PREAMBLE

DECLARATION

I, Mathilda Christina Mennen (MNNMAT003), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it is has been, is being, or is to be submitted for another degree at this or any university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 25 January 2024

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I would like to acknowledge the following co-authors on this paper:

Dr Hlengi Madlala
Division of Epidemiology and Biostatistics
School of Public Health
University of Cape Town

Prof Landon Myer
Division of Epidemiology and Biostatistics
School of Public Health
University of Cape Town

DISSERTATION ABSTRACT

Background: Gestational diabetes mellitus (GDM) poses substantial risks to both mothers and their offspring. In South Africa, screening practices vary, and pregnant women are not screened universally due to resource constraints. This study investigates the implications of using point-of-care (POC) capillary glucose measures for GDM screening and explores potential strategies to increase screening capacity by eliminating the reliance on central laboratory facilities or reducing the time spent at antenatal facilities for mothers.

Objectives: The prevalence of GDM determined by venous blood glucose (VBG) measures obtained during 2-hour oral glucose tolerance tests (OGTTs) was compared to POC capillary glucose (CBG) tests with immediate results. The agreement between VBG and CBG measures was calculated across the whole cohort and in sub-groups, and the clinical and cost implications of each method explored.

Methods: A secondary analysis was conducted on data collected from 400 pregnant participants who were enrolled at 24-28 weeks' gestation into a prospective cohort study at an antenatal clinic in Cape Town. Participants were screened for GDM using a gold-standard 75g OGTT and simultaneously underwent POC capillary glucose testing. GDM was diagnosed via each method according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. We calculated the sensitivity and specificity of CBG in detecting VBG-defined GDM at different thresholds and Bland-Altman analyses examined agreement between CBG and VBG.

Results: The GDM prevalence was 7% among all participants, resulting from a prevalence of 6% among patients with no risk factors, and 8% among patients with risk factors. Four percent of the cohort was diagnosed with GDM despite having no risk factors. Most cases (96%) were diagnosed on fasting venous measures. Capillary measures overestimated the prevalence of GDM at IADPSG thresholds (25%) and had poor sensitivity (73%). Correlation between venous and capillary measures was lowest in the fasting state ($r=0.22$, $p<0.001$). Bland Altman analyses found the average agreement between methods to be lowest in the fasting state.

Conclusion: Capillary measures demonstrate poor correlation and agreement with venous measures at 24-28 weeks' gestation, particularly in the fasting state when almost all GDM cases are diagnosed. A fasting plasma glucose, if performed universally as a single measure, outperforms selective risk factor-based OGTT screening and fasting capillary blood glucose in terms of sensitivity and specificity, while reducing the overall number of laboratory-dependent glucose tests performed.

LIST OF ABBREVIATIONS

BMI = Body Mass Index

CBG = Capillary Blood Glucose

FPG = fasting plasma glucose

FCG = fasting capillary glucose

GDM = Gestational Diabetes Mellitus

IADPSG = International Association of Diabetes and Pregnancy Study Groups

MOU = Midwife Obstetrics Unit

NCD = Non-Communicable Disease

NHLS = National Health Laboratory Service (South Africa)

OGTT = Oral Glucose Tolerance Test

POC = Point-of-care

ROC = Receiver Operator Characteristics

T2DM = Type 2 Diabetes Mellitus

VBG = Venous Blood Glucose

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PART A: RESEARCH PROTOCOL

PROTOCOL SUMMARY

Title	An Evaluation of Diagnostic Approaches for Gestational Diabetes Screening in South Africa
Research questions	1. In a cohort of pregnant women receiving antenatal care at Gugulethu MOU in South Africa, what is the prevalence of GDM when using 2-hour OGTT (VBG) compared to POC capillary blood glucose (CBG) tests, in the context of both universal and selective risk factor-based screening? 2. What is the agreement between VBG and CBG and what are the clinical implications of each method? 3. Is the agreement better within certain subgroups of pregnant women?
Aims and objectives	1. To compare the prevalence of GDM determined via 2-hour OGTT (VBG) vs POC capillary blood glucose (CBG) tests with immediate results, in the context of both universal and selective risk factor-based screening 2. To calculate the agreement between VBG (reference) and CBG (comparative) measures and explore the clinical implications of each method 3. To determine whether the agreement changes in certain sub-groups of pregnant women, comparing BMI categories, age categories and HIV status

BACKGROUND AND RATIONALE

Introduction

Development of gestational diabetes mellitus (GDM) in pregnancy is not only a major contributor to adverse pregnancy and birth outcomes including stillbirths and neonatal death, but also elevates the risk of non-communicable diseases (NCDs) such as obesity, type II

diabetes mellitus and cardiovascular disease later in life for both mothers and their offspring.[1-4]

Pregnancy itself is a metabolically vulnerable state, and is characterised by insulin resistance and hyperinsulinaemia which predisposes women to the development of GDM.[5] GDM is further linked to the nutrition transition South Africa has undergone in recent years, which has led to rising levels of obesity and NCDs.[6] Rapid urbanisation along with low income has resulted in increased consumption of processed foods that are energy dense but nutrient poor.[6] Consequently, South Africa has become one of the world's most obese nations, with the highest prevalence of obesity in sub-Saharan Africa present among South African women of childbearing age.[5, 7]

Global trends

Maternal obesity is associated with a substantially higher risk of GDM.[6, 8] The risk for GDM increases with BMI, and has been reported to be 4-9 times higher for obese women compared to normal weight women.[6] GDM in turn is well-known to increase the risk of obesity in children and postpartum glucose disorders in women.[5, 8] The HAPO study, a recent multi-national prospective cohort of nearly 5000 mother-infant pairs, demonstrated, in keeping with prior findings, that GDM was associated with a 3-fold increased odds at 10-14 years postpartum of a maternal glucose disorder, as well as a higher prevalence of obesity in children.[4, 9] It also found that the risk for foetal and maternal morbidity exists on a spectrum and is proportional to the degree of hyperglycaemia experienced in pregnancy.[9] Although mild hyperglycaemia in pregnancy may be of limited clinical concern in the short term, it is suspected that even mild foetal exposure to hyperglycaemia immortalizes the obesity cycle and increases transgenerational metabolic risks, which are yet to be accurately quantified.[7] Strategies to improve prevention, early detection and optimal management of both maternal obesity and GDM are therefore of increasing importance to interrupt intergenerational cycles of rising obesity and diabetes.

The South African context

In South Africa, GDM or glucose intolerance that is initially detected during pregnancy affects up to 26% of women, although discrepancies do exist in reported prevalence statistics.[5] This is due to GDM screening and diagnostic approaches still varying substantially between hospitals

and provinces and remaining disorderly.[5] International organisations have recommended a vast range of screening and diagnostic algorithms for GDM. The International Association for Diabetes in Pregnancy Study Group (IADPSG) proposes selective screening of high risk women (women with one or more risk factor) at booking to improve early detection of undiagnosed diabetes.[7] Diabetic screening in the non-pregnant population of South Africa occurs minimally, therefore glucose abnormalities are often first detected in pregnancy, including Type 2 Diabetes Mellitus.[7] Furthermore, the IADPSG encourages universal screening for GDM with a 75g 2-hour OGTT at 24-28 weeks' gestation.[7]

Universal screening via OGTT is not feasible in South Africa's resource-limited public health sector, therefore selective risk-factor based screening remains the predominant practice in South Africa.[7] Only pregnant women with one or more of the following criteria undergo a 2-hour OGTT between 24 and 28 weeks' gestation[5, 10]:

- Women of Indian ethnic origin
- BMI >35kg/m2
- Age >40 years of age
- GDM in previous pregnancy
- Family history (first degree relative) of diabetes
- Previous unexplained third trimester foetal death
- Previous baby with birthweight >4 kg
- Polyhydramnios in index pregnancy
- Glycosuria (≥1+ glucose in urine)
- A foetus that is large for gestational age

While GDM is certainly linked to definable risk factors, selective screening based on risk factors alone may result in a significant proportion of women with GDM being missed and left untreated.[5] Ideally, pregnant women should be universally screened for GDM. This was demonstrated by Adam *et al.* who conducted a prospective cohort observational study in 2017 to determine the prevalence of GDM in a South African population.[5] They found a prevalence of 25.8% with universal screening, and only 15.2% with selective risk factor-based screening.

Limitations of existing methods

The 75-gram OGTT is considered the gold standard for diagnosing GDM, but is cumbersome and time consuming, creating several challenges for under-resourced healthcare facilities with large patient burdens, which were exaggerated by the recent COVID-19 pandemic and increased the urgency for alternative screening approaches to be found.[7] Apart from the human resources, clinic space and adequate laboratory facilities required to perform OGTTs, as well as the associated laboratory costs for our health system, patients are also expected to spend a minimum of 120 minutes at the clinic and often experience nausea and vomiting from glucose ingestion.[7] Turnaround times for results take much longer for venous samples, creating challenges in relaying results to patients once they have left their respective healthcare facilities and potentially delaying treatment.

HbA1c testing is globally accepted as a useful modality for monitoring diabetic control in the non-pregnant population.[7] Although it has been postulated that HbA1c levels decrease in pregnancy due to increased red cell turnover, HbA1c testing has been evaluated in the pregnant population too, given that it only requires one sample and no fasting.[7] A meta-analysis was done by Renz *et al.* in 2018 to evaluate its accuracy as a screening tool for GDM diagnosis. They found it to have a high specificity (95% at a threshold of 5.7%), but sensitivity remained low at various thresholds, demonstrating its usefulness only in ruling-in GDM, not excluding it.[11]

The search for more practical, cost-effective, universally implementable, and contextually suitable approaches for GDM diagnosis in resource-constrained settings must therefore continue. Point-of-care (POC) tests have gained traction in recent years for their ability to provide faster turnaround times than tests performed in central laboratories, while also needing less sample volume.[12] These practical advantages need to be weighed up against the challenges related to POC testing, which largely involve relying on busy clinical staff to implement quality assurance measures to maintain test accuracy and patient safety – tasks they are often not trained in appropriately, or don't appreciate the importance of.[12] Multiple factors related to quality assurance may interfere with the accuracy of using capillary blood and portable blood glucose devices to screen for GDM. These include strip factors, manufacturer variances, and storage conditions including temperature and humidity.[13] Patient factors include interference from drugs and haematocrit values, which tend to drop during pregnancy as plasma volume expands over blood volume, leading to potentially inaccurate estimations of blood glucose.[13]

Bearing this in mind, some studies have suggested that using adjusted cut-off values for capillary blood glucose measures may be useful for GDM screening in resource-constrained settings.[14, 15]

Rationale for this study

Given the limitations of the laboratory-dependent OGTT for GDM screening, as well as the shortcomings of HbA1C as a screening test, this protocol proposes to evaluate the utility of capillary blood glucose for GDM detection, assessed using a POC device, in a South African setting, thereby eliminating the need for laboratory facilities and potentially reducing time spent at antenatal facilities for pregnant women.

