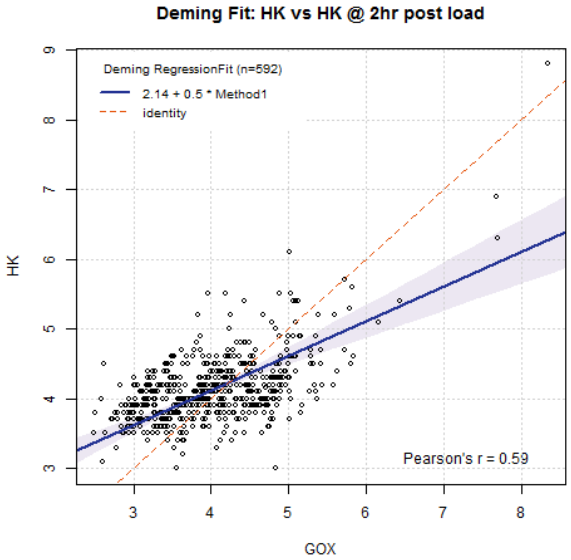
Figure S11. Deming Regression Plots for HK and GOx laboratory methods



The 0.95-confidence bounds are calculated with the bootstrap(quantile) method.



The 0.95-confidence bounds are calculated with the bootstrap(quantile) method.



The 0.95-confidence bounds are calculated with the bootstrap(quantile) method.

Table S6. Deming Regression Summary Statistics of Glucose values Measured by POC, GOx anf HK at Fasting, 1hr and 2hr of the OGTT

						95% CI	
Regression method	New methods	Old method	Time point	effect	int/slope estimate	LCI	UCI
deming	poc	hk	0	Intercept	-1.79	-3.10	-0.92
deming	poc	hk	0	Slope	1.49	1.27	1.81
deming	poc	hk	60	Intercept.1	1.21	0.86	1.54
deming	poc	hk	60	Slope.1	0.95	0.90	1.02
deming	poc	hk	120	Intercept.2	0.90	0.54	1.20
deming	poc	hk	120	Slope.2	0.97	0.91	1.04
deming	poc	gox	0	Intercept.3	1.37	0.89	1.87
deming	poc	gox	0	Slope.3	0.74	0.62	0.86
deming	poc	gox	60	Intercept.4	1.96	1.58	2.33
deming	poc	gox	60	Slope.4	0.85	0.79	0.92
deming	poc	gox	120	Intercept.5	1.86	1.53	2.14
deming	poc	gox	120	Slope.5	0.81	0.76	0.88
deming	hk	gox	120	Intercept.6	0.88	0.59	1.12
deming	hk	gox	120	Slope.6	0.86	0.81	0.91
deming	hk	gox	60	Intercept.7	0.70	0.43	0.94
deming	hk	gox	60	Slope.7	0.91	0.87	0.96
deming	hk	gox	0	Intercept.8	2.14	1.70	2.56
deming	hk	gox	0	Slope.8	0.50	0.39	0.61

E. Pitmans Test Results

Table S7. Pitmans test for equal variances (assuming bivar normality) for 5992 participants

Variable	POC_GOx t0	POC_GOx t60	POC_GOx t=120	POC_HK t0	POC_HK t60	POC_HK t120	GOx_HK t=0	GOx_HK t60	GOx_HK_t120
Bland–Altman comparison	LoA -1.07–1.74 Mean=0.34 (CI 0.28 – 0.40)	LoA -0.91–3.23 Mean=1.16 (CI 1.08 – 1.24)	LoA -1.08–2.84 Mean=0.88 (CI 0.80 – 0.96)	LoA -0.71–1.14 Mean=0.22 (CI 0.18 – 0.26)	LoA -0.68–2.59 Mean=0.96 (CI 0.89 – 1.02)	LoA -0.76–2.22 Mean=0.73 (CI 0.67 – 0.79	LoA -1.34–1.10 Mean -0.12 (CI -0.17 – -0.17)	LoA -1.83–1.43 Mean= -0.20 (CI -0.27 – -0.14)	LoA -1.73–1.43 Mean -0.15 (CI -0.22– -0.09)
Pitman's test of Difference in variance	r= -1.17 p<0.001	r= -0.18 p<0.001	r= -0.21 p<0.001	r= 0.31 p<0.001	r= -0.07 p=0.108	r= -0.05 p=0.280	r= 0.48 p<0.001	r=0.150 p<0.001	r=0.22 p<0.001