METHODOLOGY

Study design

The CAMP study is a prospective cohort study that enrolled a cohort of 400 mother-infant pairs from Gugulethu MOU in Cape Town and followed them up from mid-pregnancy (24-28 weeks' gestation) through to 6-24 months postpartum. This protocol proposes to conduct a secondary analysis of the CAMP study data collected at enrolment (24-28 weeks' gestation). The analysis will entail a cross-sectional comparison of two methods for bloods glucose assessment in pregnancy, namely VBG analysed in a standardised laboratory and CBG analysed on a POC glucometer.

Study setting

Gugulethu is a settlement in Cape Town with high levels of poverty and unemployment.[16] Prior to delivery, pregnant women in the area receive antenatal care from Gugulethu MOU, where this research is focused.

Study population

Women enrolled in the CAMP study were ≥18 years of age, of 24-28 weeks' gestation at the time of enrolment, and did not have a previous diagnosis of T2DM at the time of enrolment. The rationale for enrolling women after 20 weeks' gestation is that metabolic abnormalities tend to unmask or develop around this time.[17]

Inclusion and exclusion criteria for CAMP study enrolment

Inclusion Criteria

- At least 18 years old
- Pregnant, at 24-28 week's gestation
- English or isiXhosa speaking
- Willingness to participate in all study procedures, including allowing access to medical records

Exclusion Criteria

- Inability to comprehend the consent process
- Previous diagnosis or currently receiving treatment for T2DM

Recruitment and enrolment

No new data will be collected for the purposes of this study, which will entail a secondary analysis of existing data from the CAMP study. Women who sought antenatal care at Gugulethu MOU, and who met eligibility criteria, were approached and enrolled at random after consenting to study procedures. Research staff who conducted consent processes were fluent in English and isiXhosa, and were trained in research integrity and ethical consenting protocols. Participation was entirely voluntary and didn't impact medical care in any way.

Study procedures

Participants in the CAMP study underwent three study visits – two antenatal visits and one postpartum visit. The baseline visit conducted at 24-28 weeks' gestation will be the primary visit of interest for this proposed study.

At enrolment, participants were screened for GDM via a fasted 2-hour OGTT. This entailed measuring fasted blood glucose, after which women ingested 75g glucose dissolved in 250-300 mL water. A second and third blood samples were taken at 1 and 2 hours post glucose ingestion. These were assessed at the NHLS laboratory on the same day of collection. Additionally, participants underwent POC capillary glucose testing for serum glucose estimation using a Freestyle Optium glucometer at each point of venesection. Table 1 summarises the variables collected at baseline that are of interest to this study.

Variable	Type	Data collection
Age at date of recruitment (years)	Numerical (continuous)	Baseline visit
Pre-pregnancy BMI (Kg/m^2)	Numerical (continuous)	Baseline visit
Home language	Categorical (nominal)	Baseline visit
Highest level of education	Categorical (ordinal)	Baseline visit
HIV	Categorical (binary)	Baseline visit
GDM in previous pregnancy	Categorical (binary)	Baseline visit
Family history of diabetes	Categorical (binary)	Baseline visit
Previous 3rd trimester foetal death	Categorical (binary)	Baseline visit
Previous baby birth weight >4kg	Categorical (binary)	Baseline visit
Glycosuria	Categorical (binary)	Baseline visit
Capillary blood glucose (mmol/L) • Fasting • 1-hour post glucose intake • 2-hrs post glucose intake	Numerical (continuous)	Baseline visit
Venous blood glucose (mmol/L) • Fasting • 1-hour post glucose intake • 2-hrs post glucose intake	Numerical (continuous)	Baseline visit

Table 1. *Study variables of interest*

Definitions of GDM

In this study, GDM will be diagnosed if fasting blood glucose measures >5.1 mmol/L; 1-hour blood glucose, after oral glucose ingestion, measures > 10.0 mmol/L; or 2-hour blood glucose measures > 8.5 mmol/L. These diagnostic thresholds are in accordance with the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria, which is associated with a 2.4 times higher GDM detection rate compared to older methods.[18, 19] There are currently no defined diagnostic thresholds for CBG in pregnancy, therefore different diagnostic thresholds for CBG will be evaluated during data analysis to explore the trade-offs in sensitivity and specificity at different values.[15]

Data analysis

Data will be imported into R Studio version 1.4.1106 for analysis. All data entries with missing data points will be automatically excluded from the analysis. GDM prevalence will be calculated as proportions using IADPSG criteria for VBG and CBG.

Scatter plots will be generated and Pearson's correlation coefficients calculated as a preliminary exploration of the relationship between venous and capillary measures. This will be followed by a Bland & Altman (B&A) analysis to assess the agreement between VBG and CBG measures, by evaluating the difference in means and estimating an agreement interval, within which 95% of the differences between means will fall.[20] First the differences between VBG (method A) and CBG (method B) measurements will be calculated. The mean measurements of methods A and B will then be calculated, followed by the line of bias and limits of agreement:

Bias = mean of differences
Lower limit (LL) = mean difference – (1.96 x Standard deviation of difference)
Upper limit (UL) = mean difference + (1.96 x Standard deviation of difference)

The differences in measurements (A-B) will be plotted on the Y-axis, against the mean of differences on the X-axis. The closer data points are to the mean of difference line, the stronger the agreement as demonstrated in Figure 1 below.

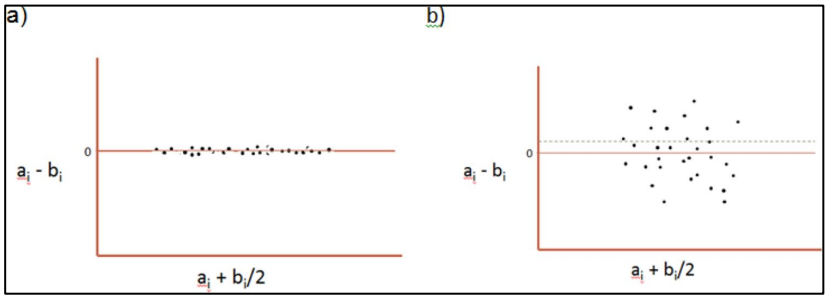

Figure 1. *Hypothetical illustrations of B&A plots.*[21]

A B&A analysis will be conducted for fasted measures, as well as 1- and 2-hour post glucose ingestion. The analysis will be repeated across subgroups. Additional diagnostic thresholds for CBG will be explored through plotting Receiver Operator Characteristics (ROC) curves using sensitivity and specificity values calculated for each cut-off. The study aims, data analysis approaches and expected outcomes are outlined in Table 2.

Aims	Data analysis approach	H^1	H^0
1: To compare the prevalence of GDM determined via 2-hour OGTT vs POC capillary glucose tests with immediate results	The prevalence of GDM will be calculated as proportions; first using venous measures (method A), then capillary measures (method B) at 0-, 1- and 2-hours post glucose ingestion. This will be done in the context of both universal and selective risk factor-based screening. IADPSG diagnostic thresholds will be used.	The prevalence of GDM is lower when using venous glucose measures compared to capillary glucose measures.	There is no significant difference in the prevalence of GDM detected by OGTT vs POC capillary blood glucose tests.
2: To calculate the agreement between VBG (reference) and CBG (comparative) measures and explore the clinical implications of each method	First, Pearson's correlation will be calculated between venous and capillary measures. A B&A analysis will then be conducted to calculate the agreement between venous and capillary measures, and detect presence of systematic differences, otherwise known as bias.	There is a statistically significant difference between VBG and CBG measurements in detecting GDM, i.e., the limits of agreement exclude zero.	There is no statistically significant difference between VBG and CBG measurements in detecting GDM, i.e., the limits of agreement include zero.
3: To determine whether the agreement changes in certain sub-groups of pregnant women, comparing BMI categories, age categories and HIV status	A B&A analysis will be repeated across various sub-groups, categorizing the cohort by age, BMI, and HIV status, to see how this might change the agreement or interchangeability between methods.	There is a significant difference in the agreement between venous and capillary measures across sub-groups.	There is no significant difference in the agreement between venous and capillary measures across sub-groups.
ADDITIONAL: To explore different diagnostic thresholds for CBG measures and better understand trade-offs in sensitivity and specificity at different values.	Receiver Operator Characteristics (ROC) curves will be plotted using sensitivity and specificity values calculated for each cut-off.		

Table 2. *Outline of the data analysis approach for this study*

Sample size

A secondary data analysis will be performed on a sample size of 400 that was calculated and recruited historically. Using OpenEpi, an open-source online sample size calculator, it appears that a sample size of n=400 is more than sufficient to detect clinically significant mean differences between VBG (reference method) and CBG (comparison method) measures with a 95% confidence interval. Means and standard deviations for each method were extracted from existing literature comparing VBG and CBG in detection of GDM and used as input in OpenEpi.[22] P-values of 0.05 will be considered significant.

ETHICAL CONSIDERATIONS

Risks and benefits

Recruitment for the parent study occurred historically. This study will be a retrospective analysis of existing data and therefore won't impose any further risks or benefits onto participants directly. More broadly, the findings from this study will contribute to the growing body of literature at the intersection of perinatal health, NCDs and infectious diseases in resource-constrained settings.

Informed consent and assent

All participants completed an informed consent process prior to enrolment into the CAMP study. All informed consent procedures were approved by the University of Cape Town's HREC. Consent and all further study procedures were conducted in either English or isiXhosa, according to the participants' preference, to ensure the participants' full understanding prior to consenting. All staff members conducting consent procedures were trained in research ethics and consenting protocols for the CAMP study.

Privacy and confidentiality

Breaches in confidentiality were minimized by using unique patient identifiers (PIDs) on all data to avoid use of identifying information such as participant names. The CAMP study data are de-identified prior to analysis or dissemination to collaborators.

Reimbursement

Participant reimbursement is not applicable to this study as no further follow up visits will be conducted. Data collection for the parent study is complete.

Storage of biological specimens

Blood samples for the CAMP study were analyzed by the National Health Laboratory Service on the day of collection. No additional laboratory analyses will be performed for this study, which will solely utilize raw provided by the parent study investigators.

Ethical and Regulatory Compliance

All CAMP study procedures – including recruitment, consent processes, interviews and assessments – were approved by the University of Cape Town HREC (see approval letter attached) and complied with the Declaration of Helsinki (2013) and the South African Department of Health: Ethics in Health Research Principles, Structures and Processes (2004) (see approval letter attached).

Conflicts of interest

No conflicts of interest exist.

REFERENCES

1. Pastakia SD, Njuguna B, Onyango BA, Washington S, Christoffersen-Deb A, Kosgei WK, et al. Prevalence of gestational diabetes mellitus based on various screening strategies in western Kenya: a prospective comparison of point of care diagnostic methods. BMC pregnancy and childbirth. 2017;17(1):1-9. Available from: https://doi.org/10.1186/s12884-017-1415-4

2. Monteiro LJ, Norman JE, Rice GE, Illanes SE. Fetal programming and gestational diabetes mellitus. Placenta. 2016;48:S54-S60. Available from: https://doi.org/10.1016/j.placenta.2015.11.015

3. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9. Available from: https://doi.org/10.1016/S0140-6736(09)60731-5

4. Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. Jama. 2018;320(10):1005-16. DOI: 10.1001/jama.2018.11628

5. Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. South African medical journal. 2017;107(6):523-7. Available from: https://hdl.handle.net/10520/EJC-7b5e0e7d5

6. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. The lancet Diabetes & endocrinology. 2016;4(12):1025-36. Available from: https://doi.org/10.1016/S2213-8587(16)30217-0

7. Coetzee A, Hall DR, Conradie M. Hyperglycemia First Detected in Pregnancy in South Africa: Facts, Gaps, and Opportunities. Frontiers in Clinical Diabetes and Healthcare. 2022;3:895743. Available from: https://doi.org/10.3389/fcdhc.2022.895743

8. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes care. 2007;30(8):2070-6. Available from: https://doi.org/10.2337/dc06-2559a

9. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. Diabetes care. 2012;35(3):574-80. Available from: https://doi.org/10.2337/dc11-1687

10. Department of Health, Republic of South Africa. Guidelines for Maternity Care in South Africa. 2016. p. 97.

11. Renz PB, Chume FC, Timm JR, Pimentel AL, Camargo JL. Diagnostic accuracy of glycated hemoglobin for gestational diabetes mellitus: a systematic review and meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2019;57(10):1435-49. Available from: https://doi.org/10.1515/cclm-2018-1191

12. Shaw JL. Practical challenges related to point of care testing. Practical laboratory medicine. 2016;4:22-9. Available from: https://doi.org/10.1016/j.plabm.2015.12.002

13. Muhandiram S, Suranimala D, Weerasekara N, Ratnayake C. Validity of over-the-counter finger stick glucose measurement devices in comparison with laboratory venous plasma glucose measurements on pregnant women with diabetes. 2018.

14. Boriboonhirunsarn D, Robkhonburi A, Asad-Dehghan M. Accuracy of capillary blood glucose for 50-g glucose challenge test for gestational diabetes screening. Diabetology international. 2022;13(3):561-5. Available from: https://doi.org/10.1007/s13340-022-00572-3

15. Bhavadharini B, Mahalakshmi MM, Maheswari K, Kalaiyarasi G, Anjana RM, Deepa M, et al. Use of capillary blood glucose for screening for gestational diabetes mellitus in resource-constrained settings. Acta diabetologica. 2016;53:91-7. Available from: https://doi.org/10.1007/s00592-015-0761-9

16. CITY OCT. City of Cape Town-2011 Census Suburb Gugulethu2013.

17. Myer L. Addressing the dual burden of HIV and non-communicable disease in pregnancy in South Africa: Research Protocol Version 2, University of Cape Town. 2020.

18. Lapolla A, Metzger B, Gabbe S, Persson B, Buchanan T, Catalano P, et al. International Association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperlgycemia in pregnancy. Diabetes Care. 2010;33:676-82.

19. Jenum AK, Mørkrid K, Sletner L, Vange S, Torper JL, Nakstad B, et al. Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. European journal of endocrinology. 2012;166(2):317-24. Available from: https://doi.org/10.1530/EJE-11-0866

20. Giavarina D. Understanding bland altman analysis. Biochemia medica. 2015;25(2):141-51. Available from: https://doi.org/10.11613/BM.2015.015

21. Timmins KA, Edwards KL. Validation of spatial microsimulation models: a proposal to adopt the Bland-Altman method. International Journal of Microsimulation. 2016;9(2):106-22. Available from: https://nottingham-repository.worktribe.com/output/790394

22. Gallardo-Rincón H, Lomelin-Gascon J, Martinez-Juarez LA, Montoya A, Ortega-Montiel J, Galicia-Hernandez V, et al. Diagnostic Accuracy of Capillary Blood Glucometer Testing for Gestational Diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022:3855-70. Available from: https://doi.org/10.2147/DMSO.S389420

PART B: JOURNAL MANUSCRIPT

An Evaluation of Diagnostic Approaches for Gestational Diabetes Screening in South Africa

Mathilda Mennen,[1§*] MBChB

[1]Division of Epidemiology and Biostatistics, School of Public Health, University of Cape Town, Cape Town, South Africa

[§]Corresponding author: Dr Mathilda Mennen

Address: Division of Epidemiology and Biostatistics
School of Public Health
University of Cape Town
Anzio Road, Observatory
Cape Town, 7925
South Africa

Email: mathilda.mennen@uct.ac.za

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) poses substantial risks to both mothers and their offspring. In South Africa, screening practices vary, and pregnant women are not screened universally due to resource constraints. This study investigates the implications of using point-of-care (POC) capillary glucose measures for GDM screening and explores potential strategies to increase screening capacity by eliminating the reliance on central laboratory facilities or reducing the time spent at antenatal facilities for mothers.

Objectives: The prevalence of GDM determined by venous blood glucose (VBG) measures obtained during 2-hour oral glucose tolerance tests (OGTTs) was compared to POC capillary glucose (CBG) tests with immediate results. The agreement between VBG and CBG measures was calculated across the whole cohort and in sub-groups, and the clinical and cost implications of each method explored.

Methods: A secondary analysis was conducted on data collected from 400 pregnant participants who were enrolled at 24-28 weeks' gestation into a prospective cohort study at an antenatal clinic in Cape Town. Participants were screened for GDM using a gold-standard 75g OGTT and simultaneously underwent POC capillary glucose testing. GDM was diagnosed via each method according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. We calculated the sensitivity and specificity of CBG in detecting VBG-defined GDM at different thresholds and Bland-Altman analyses examined agreement between CBG and VBG.

Results: The GDM prevalence was 7% among all participants, resulting from a prevalence of 6% among patients with no risk factors, and 8% among patients with risk factors. Four percent of the cohort was diagnosed with GDM despite having no risk factors. Most cases (96%) were diagnosed on fasting venous measures. Capillary measures overestimated the prevalence of GDM at IADPSG thresholds (25%) and had poor sensitivity (73%). Correlation between venous and capillary measures was lowest in the fasting state ($r=0.22$, $p<0.001$). Bland Altman analyses found the average agreement between methods to be lowest in the fasting state.

Conclusion: Capillary measures demonstrate poor correlation and agreement with venous measures at 24-28 weeks' gestation, particularly in the fasting state when almost all GDM cases are diagnosed. A fasting plasma glucose, if performed universally as a single measure, outperforms selective risk factor-based OGTT screening and fasting capillary blood glucose in terms of sensitivity and specificity, while reducing the overall number of laboratory-dependent glucose tests performed.

INTRODUCTION

Gestational diabetes mellitus (GDM) affects one in seven births according to the International Diabetes Federation.[1] GDM is defined as new-onset hyperglycaemia that occurs towards the second half of pregnancy and resolves after delivery.[2] Hyperglycaemia in pregnancy not only increases the risk of adverse pregnancy outcomes such as still births and neonatal deaths, but also increases the susceptibility for both mothers and their offspring to develop non-communicable diseases (NCDs) such as obesity, type II diabetes, and cardiovascular conditions in the future.[3-6] The risk for foetal and maternal morbidity has been found to exist on a spectrum and is proportional to the degree of hyperglycaemia experienced in pregnancy.[7] While mild hyperglycaemia during pregnancy may be of limited immediate clinical concern, it is suspected that even mild foetal exposure to hyperglycaemia perpetuates a cycle of obesity and increases transgenerational metabolic risks, though the exact quantification of these risks remains to be quantified.[8]

From around 24 week's gestation onwards, sufficient levels of placental hormones begin to cause insulin resistance and hyperinsulinaemia to various degrees, rendering pregnant women metabolically vulnerable and predisposed to the development of GDM.[8, 9] Furthermore, South Africa has become one of the world's most obese nations, with the highest prevalence of obesity in sub-Saharan Africa present among South African women of childbearing age.[8, 9] Obese women have a 4-9 times higher risk of developing GDM compared to normal weight women.[10] Improving strategies for prevention, early detection and optimal management of both maternal obesity and GDM is crucial in interrupting the intergenerational cycle of escalating obesity and diabetes.

The International Association of Diabetes in Pregnancy Study Groups (IADPSG) proposes selective screening of high risk women (women with one or more risk factor for GDM) at booking to improve early detection of undiagnosed diabetes, and further encourages universal screening for GDM with a 75g 2-hour oral glucose tolerance test (OGTT) at 24-28 weeks' gestation.[8] The 75-gram OGTT is considered the gold standard for diagnosing GDM, but is time consuming and resource-intensive, making it challenging to perform universally in under-resourced settings with large patient burdens – such as most public healthcare facilities in South Africa.[8] Selective screening via OGTT of only pregnant women with one or more risk factors for GDM remains the predominant practice in South Africa.[8]

This study aims to explore the clinical considerations associated with selective vs. universal GDM screening within a South African context. Additionally, it assesses the diagnostic accuracy of using a point-of-care (POC) glucometer to assess capillary blood glucose as an alternative to laboratory-dependent venous measures.