F. Analysis of Cutpoints of Fasting Plasma Glucose Concentrations

Figure 12. Analysis of Cutpoints of Fasting Plasma Glucose Concentrations – GOx laboratory method

Analysis of Cutpoints of Fasting Plasma Glucose Concentrations – GOX laboratory method						
Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-	Youden
3	100,00%	0,00%	6,96%	1		0,00%
3,1	100,00%	0,18%	7,13%	1,0018	0	0,18%
3,2	100,00%	0,73%	7,64%	1,0074	0	0,73%
3,3	100,00%	1,09%	7,98%	1,0111	0	1,09%
3,4	100,00%	2,19%	9,00%	1,0224	0	2,19%
3,5	100,00%	5,47%	12,05%	1,0579	0	5,47%
3,6	100,00%	6,57%	13,07%	1,0703	0	6,57%
3,7	100,00%	10,40%	16,64%	1,1161	0	10,40%
3,8	100,00%	15,15%	21,05%	1,1785	0	15,15%
3,9	97,56%	20,80%	26,15%	1,2319	0,1172	18,36%
4	95,12%	27,19%	31,92%	1,3064	0,1794	22,31%
4,1	92,68%	33,39%	37,52%	1,3915	0,2191	26,07%
4,2	92,68%	43,43%	46,86%	1,6384	0,1685	36,11%
4,3	90,24%	51,46%	54,16%	1,8592	0,1896	41,70%
4,4	80,49%	59,31%	60,78%	1,9779	0,329	39,80%
4,5	75,61%	67,52%	68,08%	2,3278	0,3612	43,13%
4,6	75,61%	72,26%	72,50%	2,7259	0,3375	47,87%
4,7	68,29%	79,01%	78,27%	3,2543	0,4013	47,30%
4,8	65,85%	84,85%	83,53%	4,3479	0,4024	50,70%
4,9	60,98%	87,77%	85,91%	4,9873	0,4446	48,75%
5	51,22%	89,60%	86,93%	4,9243	0,5444	40,82%
5,1	43,90%	91,61%	88,29%	5,2301	0,6124	35,51%
5,2	43,90%	94,16%	90,66%	7,5183	0,5958	38,06%
5,3	41,46%	95,99%	92,19%	10,3281	0,6098	37,45%
5,4	36,59%	97,26%	93,04%	13,3659	0,652	33,85%
5,5	34,15%	97,45%	93,04%	13,3659	0,6758	31,60%
5,6	29,27%	97,99%	93,21%	14,5809	0,7218	27,26%
5,8	29,27%	98,18%	93,38%	16,039	0,7205	27,45%
5,9	26,83%	98,54%	93,55%	18,378	0,7425	25,37%
6	24,39%	98,72%	93,55%	19,094	0,7659	23,11%
6,1	19,51%	98,91%	93,38%	17,8212	0,8138	18,42%
6,2	17,07%	99,09%	93,38%	18,7122	0,8369	16,16%
6,5	14,63%	99,09%	93,21%	16,0391	0,8615	13,72%
6,6	12,20%	99,27%	93,21%	16,7073	0,8845	11,47%
6,7	12,20%	99,82%	93,72%	66,83	0,8797	12,02%
6,8	9,76%	99,82%	93,55%	53,464	0,9041	9,58%
6,9	9,76%	100,00%	93,72%	0,9024		9,76%
7,2	4,88%	100,00%	93,38%	0,9512		4,88%
8,6	2,44%	100,00%	93,21%	0,9756		2,44%
8,6	0,00%	100,00%	93,04%	1		0,00%

Figure 13. Analysis of Cutpoints of Fasting Plasma Glucose Concentrations – HK laboratory method

Analysis of Cutpoints of Fasting Plasma Glucose Concentrations – HK laboratory method

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-	Youden
3	100,00%	0,00%	5,09%	1		0,00%
3,1	100,00%	0,18%	5,26%	1,0018	0	0,18%
3,2	100,00%	0,72%	5,77%	1,0072	0	0,72%
3,3	100,00%	1,07%	6,11%	1,0108	0	1,07%
3,4	100,00%	2,15%	7,13%	1,0219	0	2,15%
3,5	100,00%	5,37%	10,19%	1,0567	0	5,37%
3,6	100,00%	6,44%	11,21%	1,0688	0	6,44%
3,7	100,00%	10,20%	14,77%	1,1135	0	10,20%
3,8	100,00%	14,85%	19,19%	1,1744	0	14,85%
3,9	96,67%	20,39%	24,28%	1,2143	0,1635	17,06%
4	96,67%	26,83%	30,39%	1,3212	0,1242	23,50%
4,1	90,00%	32,74%	35,65%	1,338	0,3055	22,74%
4,2	90,00%	42,58%	44,99%	1,5673	0,2349	32,58%
4,3	90,00%	50,63%	52,63%	1,8228	0,1975	40,63%
4,4	86,67%	58,86%	60,27%	2,1064	0,2265	45,53%
4,5	86,67%	67,26%	68,25%	2,6474	0,1982	53,93%
4,6	86,67%	71,91%	72,67%	3,0858	0,1854	58,58%
4,7	86,67%	79,07%	79,46%	4,1407	0,1686	65,74%
4,8	83,33%	84,79%	84,72%	5,4804	0,1966	68,12%
4,9	80,00%	87,84%	87,44%	6,5765	0,2277	67,84%
5	73,33%	89,98%	89,13%	7,3202	0,2964	63,31%
5,1	70,00%	92,31%	91,17%	9,1	0,325	62,31%
5,2	70,00%	94,81%	93,55%	13,4931	0,3164	64,81%
5,3	70,00%	96,78%	95,42%	21,7389	0,31	66,78%
5,4	63,33%	98,03%	96,26%	32,1849	0,374	61,36%
5,5	56,67%	98,03%	95,93%	28,797	0,442	54,70%
5,6	46,67%	98,39%	95,76%	28,9852	0,5421	45,06%
5,8	46,67%	98,57%	95,93%	32,6085	0,5411	45,24%
5,9	43,33%	98,93%	96,10%	40,3724	0,5728	42,26%
6	36,67%	98,93%	95,76%	34,1612	0,6402	35,60%
6,1	30,00%	99,11%	95,59%	33,54	0,7063	29,11%
6,2	23,33%	99,11%	95,25%	26,0867	0,7736	22,44%
6,5	23,33%	99,28%	95,42%	32,6081	0,7722	22,61%
6,6	16,67%	99,28%	95,08%	23,2915	0,8393	15,95%
6,7	13,33%	99,64%	95,25%	37,2668	0,8698	12,97%
6,8	10,00%	99,64%	95,08%	27,9501	0,9032	9,64%
6,9	10,00%	99,82%	95,25%	55,899	0,9016	9,82%
7,2	6,67%	100,00%	95,25%	0,9333		6,67%
8,6	3,33%	100,00%	95,08%	0,9667		3,33%
8,6	0,00%	100,00%	94,91%	1		0,00%

IV. Published manuscripts and/or letter of acceptance

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Original research

Accuracy of five plasma calibrated glucometers to screen for and diagnose gestational diabetes mellitus in a low resource clinic setting

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ABSTRACT

Aims: We investigated the clinical and analytic accuracy of five plasma calibrated glucometers, the use of which is advocated by the World Health Organisation and the International Federation of Gynaecology and Obstetrics, to screen for and diagnose gestational diabetes mellitus (GDM) in low resource settings.
Methods: 592 consecutive black African women underwent a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks gestation at an urban South African community health clinic. Capillary glucose was measured by one of five glucometer brands, each paired with a routine laboratory hexokinase method of plasma glucose measurement. The laboratory results served as the gold standard reference test for GDM diagnosis. World Health Organisation GDM diagnostic thresholds were applied to glucometer and laboratory results.
Results: Glucometer and laboratory determined GDM prevalence was 75/592 (12.7%) and 30/592 (5.1%) with an elevated fasting glucose diagnostic in 64/75 (85%) and 24/30 (80%) of cases respectively. The proportion of glucometer results fulfilling ISO 15197:2013 recommended analytic accuracy at fasting, 60, and 120 min of the OGTT was 92.4%, 49.8% and 61.5%, with Bland Altman method revealing a positive glucometer bias of 0.22 mmol/l (−0.69–1.12 mmol/l), 0.96 mmol/l (−0.65–2.56 mmol/l) and 0.73 mmol/l (−0.73–2.19 mmol/l) respectively. Only three of the glucometer brands evaluated fulfilled ISO 15197:2013 analytic accuracy requirements and this was only achieved at fasting. All glucometers tested were inaccurate at one and two hours of the OGTT.
Conclusions: Not all glucometers may be suitable for GDM screening as only three were accurate compared to the reference test and then only at fasting of the OGTT. Importantly, laboratory fasting glucose was diagnostic of GDM in 80% of cases in this study population.