METHODS

Study design

This study is a cross-sectional comparison of two methods for blood glucose determination in pregnancy, namely venous blood glucose analysed in a standardised laboratory and capillary blood glucose analysed on a point-of-care (POC) glucometer. It is a secondary analysis of data that was collected during a prospective cohort study titled "Addressing the dual burden of HIV and non-communicable disease in pregnancy in South Africa (CAMP)", in which 400 pregnant women attending Gugulethu Midwife Obstetrics Unit (MOU) for antenatal care between November 2019 and June 2022 were enrolled and followed up from mid-pregnancy (24-28 weeks' gestation) to 6-14 months postpartum. This study's cross-sectional analysis focused only on the enrolment visit, when baseline characteristics of participants were obtained, along with venous and capillary blood glucose measures.

Study setting

Gugulethu is a peri-urban settlement in Cape Town, South Africa, with high levels of poverty and unemployment.[11] It is home to roughly 300,000 people.[12] The MOU, at which > 4000 pregnant women seek antenatal care annually, is run by nurse-midwives with on-site obstetric support bi-weekly.[13] At the time the CAMP study was conducted, other studies in similar South African settings reported varying GDM prevalence statistics ranging between 7% to 26%.[9, 14]

Study population

Pregnant women who presented to Gugulethu MOU during the study period were consecutively approached and enrolled if they were over the age of 18, between 24-28 weeks' gestation, and willing to participate in all study procedures, including allowing access to their medical records. Pregnant women with known type 2 diabetes were excluded from the study.

Due to the parent study's focus on addressing the dual burden of HIV and non-communicable disease in pregnancy, the cohort was deliberately stratified based on HIV status. Out of the 400 participants enrolled, 200 were persons living with HIV, and 200 without HIV.

Measures

Descriptive data of the study population were collected at enrolment, including maternal age, pre-pregnancy body mass index (BMI), HIV status, obstetric history, and presence of risk factors for GDM. These include Indian ethnicity, BMI > 35 kg/m^2, age > 40 years, previous history of GDM, first degree family history of diabetes, previous unexplained third trimester fetal death, previous macrosomic baby (birthweight > 4kg), and glycosuria.[15] Each participant underwent a glucose assessment, which entailed a 2-hour 75g OGTT after an overnight fast. Both venous and capillary samples were collected at 0-, 1- and 2-hours post 75g glucose ingestion. All venous samples were delivered to an offsite standardized laboratory for analysis while capillary blood glucose was measured in real time using a Freestyle Optium (Abbott Diagnostics) hand-held glucometer. This device uses glucose test strips that are calibrated for whole blood and determines capillary blood glucose concentration by means of electrochemical technology.[16] GDM was diagnosed if fasting blood glucose was ≥ 5.1 mmol/L, and/or blood glucose at 1-hour post glucose intake was ≥ 10.0 mmol/L, and/or blood glucose at 2-hours post glucose intake was ≥ 8.5 mmol/L. These thresholds are in accordance with the IADPSG diagnostic criteria.[17]

Statistical analysis

Statistical analysis was performed using R Studio Version 2023.06.2+561. All data entries with missing data points were excluded from the analysis. The Shapiro-Wilk test was used to test for normality, due to it being the most powerful test for normality for all sample sizes.[18] Skewed data are reported as median and interquartile range (IQR) and include age and body mass index (BMI). Categorical variables are reported as proportions. GDM prevalence was calculated using venous and capillary measures respectively, according to IADPSG criteria. The McNemar's test for matched pairs was used to obtain p-values for the paired comparison of GDM prevalence via venous and capillary measures. The GDM prevalence was calculated at different capillary cutoffs, and sensitivities and specificities calculated for each adjusted cutoff. A ROC curve was generated to visualize the diagnostic performance of capillary measures at

different cutoffs. Participant characteristics were described among those who tested falsely positive via capillary screening and compared to the remaining cohort. T-tests were done to compare continuous variables and Chi-squared tests to compare categorical variables. Scatter plots were generated and Pearson's correlation coefficients calculated as a preliminary exploration of the relationship between venous and capillary measures, followed by Bland Altman analyses to evaluate the agreement.

Ethical considerations

The parent study (CAMP) received ethical approval from the University of Cape Town's Human Research Ethics Committee (HREC ref. no. 505/2020), as did this study (HREC ref. no. 779/2023). Prior to enrolment all participants gave written informed consent. This study conducted a secondary analysis of CAMP study data. All data shared for the purpose of this study were rigorously deidentified to avoid breaches in patient confidentiality.

RESULTS

Descriptive characteristics

The study population had a median age of 30 years (IQR 25; 34), and 52% were obese, with a BMI of over 30 kg/m^2 (Table 1). Participants were categorized according to presence of risk factors for GDM: 61% had none, 32% had at least one, and 7% had two or more risk factors.

Glucose evaluation

Based on venous measures obtained during 75 g OGTTs, a GDM prevalence of 7% was detected in the context of universal screening, whereas in the context of selective risk-factor based screening a prevalence of only 2% was detected when screening those with one risk factor, and 1% when screening those with two risk factors (Table 2). Among those with no risk factors, 14 women tested positive for GDM, which constitutes 4% of the total study population. Out of the 27 cases of GDM identified through universal screening, 26 (96%) were diagnosed in the fasting state. Among these, 7 cases (26%) remained positive after glucose ingestion, while only 1 case (4%) initially tested positive post-glucose ingestion.

Population characteristic		All participants (n=400)
Age (years)	Median (IQR)	30 (25; 34)
	18-35	317 (79%)
	>35	83 (21%)
	>40	16 (4%)
Pre-pregnancy BMI (kg/m^2)	Median (IQR)	30.12 (25.81; 34.96)
	Non-obese (<30)	193 (48%)
	Obese (>30)	206 (52%)
Home language	isiXhosa	380 (95%)
	isiZulu	1 (0%)
	English	2 (1%)
	Other	17 (4%)
Highest level of education	No education	0 (0%)
	Part of primary school education	4 (1%)
	Completed primary school	6 (2%)
	Part of high school education	236 (59%)
	Completed grade 12	133 (33%)
	Part of post-matric education	11 (3%)
	Completed post-matric education	10 (3%)
Primigravida	Yes	74 (19%)
	No	326 (82%)
HIV status	Positive	200 (50%)
	Negative	200 (50%)
Presence of risk factors for GDM (n = 391)	No risk factors	240 (61%)
	1 risk factor	125 (32%)
	2 risk factors	23 (6%)
	3 risk factors	3 (1%)
Risk factors for GDM		
Age > 40		16 (4%)
BMI > 35 kg/m^2		98 (25%)
Women of Indian ethnic origin		0 (0%)
GDM in previous pregnancy		3 (1%)
Family history of diabetes		39 (10%)
Previous 3rd trimester fetal death		8 (2%)
Previous baby birth weight > 4 kg		22 (6%)
Glycosuria		0 (0%)

***Table 1**. Descriptive characteristics of the study population (BMI = body mass index; GDM = gestational diabetes mellitus; glycosuria = ≥1+ glucose on urine dipstick)*

Capillary measures over-estimated the prevalence of GDM at 25% (Table 2). Using IADPSG cut-offs, capillary screening resulted in 80 false positive diagnoses (Supplementary Tables 1 and 2). Those in whom false positive diagnoses were made were more obese compared to the rest of the cohort (59% vs. 50%; p-value = 0.42) and had a higher median BMI (31.86 vs. 30.12; p-value = 0.10). They had a higher prevalence of HIV (65% vs. 46%; p-value = 0.004), multigravida mothers (91% vs. 79%; p-value 0.02), and higher systolic (118 vs. 114; p-value = 0.02) and diastolic (71 vs. 68; p-value = 0.01) blood pressures.

	Method	GDM prevalence via venous blood glucose (n=400)	GDM prevalence via capillary blood glucose (n=400)	P-value
Universal screening	Fasting (BG ≥ 5.1 mmol/L)	26 (7%)	96 (24%)	
	1-hour post glucose (BG ≥ 10.0 mmol/L)	5 (1%)	4 (1%)	
	2-hour post glucose (BG ≥ 8.5 mmol/L)	3 (1%)	5 (1%)	
	Overall	**27 (7%)**	**99 (25%)**	< 0.001
Selective screening for patients with no risk factors	Fasting (BG ≥ 5.1 mmol/L)	14 (4%)	49 (12%)	
	1-hour post glucose (BG ≥ 10.0 mmol/L)	2 (1%)	2 (1%)	
	2-hour post glucose (BG ≥ 8.5 mmol/L)	2 (1%)	3 (1%)	
	Overall	**14 (4%)**	**51 (13%)**	< 0.001
Selective screening for patients with 1 risk factor only	Fasting (BG ≥ 5.1 mmol/L)	7 (2%)	35 (9%)	
	1-hour post glucose (BG ≥ 10.0 mmol/L)	2 (1%)	1 (0%)	
	2-hour post glucose (BG ≥ 8.5 mmol/L)	0 (0%)	0 (0%)	
	Overall	**8 (2%)**	**36 (9%)**	< 0.001
Selective screening for patients with 2 risk factors	Fasting (BG ≥ 5.1 mmol/L)	4 (1%)	8 (2%)	
	1-hour post glucose (BG ≥ 10.0 mmol/L)	1 (0%)	1 (0%)	
	2-hour post glucose (BG ≥ 8.5 mmol/L)	1 (0%)	2 (1%)	
	Overall	**4 (1%)**	**8 (2%)**	0.13

***Table 2**. GDM prevalence via venous (reference) and capillary (comparison) blood glucose*

Capillary outcomes at different cut-offs were contrasted to explore the trade-offs in sensitivity and specificity at different diagnostic thresholds (Supplementary Table 3). Adjusting capillary cut-offs to IADPSG values + 0.7 mmol/L reduces the sensitivity from 73% to 62% but increases the specificity from 78% to 97%. A receiver operating characteristic (ROC) curve illustrates the improved diagnostic accuracy of using these adjusted cut-offs for capillary measures, with the area under the curve (AUC) increasing from 76% to 79% (Figure 1).

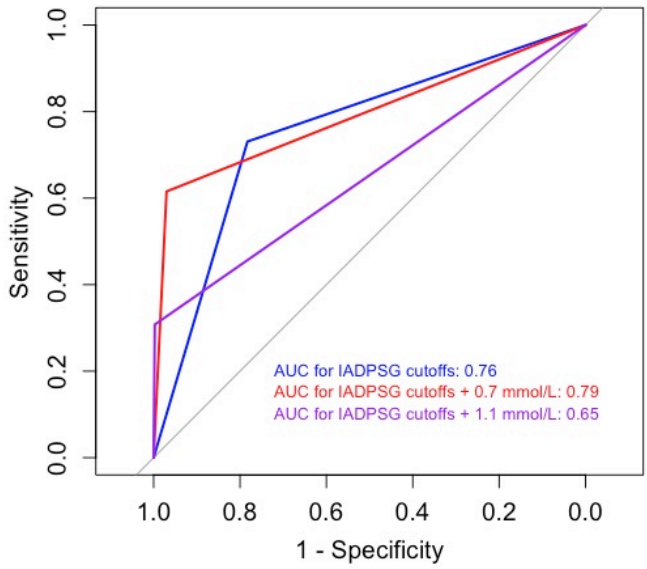


Figure 1. *ROC curves demonstrating the accuracy of GDM detection at different capillary glucose cutoffs (diagnostic accuracy improves as AUC approximates 1)*

Scatter plots correlating antenatal venous and capillary measures at 0-, 1- and 2-hours post glucose intake are shown in Figure 2. Correlation appears to be worst in the fasting state ($r = 0.22$, $p < 0.001$), and improves after glucose intake, with Pearson's Correlation Coefficient being highest at 2-hours post glucose intake ($r = 0.91$, $p < 0.001$).

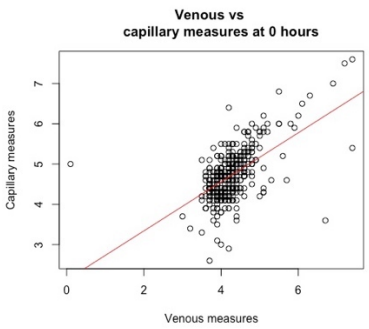
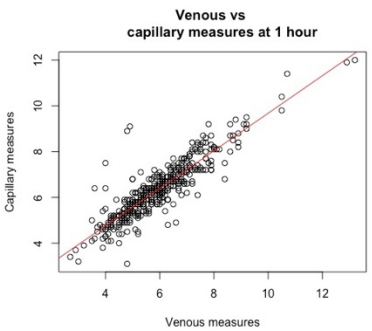
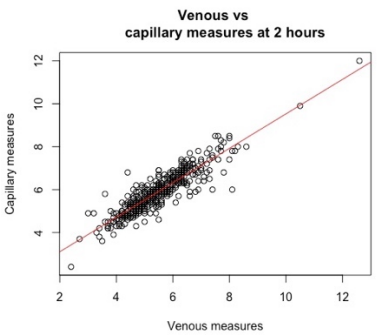
24-28 weeks' gestation		
		
Pearson Correlation Coefficient = 0.22 P < 0.001	Pearson Correlation Coefficient = 0.89 P < 0.001	Pearson Correlation Coefficient = 0.91 P < 0.001

Figure 2. *Scatter plots correlating venous and capillary measures at 0-, 1- and 2-hours post glucose intake – at 24-28 weeks' gestation*

Bland Altman analyses were performed to contrast the mean differences between venous and POC capillary measures at the same time points and across different subgroups (Supplementary Figure 1). In the whole cohort, the average difference between methods is highest in the fasting state, and improves minimally after glucose intake, from -0.46 to -0.41. The fasting state remains the timepoint with the highest average differences across subgroups, excepting for among those with BMI < 30. In the fasting state, the highest difference is found among HIV positive women (-0.50 in the fasting state; -0.49 at 1 hour post glucose intake, and -0.46 at 2 hours post glucose intake).

DISCUSSION

This study found a GDM prevalence of 7% in a cohort of 400 pregnant women but over half of those diagnosed with GDM (52%) had no apparent risk factors for GDM. POC capillary measures were found to underperform compared to venous measures. They dramatically overestimated the prevalence of GDM at 25% and demonstrated poor specificity, falsely diagnosing 20% of the cohort with GDM. Venous measures were consistently lower than capillary measures, in keeping with prior literature. Adjusting capillary thresholds by adding 0.7mml/L to IADPSG thresholds at all time points improves the diagnostic accuracy of capillary measures by increasing specificity, albeit in exchange for sensitivity. Venous and capillary measures demonstrate poor correlation and agreement in the fasting state, which is when the vast majority of GDM cases (96%) were diagnosed. Study findings support the notion that the diagnostic focus of GDM should be on fasting venous measures.

Underperformance of capillary blood glucose

In the search for more cost-effective and universally implementable methods for GDM diagnosis in resource-constrained settings, point-of-care (POC) tests have gained interest for their ability to provide faster turnaround times while needing less sample volume.[19] An accurate and reliable POC screening device should in theory increase screening capacity by eliminating the reliance on central laboratory facilities and potentially reducing the time spent at antenatal facilities for pregnant people. In reality, many factors related to quality assurance may interfere with the accuracy of portable glucometers, including strip factors, manufacturer variances, and storage conditions such as changes in temperature and humidity.[20] Patient factors such as pregnancy-induced changes in haematocrit values may also interfere with the accuracy of capillary blood glucose measures.[20]

This study confirmed the findings of previous studies that capillary measures underperform in the diagnosis of GDM and cannot be recommended for use.[20, 21] The glucometer evaluated in this study dramatically over-estimated the prevalence of GDM by almost four-fold and resulted in 80 false positive cases needing confirmatory testing (Supplementary Table 1).

Venous measures were consistently lower than capillary measures. This phenomenon may occur, among other reasons, as a result of venous samples undergoing glycolysis by red blood cells at room temperature, which will decrease plasma glucose.[22] Bearing this in mind, some studies have suggested that using adjusted cut-off values for capillary measures may be worth evaluating.[23, 24] This study found that adjusting capillary cut-offs by adding 0.7mml/L to IADPSG thresholds at all time points improves the diagnostic accuracy of capillary measures slightly, with an increase in specificity (from 78% to 97%) while trading off sensitivity (from 73% to 62%).

Importance of universal screening

Existing literature has shown the limitations associated with risk factor-based screening methods for GDM. Adam et al found in their prevalence study conducted in Johannesburg in 2017 that the presence of one or more risk factors for GDM has both a poor sensitivity (59%) and specificity (59%) and therefore is insufficient as a screening test for GDM.[9] They found that the prevalence of GDM is substantially higher if universal screening is employed.[9] The significant proportion of women (4%) found to have GDM in this study despite having no apparent risk factors, supports this finding and highlights the importance of universal screening for GDM to avoid cases being missed as a result of selective risk-factor based screening. Untreated cases may result in adverse birth outcomes and long-term metabolic complications for mothers and their offspring.

Of concern also are rising levels of obesity and non-communicable diseases (NCDs) in South Africa's general population. Diabetic screening in the non-pregnant population occurs rarely, and women often access NCD screening for the first time in pregnancy.[8] Selective screening would, in the context of this study, result in missed NCD screening opportunities for the majority (61%) of the study population.

Diagnostic focus on fasting measures

Pregnancy-induced insulin insensitivity results in a rise in post-prandial glucose levels.[25] The diabetogenic stress of pregnancy is therefore understood to be best recognised in the fed state, and this remains the rationale for OGTTs being considered the gold-standard test for detecting hyperglycaemia in pregnancy.[25] The OGTT however does not come without its challenges. Apart from the clinic space, human resources and adequate laboratory facilities required to perform OGTTS, as well as the associated laboratory costs for our health system, patients are expected firstly to fast, and then to spend a minimum of 2 hours at the clinic, while often experiencing nausea and vomiting as a result of glucose ingestion.[8] For these reasons universal OGTTs are simply not feasible.

Some studies have investigated the role of a single fasting plasma glucose (FPG) as a low-cost alternative to universal OGTTs.[14, 26, 27] The WHO 2013 recommendation states that an FPG value ≥5.1 mmol/L is 100% specific for GDM.[28] Sensitivities, however, vary between ethnicities.[29] The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study group suggested that in population groups where FPG is diagnostic in more than half of those with GDM, it may be reasonable to perform an FPG as an initial step and reserve full OGTTs for those with a non-diagnostic FPG.[29] The vast majority (96%) of GDM cases in this study population were diagnosed on the basis of fasting venous measures, which supports this notion.

The IADPSG acknowledge that women with an FPG < 4.5 mmol/L are at low risk of GDM and may not require an OGTT, while women with an FPG between 4.5 - 5.1 mmol/L are at intermediate risk and would require an OGTT.[26] Simply put, a two-threshold approach could use the higher cut-off (5.1 mmol/L) to rule in GDM, and the lower cut-off (4.5 mmol/L) to rule out GDM, while those with values in between these cut-offs can be referred for a confirmatory OGTT.[30] In this study, an FPG < 4.5 mmol/L had a 96% sensitivity for diagnosing GDM, with only 1 out of 27 cases being missed. Laboratory-dependent glucose tests were used as a metric to compare the costs of different diagnostic models applied to this study population (Table 3). Model 3, which uses a universal two-threshold FPG approach, and identifies candidates with non-diagnostic FPGs for confirmatory OGTTs, reduces the total number of laboratory-dependent glucose tests performed by almost half and results in only 1 missed case (4%), which is a substantial improvement from 14 cases (52%) being missed through selective risk-factor based screening.