Introduction

The prevalence of Gestational Diabetes Mellitus (GDM) is increasing in parallel with that of type 2 diabetes mellitus. Identifying this usually transient and asymptomatic condition will allow clinical interventions to reduce the perinatal morbidity associated with these high-risk pregnancies [1]. An estimated 16% of pregnancies are affected globally [2]. The World Health Organization (WHO) has adopted the diagnostic criteria for GDM advocated by the International Association of Diabetes in Pregnancy Study Group (IADPSG) [1,3]. Universal screening by means of a 75 g two-hour oral glucose tolerance test (OGTT) at 24–28 weeks gestation is recommended [1]. Several low-middle income countries have adopted the WHO diagnostic criteria, including the recommendation for universal screening for GDM. In 2017, the Society for Endocrinology, Metabolism, and Diabetes of South Africa (SEMDSA) adopted these guidelines [4]. The South African National Department of Health's policy is guided by the WHO and SEMDSA recommendations, although universal screening for GDM has not yet been implemented in South Africa. Potential barriers to implementing universal screening in low resourced clinic settings include the limitations of administering

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The impact of differences in plasma glucose between glucose oxidase and hexokinase methods on estimated gestational diabetes mellitus prevalence

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We evaluated the extent of measurement discordance between glucose oxidase and hexokinase laboratory methods and the effect of this on estimated gestational diabetes mellitus (GDM) prevalence in a routine clinical setting. 592 consecutive urban African women were screened for GDM. Paired venous specimens were submitted to two independent calibrated laboratories that used either method to measure plasma glucose concentrations. World Health Organisation diagnostic criteria were applied. GDM prevalence determined by the glucose oxidase and hexokinase methods was 6.9% and 5.1% respectively. The overall GDM prevalence was 9%. Only 34% of GDM positive diagnoses were common to both laboratory methods. Bland Altman plots identified a bias of 0.2 mmol/l between laboratory methods. Plasma glucose concentrations measured by the glucose oxidase method were more platykurtic in distribution. Low diagnostic agreement between laboratory methods was further indicated by a Cohen's kappa of 0.48 ($p < 0.001$). Reports of GDM prevalence using either the glucose oxidase or hexokinase laboratory methods may not be truly interchangeable or directly comparable.

Identifying usually asymptomatic gestational diabetes mellitus (GDM) will allow interventions to improve perinatal and long-term outcomes for both mother and her child[1,2]. In the Hyperglycaemia and Adverse Pregnancy Outcome study, which investigated the relationship between glycemia and birth outcomes, stringent research laboratory standards were applied across multiple research centres[3]. Evidence from controlled research laboratory settings, rather than routine clinical settings, informed the GDM clinical diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Group (IADPSG)[1]. These recommendations were later adopted by the World Health Organisation (WHO)[2]. The WHO recommended gold standard 75 g oral glucose tolerance test (OGTT), which is used in both research and routine clinical settings to identify dysglycaemia, describes blood sample collection and transport methods[4]. However, it does not indicate a standardized laboratory method of measurement of plasma glucose concentrations[4].

Laboratory methods commonly used to measure plasma glucose concentrations include the enzymatic glucose oxidase (GOx) and hexokinase (HK) methods[5]. It has been reported that results of the HK method are negatively biased relative to the GOx method[6,7] but this does not affect the estimated prevalence of overt diabetes mellitus[5]. GDM has lower diagnostic thresholds than dysglycaemia in a non-pregnant adult[2,4]. Typically, GDM prevalence studies use either GOx[3,8–11] or HK laboratory methods[12–14] to measure plasma glucose concentrations. Meta-analyses on GDM prevalence often do not distinguish between laboratory methods used to measure plasma glucose concentrations[15–20]. The effect of measurement discordance between laboratory methods on the determined prevalence of GDM remains unknown. The presence of significant discordance between laboratory

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SAMJ RESEARCH

Fasting plasma glucose and risk factor assessment: Comparing sensitivity and specificity in identifying gestational diabetes in urban black African women