Model	Population size	Total number of laboratory-dependent glucose tests done	Number of missed cases (False Negatives)
1. Universal screening via venous OGTT	Total population: n=400	400 x 3 = **1200**	0
2. Selective risk-factor based screening via venous OGTT	Those with 1 or more risk factors: n=160	160 x 3 = **480**	14
3. Universal FPG + confirmatory OGTT for those with a non-diagnostic FPG	Total population: n=400 Those with a non-diagnostic FPG (i.e., FPG 4.5 - 5.1 mmol/L): n=73	400 + (73 x 3) = **619**	1
4. Universal FCG + confirmatory OGTT for those with FCG ≥ 4.5 mmol/L	Those with FCG ≥ 4.5 mmol/L: n=248	248 x 3 = **744**	5

Table 3: *Comparison of three GDM screening models in this study population, based on number of laboratory-dependent glucose tests required and false negative results (OGTT = 3 laboratory-dependent glucose tests per person; FPG = fasting plasma glucose; FCG = fasting capillary glucose)*

Shortcomings of the two-threshold FPG approach include the prerequisite that women undergoing testing still need to fast overnight, as well as long turnaround times for laboratories to report results. Model 4 seeks to overcome the latter by replacing FPGs with FCGs at the same lowered threshold but doesn't succeed. Although an FCP < 4.5 mmol/L is 81% sensitive, with only 5 out of 26 cases being missed, specificity is very low (40%) and would require all women with an FCG ≥ 4.5 mmol/L to undergo a confirmatory OGTT to accurately rule in GDM. Model 4 therefore outperforms risk-factor based screening (model 2) in terms of ruling out GDM but unfortunately increases the total number of laboratory-dependent glucose tests performed. Model 3 remains superior in terms of cost, sensitivity, and specificity.

Study strengths and limitations

This study took place in a real-world setting, making the results representative of the population being studied. However, being a single-location study may hinder the generalizability of results. The ethnically homogeneous study population may not fully reflect the diverse patient demographics across South Africa. Additionally, the evaluation of only one type of POC

glucometer limits the applicability of study findings. A larger sample size would reduce the influence of random variation and improve validity of study findings.

Despite its limitations, this study highlights the potential policy impact of leveraging existing technology more efficiently. Universally applying a two-threshold FPG, while requiring a slightly higher number of lab-dependent glucose tests than selective risk factor-based OGTTs, will still halve the number of glucose tests needed for universal OGTTs. Additionally, this approach can lead to cost savings by preventing hospital admissions and chronic care associated with untreated cases.

Implications for future research

The subgroup of women who were falsely diagnosed with GDM on capillary blood had higher proportions of multigravidity, hypertension and HIV compared to the rest of the study population. Investigating the association between these characteristics and the risk of misdiagnosis was beyond the scope of this study. It may be of value to investigate whether multigravidity, hypertension or HIV interfere with capillary testing.

An accurate cost-benefit analysis of the screening models proposed in Table 3, although also out of the scope of this study, could assist policy makers to design better informed guidelines for increasing screening capacity across South Africa.

Although it has been postulated that HbA1c levels decrease in pregnancy due to increased red cell turnover, HbA1c is another modality of interest for assessing glucose control, with its most attractive features being that it requires only one sample and no fasting.[8] Some studies have demonstrated its usefulness as a rule-in test for GDM with high specificity, but low sensitivity.[31] Investigating its use in combination with fasting capillary or plasma measures in a low-cost algorithm may be of interest.

CONCLUSION

Universal GDM screening is essential to prevent missed cases in individuals without apparent risk factors. Untreated cases can lead to costly long-term complications for mothers and their offspring. Capillary measures demonstrate poor correlation and agreement with venous measures at 24-28 weeks' gestation, particularly in the fasting state when almost all GDM cases

are diagnosed and cannot be reliably used to replace laboratory dependent OGTTs in universal screening. A fasting plasma glucose, if performed universally as a single measure, outperforms both risk-factor based screening and fasting capillary glucose in terms of sensitivity and specificity, while reducing the overall number of laboratory-dependent glucose tests performed.

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REFERENCES

1. Atlas D. International diabetes federation. IDF Diabetes Atlas, 7th edn Brussels, Belgium: International Diabetes Federation. 2015;33(2).

2. Coetzee A, van de Vyver M, Hoffmann M, Hall D, Mason D, Conradie M. A comparison between point-of-care testing and venous glucose determination for the diagnosis of diabetes mellitus 6–12 weeks after gestational diabetes. Diabetic Medicine. 2019;36(5):591-9. Available from: https://doi.org/10.1111/dme.13903

3. Pastakia SD, Njuguna B, Onyango BA, Washington S, Christoffersen-Deb A, Kosgei WK, et al. Prevalence of gestational diabetes mellitus based on various screening strategies in western Kenya: a prospective comparison of point of care diagnostic methods. BMC pregnancy and childbirth. 2017;17(1):1-9. Available from: https://rdcu.be/dLQZ1

4. Monteiro LJ, Norman JE, Rice GE, Illanes SE. Fetal programming and gestational diabetes mellitus. Placenta. 2016;48:S54-S60. Available from: https://doi.org/10.1016/j.placenta.2015.11.015

5. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9. Available from: https://doi.org/10.1016/S0140-6736(09)60731-5

6. Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. Jama. 2018;320(10):1005-16. DOI: 10.1001/jama.2018.11628

7. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. Diabetes care. 2012;35(3):574-80. Available from: https://doi.org/10.2337/dc11-1687

8. Coetzee A, Hall DR, Conradie M. Hyperglycemia First Detected in Pregnancy in South Africa: Facts, Gaps, and Opportunities. Frontiers in Clinical Diabetes and Healthcare. 2022;3:895743. Available from: https://doi.org/10.3389/fcdhc.2022.895743

9. Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. South African medical journal. 2017;107(6):523-7. Available from: https://hdl.handle.net/10520/EJC-7b5e0e7d5

10. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. The lancet Diabetes & endocrinology. 2016;4(12):1025-36. Available from: https://doi.org/10.1016/S2213-8587(16)30217-0

11. CITY OCT. City of Cape Town-2011 Census Suburb Gugulethu2013.

12. Bengtson AM, Madlala H, Matjila MJ, Levitt N, Goedecke JH, Cu-Uvin S, et al. Associations of HIV and antiretroviral therapy with gestational diabetes in South Africa. AIDS. 2023;37(13):2069-79. DOI: 10.1097/QAD.0000000000003678

13. Myer L, Phillips TK, Zerbe A, Ronan A, Hsiao N-Y, Mellins CA, et al. Optimizing antiretroviral therapy (ART) for maternal and child health (MCH): rationale and design of the MCH-ART study. Journal of acquired immune deficiency syndromes (1999). 2016;72(Suppl 2):S189. DOI: 10.1097/QAI.0000000000001056

14. Dickson L, Buchmann E, Janse van Rensburg C, Norris S. Fasting plasma glucose and risk factor assessment: Comparing sensitivity and specificity in identifying gestational diabetes in urban black African women. South African Medical Journal. 2020;110(1):21-6. Available from: https://hdl.handle.net/10520/EJC-1bc0bb512e

15. Department of Health, Republic of South Africa. Guidelines for Maternity Care in South Africa. 2016. p. 97.

16. Abbott. Freestyle Optium User's Manual.

17. Metzger BE, Gabbe SG, Persson B, Lowe LP, Dyer AR, Oats JJ, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy: response to Weinert. Diabetes care. 2010;33(7):e98-e. Available from: https://doi.org/10.2337/dc10-0719

18. Razali NM, Wah YB. Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. Journal of statistical modeling and analytics. 2011;2(1):21-33.

19. Shaw JL. Practical challenges related to point of care testing. Practical laboratory medicine. 2016;4:22-9. Available from: https://doi.org/10.1016/j.plabm.2015.12.002

20. Muhandiram S, Suranimala D, Weerasekara N, Ratnayake C. Validity of over-the-counter finger stick glucose measurement devices in comparison with laboratory venous plasma glucose measurements on pregnant women with diabetes. 2018. Available from: https://doi.org/10.4038/cmj.v63i4.8769

21. Adam S, Rheeder P. Evaluating the utility of a point-of-care glucometer for the diagnosis of gestational diabetes. International Journal of Gynecology & Obstetrics. 2018;141(1):91-6. Available from: https://doi.org/10.1002/ijgo.12399

22. Colagiuri S, Sandbaek A, Carstensen B, Christensen J, Glumer C, Lauritzen T, et al. Comparability of venous and capillary glucose measurements in blood. Diabetic medicine. 2003;20(11):953-6. Available from: https://doi.org/10.1046/j.1464-5491.2003.01048.x

23. Boriboonhirunsarn D, Robkhonburi A, Asad-Dehghan M. Accuracy of capillary blood glucose for 50-g glucose challenge test for gestational diabetes screening. Diabetology international. 2022;13(3):561-5. Available from: https://doi.org/10.1007/s13340-022-00572-3

24. Bhavadharini B, Mahalakshmi MM, Maheswari K, Kalaiyarasi G, Anjana RM, Deepa M, et al. Use of capillary blood glucose for screening for gestational diabetes mellitus in resource-constrained settings. Acta diabetologica. 2016;53:91-7. Available from: https://doi.org/10.1007/s00592-015-0761-9

25. Hanna F, Peters J. Screening for gestational diabetes; past, present and future. Diabetic Medicine. 2002;19(5):351-8. Available from: https://doi.org/10.1046/j.1464-5491.2002.00684.x

26. Agarwal MM, Weigl B, Hod M. Gestational diabetes screening: the low-cost algorithm. International Journal of Gynecology & Obstetrics. 2011;115:S30-S3. Available from: https://doi.org/10.1016/S0020-7292(11)60009-X

27. Saeedi M, Hanson U, Simmons D, Fadl H. Characteristics of different risk factors and fasting plasma glucose for identifying GDM when using IADPSG criteria: a cross-sectional study. BMC Pregnancy and Childbirth. 2018;18(1):1-6. Available from: https://doi.org/10.1186/s12884-018-1875-1

28. Organization WH. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. World Health Organization; 2013.

29. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes care. 2012;35(3):526-8. Available from: https://doi.org/10.2337/dc11-1641

30. Agarwal M, Hughes P, Punnose J, Ezimokhai M. Fasting plasma glucose as a screening test for gestational diabetes in a multi-ethnic, high-risk population. Diabetic medicine. 2000;17(10):720-6. Available from: https://doi.org/10.1046/j.1464-5491.2000.00371.x

31. Renz PB, Chume FC, Timm JR, Pimentel AL, Camargo JL. Diagnostic accuracy of glycated hemoglobin for gestational diabetes mellitus: a systematic review and meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2019;57(10):1435-49. Available from: https://doi.org/10.1515/cclm-2018-1191

SUPPLEMENTARY MATERIALS

	VBG-defined GDM +	**VBG-defined GDM -**	**Total**	
Capillary screening +	19	80	99	PPV = 19.2%
Capillary screening -	7	288	295	NPV = 97.6%
Total	26	368	394	
	Sensitivity = 73.1%	Specificity = 78.3%		Prevalence = 6.6%

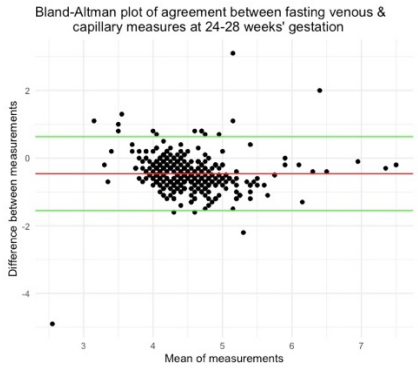
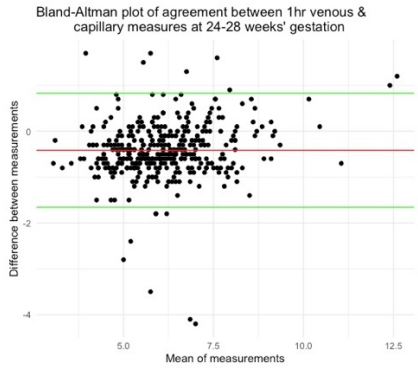
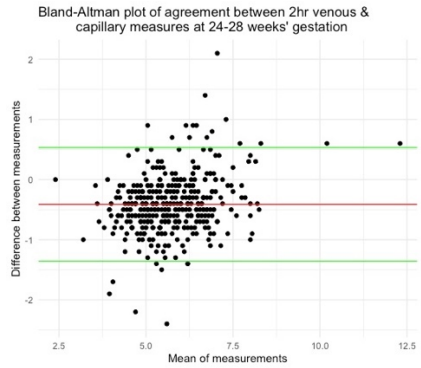
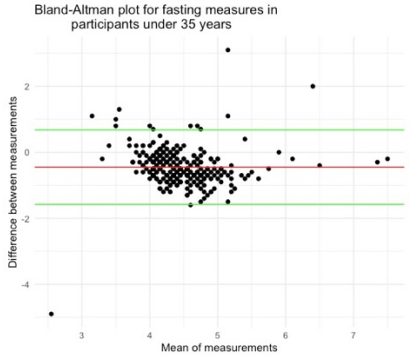
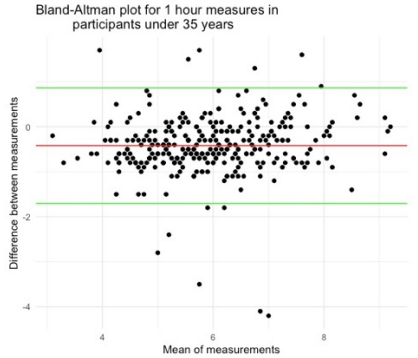
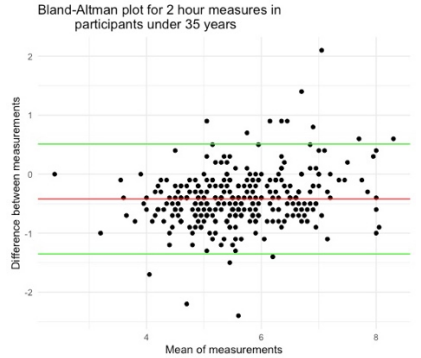
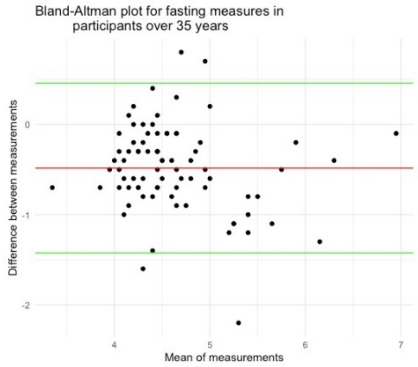
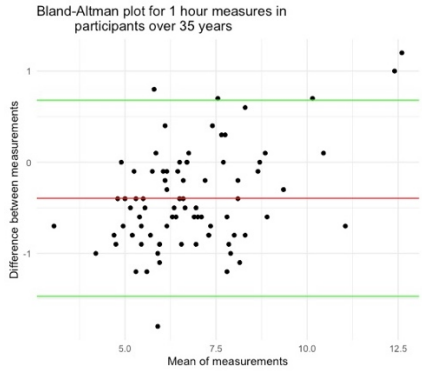
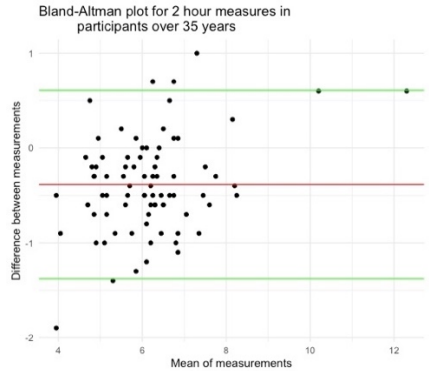
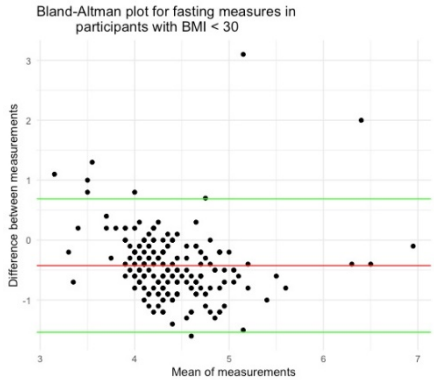
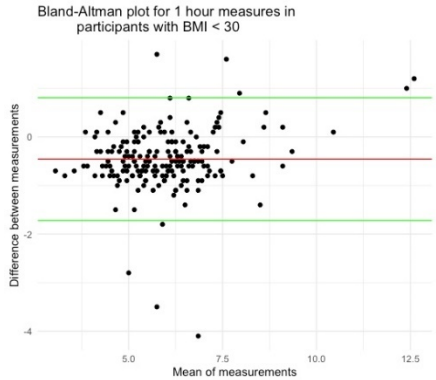
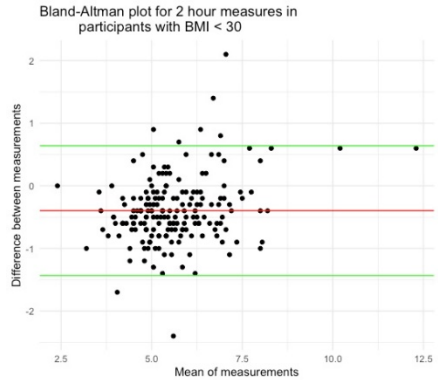
Supplementary table 1. *2x2 table showing GDM prevalence vs. capillary screening using IADPSG cutoffs (n = 394)*

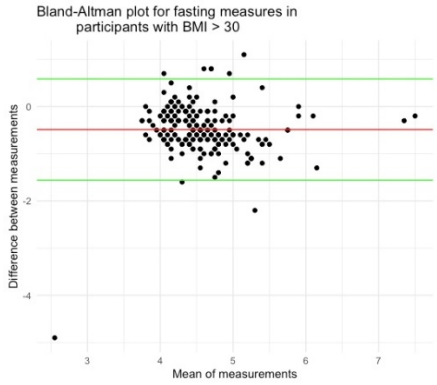
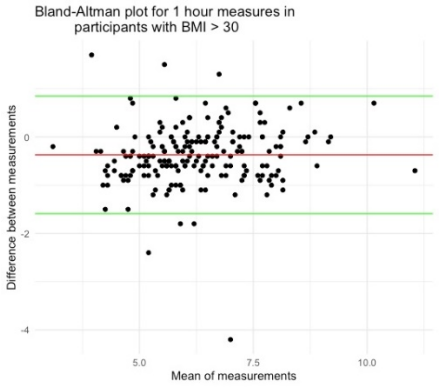
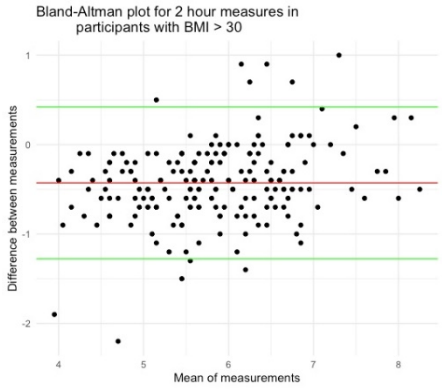
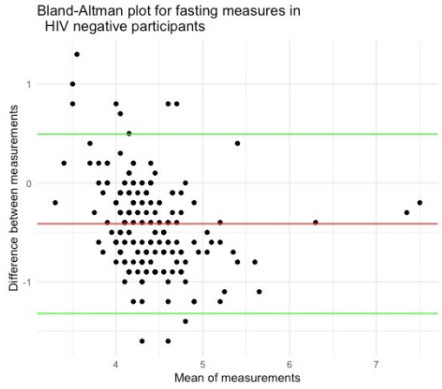
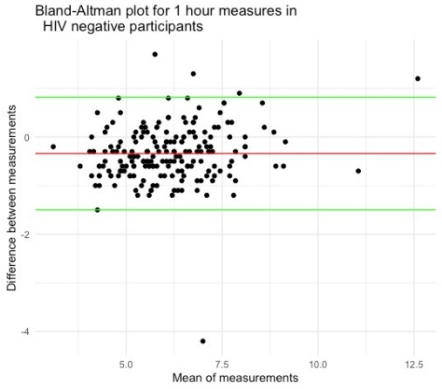
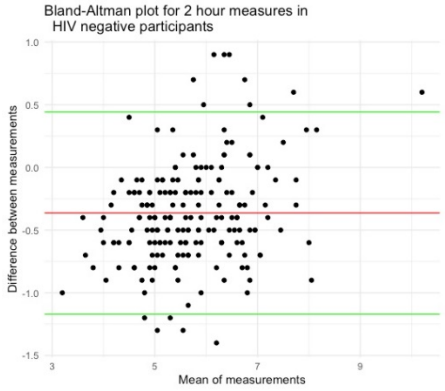
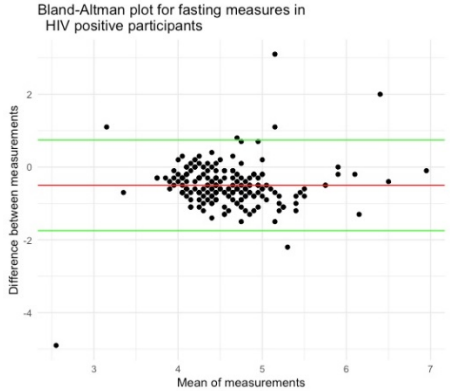
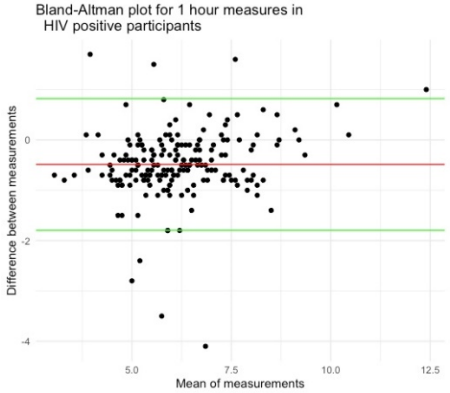
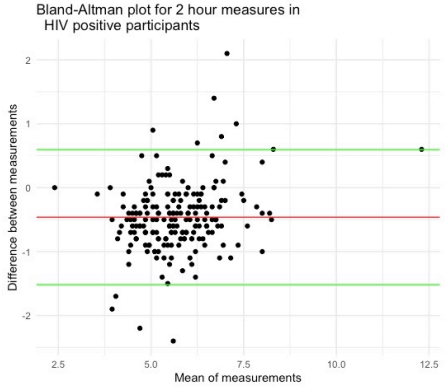
Population characteristic		**False positives using IADPSG cutoffs N = 80**	**Rest of cohort N = 320**	**P-value**
Age (years)	Median (IQR)	30 (27; 34)	30 (25; 34)	0.21
	18-35	65 (81%)	252 (79%)	0.50
	>35	15 (19%)	68 (21%)	-
	>40	2 (3%)	14 (4%)	-
Pre-pregnancy BMI (kg/m^2)	Median (IQR)	31.86 (26.34; 36.28)	30.00 (25.81; 34.41)	0.10
	Non-obese (BMI < 30)	33 (41%)	160 (50%)	0.42
	Obese (BMI > 30	47 (59%)	159 (50%)	-
Obstetric history	Primigravida	7 (9%)	67 (21%)	0.02
	GDM in previous pregnancy	0 (0%)	3 (1%)	0.88
HIV	Positive	52 (65%)	148 (46%)	0.004
Blood pressure, median (IQR)	Systolic	118 (109; 127)	113 (105; 123)	0.02
	Diastolic	71 (66; 75)	68 (62; 74)	0.01
Labs, Median (IQR)	Total cholesterol	4.56 (3.98; 5.46)	4.66 (4.02; 5.29)	0.92
	HDL	1.58 (1.39; 1.78)	1.64 (1.42; 1.89)	0.09
	LDL	2.25 (1.70; 2.86)	2.26 (1.71; 2.81)	0.59
	Triglycerides	1.70 (1.44; 2.09)	1.50 (1.22; 1.84)	0.001