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Background. Identifying women with gestational diabetes mellitus (GDM) allows interventions to improve perinatal outcomes. A fasting plasma glucose (FPG) level ≥5.1 mmol/L is 100% specific for a diagnosis of GDM. The International Association of Diabetes and Pregnancy Study Groups acknowledges that FPG <4.5 mmol/L is associated with a low probability of GDM.
Objectives. The validity of selective screening based on the presence of risk factors was compared with the universal application of FPG ≥4.5 mmol/L to identify women with GDM. FPG ≥4.5 mmol/L or the presence of one or more risk factors was assumed to indicate an intermediate to high risk of GDM and therefore the need for an oral glucose tolerance test (OGTT).
Methods. Consecutive black South African (SA) women were recruited to a 2-hour 75 g OGTT at 24 - 28 weeks' gestation in an urban community health clinic. Of 969 women recruited, 666 underwent an OGTT, and of these 589 were eligible for analysis. The glucose oxidase laboratory method was used to measure plasma glucose concentrations. The World Health Organization GDM diagnostic criteria were applied. All participants underwent a risk factor assessment. The χ^2 test was used to determine associations between risk factors and a positive diagnosis of GDM. The sensitivity and specificity of a positive diagnosis of GDM were calculated for FPG ≥4.5 mmol/L, FPG ≥5.1 mmol/L, and the presence of one or more risk factors.
Results. The prevalence of overt diabetes mellitus and GDM was 0.5% and 7.0%, respectively. Risk factor-based selective screening indicated that 204/589 (34.6%) of participants needed an OGTT, but 18/41 (43.9%) of positive GDM diagnoses were missed. Universal screening using the FPG threshold of ≥4.5 mmol/L indicated that 152/589 (25.8%) of participants needed an OGTT, and 1/41 (2.4%) of positive diagnoses were missed. An FPG of ≥5.1 mmol/L identified 36/41 (87.8%) of GDM-positive participants. The sensitivity and specificity of the presence of one or more risk factors were 56% and 67%, respectively. The sensitivity and specificity of FPG ≥4.5 mmol/L were 98% and 80%, respectively.
Conclusions. Universal screening using FPG ≥4.5 mmol/L had greater sensitivity and specificity in identifying GDM-affected women and required fewer women to undergo a resource-intensive diagnostic OGTT than risk-factor based selective screening. A universal screening strategy using FPG ≥4.5 mmol/L may be more efficient and cost-effective than risk factor-based selective screening for GDM in black SA women.

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The World Health Organization (WHO) estimates that 16% of pregnancies are affected by gestational diabetes mellitus (GDM) globally.[1] Although there is a paucity of data on South African (SA) women, GDM prevalences of 9.1% and 25.8% have recently been reported.[2,3] Identifying affected women allows interventions to improve perinatal outcomes.[4] Both screening strategies and diagnostic thresholds for GDM attract controversy.[5] The International Association of Diabetes and Pregnancy Study Groups (IADPSG) advocates universal screening for GDM, but the WHO recommends that screening strategies be based on disease burden and the availability of resources.[4,6] Risk factor-based selective screening for GDM is currently applied in SA.[7] A selective screening strategy may fail to identify a high proportion of women affected by GDM.[8-10] In addition to being inadequate, this strategy is difficult to implement and women at risk may not be offered screening, even in well-resourced settings.[11,12]

An alternative to selective or universal application of the oral glucose tolerance test (OGTT) is universal screening using the fasting plasma glucose (FPG) level. According to the WHO 2013 recommendation,[4] an elevated FPG of ≥5.1 mmol/L is 100% specific for a GDM diagnosis. However, the sensitivity of this diagnostic threshold varies between countries and ethnicities.[13] The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study group has suggested that 'in populations in which FPG is diagnostic in more than half of those with GDM, it may be reasonable to perform an accurately measured FPG as an initial step, reserving a full OGTT for those with a non-diagnostic FPG'.[13] The IADPSG acknowledges the low probability of GDM and the low risk of adverse outcomes in the HAPO study cohort associated with FPG <4.5 mmol/L.[14] Women with an FPG <4.5 mmol/L are therefore at low risk of GDM and may not require an OGTT. Because women with an FPG ≥4.5 mmol/L are at intermediate to high risk for GDM,

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