Supplementary table 2. *Descriptive characteristics of mothers who falsely tested positive for GDM compared to the rest of the cohort*

	Method	Positive (n=400)	Sensitivity	Specificity
FCG only	CG ≥ 4.5 mmol/L	245 (61%)	81%	40%
IADPSG cut-offs	Fasting (CG ≥ 5.1 mmol/L)	96 (24%)	72%	79%
	1-hour post glucose (CG ≥ 10.0 mmol/L)	4 (1%)	80%	100%
	2-hour post glucose (CG ≥ 8.5 mmol/L)	5 (1%)	67%	99%
	Overall	**99 (25%)**	**73%**	**78%**
IADPSG cut-offs + 0.7mmol/L	Fasting (BG ≥ 5.8 mmol/L)	27 (7%)	64%	97%
	1-hour post glucose (CG ≥ 10.7 mmol/L)	3 (1%)	60%	100%
	2-hour post glucose (CG ≥ 9.2 mmol/L)	2 (1%)	67%	100%
	Overall	**27 (7%)**	**62%**	**97%**
IADPSG cut-offs + 1.1mmol/L	Fasting (BG ≥ 6.2 mmol/L)	9 (2%)	32%	100%
	1-hour post glucose (CG ≥ 11.1 mmol/L)	3 (1%)	60%	100%
	2-hour post glucose (CG ≥ 9.6 mmol/L)	2 (1%)	67%	100%
	Overall	**9 (2%)**	**31%**	**100%**

Supplementary table 3. *Exploring different cut-offs for capillary glucose measures (FCG = fasting capillary glucose; CG = capillary glucose)*

	Fasting glucose measures	Glucose measures at 1 hour	Glucose measures at 2 hours
Whole cohort	 Mean difference = -0.46	 Mean difference = -0.41	 Mean difference = -0.41
<35 years	 Mean difference = -0.45	 Mean difference = -0.42	 Mean difference = -0.42
>35 years	 Mean difference = -0.48	 Mean difference = -0.40	 Mean difference = -0.39
BMI <30	 Mean difference = -0.42	 Mean difference = -0.46	 Mean difference = -0.40

BMI >30	 Mean difference = -0.49	 Mean difference = -0.37	 Mean difference = -0.43
HIV -	 Mean difference = -0.41	 Mean difference = -0.34	 Mean difference = -0.36
HIV +	 Mean difference = -0.50	 Mean difference = -0.49	 Mean difference = -0.46

Supplementary figure 1. *Bland Altman plots showing agreement in whole cohort and in sub-groups at 24-28 weeks' gestation*

PART C: APPENDICES

APPENDIX A: ETHICS APPROVAL FORMS

ETHICS APPROVAL FOR THE PROPOSED STUDY

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

E-52 – Room46, E-Floor, Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-submissions@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

12 January 2024

HREC REF: 779/2023

Prof Landon Myer
School of Public Health and Family Medicine
Level 5, Falmouth Building
Faculty of Health Sciences
Email: Landon.myer@uct.ac.za
Student email: Mathilda.mennen@uct.ac.za

Dear Prof Myer

PROJECT TITLE: AN EVALUATION OF DIAGNOSTIC APPROACHES FOR GESTATIONAL DIABETES SCREENING IN SOUTH AFRICA-SUB-STUDY LINKED TO 505/2020-MASTERS' CANDIDATE-DR MATHILDA MENNEN

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review and approval.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is only granted for one year until the 30 January 2025.

Please submit a progress report, using the standardised Annual Progress Report Forms (FHS016) **or** (FHS 017) if the study continues beyond the approval period. Please submit a Standard Closure form (FHS 010) when the study has been completed, this includes after publication or thesis submission and final completion.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student Dr Mathilda Mennen will also be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF 779/2023 in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN

HREC REF NO. 779/2023

CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC REF NO. 779/2023

ETHICS APPROVAL FOR THE PARENT STUDY

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 September 2020

HREC REF: 505/2020

Prof L Myer
Division of Epidemiology & Biostatistics
Office 5.51, Level 5 Falmouth Building
FHS
Email: landon.myer@uct.ac.za

Dear Prof Myer

PROJECT TITLE: ADDRESSING THE DUAL BURDEN OF HIV AND NON-COMMUNICABLE DISEASE IN PREGNANCY IN SOUTH AFRICA"

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to ensuring that participants are appropriately followed up & treated should diagnoses of NCDs be made.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 September 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC/REF:505/2020sa

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF: 505/2020sa

APPENDIX B: PARENT STUDY DATA CAPTURE INSTRUMENT

CAMP: Maternal Physical Examination Form V1
Version 1.0, 21st August 2019

MPE V1

PWID: _ _ _ _ _ _ - _ _

MATERNAL PHYSICAL EXAMINATION FORM

This CRF applies to ALL enrolled CAMP Participants
Complete during 24-28 weeks (ENROLMENT) Study Visit

Visit Date								
D	D	M	M	M	Y	Y	Y	Y

Visit Code	
V	1

ANTHROPOMETRY		
Pre-Pregnancy Weight	☐☐☐.☐ kg	☐ Not Known
Weight	☐☐☐.☐☐ kg	☐ Not Measured
Height	☐☐☐.☐ cm	☐ Not Measured
MUAC	☐☐.☐ cm	☐ Not Measured
BLOOD PRESSURE		
Reading 1	**Time of Measurement** ☐☐:☐☐	**Systolic:** ☐☐☐ mmHg **Diastolic:** ☐☐☐ mmHg
	☐☐:☐☐	☐☐☐ mmHg ☐☐☐ mmHg
Reading 2 *(after 30 mins from R1)*	**Time of Measurement** ☐☐:☐☐	**Systolic:** ☐☐☐ mmHg **Diastolic:** ☐☐☐ mmHg
	☐☐:☐☐	☐☐☐ mmHg ☐☐☐ mmHg
Location: (tick one) ☐ Left Arm ☐ Right Arm		

GLUCOMETER CAPILLARY BLOOD READINGS		
Baseline Glucose	☐☐.☐ mmol/L	☐ Not Measured
60 min Glucose	☐☐.☐ mmol/L	☐ Not Measured
120 min Glucose	☐☐.☐ mmol/L	☐ Not Measured
LABORATORY VENOUS BLOOD RESULTS		
Baseline Glucose	☐☐.☐ mmol/L	☐ Not Measured
60 min Glucose	☐☐.☐ mmol/L	☐ Not Measured
120 min Glucose	☐☐.☐ mmol/L	☐ Not Measured
HDL	☐.☐☐ mmol/L	☐ Not Measured
LDL	☐.☐☐ mmol/L	☐ Not Measured
Triglycerides	☐.☐☐ mmol/L	☐ Not Measured
Total Cholesterol	☐.☐☐ mmol/L	☐ Not Measured

Signed Assessor of Measurements: _____ Date: _____ / _____ / _____
DD MMM YYYY

Signed QC Officer: _____ Date: _____ / _____ / _____
DD MMM YYYY

APPENDIX C: JOURNAL SUBMISSION GUIDELINES

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.