UNIVERSITY OF BIRMINGHAM
University of Birmingham Research at Birmingham

Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border

Prüst, Janna T.; Brummaier, Tobias; Wah, Mu; Yee, Htay Htay; Win, Nyo Nyo; Pimanpanarak, Mupawjay; Min, Aung Myat; Gilder, Mary Ellen; Tun, Nay Win; Ilozumba, Onaedo; Kabeer, Basirudeen Syed Ahamed; Terranegra, Annalisa; Nosten, Francois; Lee, Sue J.; McGready, Rose

DOI:
10.12688/wellcomeopenres.17743.2

License:
Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Prüst, JT, Brummaier, T, Wah, M, Yee, HH, Win, NN, Pimanpanarak, M, Min, AM, Gilder, ME, Tun, NW, Ilozumba, O, Kabeer, BSA, Terranegra, A, Nosten, F, Lee, SJ & McGready, R 2023, 'Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: An observational cohort', *Wellcome Open Research*, vol. 7, 132 . https://doi.org/10.12688/wellcomeopenres.17743.2

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 28. May. 2024

Check for updates

RESEARCH ARTICLE

REVISED Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: An observational cohort [version 2; peer review: 2 approved]

Janna T. Prüst[1,2], Tobias Brummaier[1,3,4], Mu Wah[1], Htay Htay Yee[1], Nyo Nyo Win[1], Mupawjay Pimanpanarak[1], Aung Myat Min[1], Mary Ellen Gilder[5], Nay Win Tun[1], Onaedo Ilozumba[2,6], Basirudeen Syed Ahamed Kabeer[7], Annalisa Terranegra[7], François Nosten[1,8], Sue J. Lee[8,9], Rose McGready[1,8]

[1]Shoklo Malaria Research Unit, Mahidol–Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400, Thailand
[2]Department of Health Sciences, Vrije Universiteit Amsterdam, Amsterdam, 1081, The Netherlands
[3]Swiss Tropical and Public Health Institute, Allschwill, 4123, Switzerland
[4]University of Basel, Basel, 4001, Switzerland
[5]Department of Family Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand
[6]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
[7]Research Department, Sidra Medicine, Doha, Qatar
[8]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, OX3 7LG, UK
[9]Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, 10400, Thailand

v2 **First published:** 07 Apr 2022, **7**:132
https://doi.org/10.12688/wellcomeopenres.17743.1
Latest published: 18 Jan 2023, **7**:132
https://doi.org/10.12688/wellcomeopenres.17743.2

Abstract

Background: Gestational diabetes mellitus (GDM) contributes to maternal and neonatal morbidity. As data from marginalized populations remains scarce, this study compares risk-factor-based to universal GDM screening in a low resource setting.
Methods: This is a secondary analysis of data from a prospective preterm birth cohort. Pregnant women were enrolled in the first trimester and completed a 75g oral glucose tolerance test (OGTT) at 24-32 weeks' gestation. To define GDM cases, Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO trial) criteria were used. All GDM positive cases were treated. Sensitivity and specificity of risk-factor-based selection for screening (criteria: age ≥30y, obesity (Body mass

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 18 Jan 2023	✓ view	✓ view
version 1 07 Apr 2022	? view	? view

1. **Jane E. Hirst**, University of Oxford,

index (BMI) ≥27.5kg/m^2), previous GDM, 1st degree relative with diabetes, previous macrosomia (≥4kg), previous stillbirth, or symphysis-fundal height ≥90th percentile) was compared to universal screening using the OGTT as the gold standard. Adverse maternal and neonatal outcomes were compared by GDM status.
Results: GDM prevalence was 13.4% (50/374) (95% CI: 10.3-17.2). Three quarters of women had at least one risk factor (n=271 women), with 37/50 OGTT positive cases correctly identified: sensitivity 74.0% (59.7-85.4) and specificity 27.8% (3.0-33.0). Burman women (self-identified) accounted for 29.1% of the cohort population, but 38.0% of GDM cases. Percentiles for birthweight (p=0.004), head circumference (p=0.002), and weight-length ratio (p=0.030) were higher in newborns of GDM positive compared with non-GDM mothers. 21.7% (75/346) of newborns in the cohort were small-for-gestational age (≤10th percentile). In Burman women, overweight/obese BMI was associated with a significantly increased adjusted odds ratio 5.03 (95% CI: 1.43-17.64) for GDM compared with normal weight, whereas in Karen women, the trend in association was similar but not significant (OR 2.36; 95% CI 0.95-5.89).
Conclusions: Risk-factor-based screening missed one in four GDM positive women. Considering the benefits of early detection of GDM and the limited additional cost of universal screening, a two-step screening program was implemented.

Keywords
Gestational diabetes mellitus, HAPO trial, Maternal and neonatal anthropometry, Oral glucose tolerance test, Symphysis-fundal height measurements, Migrants, Risk-factor-based screening, thin-diabetic

This article is included in the Mahidol Oxford Tropical Medicine Research Unit (MORU) gateway.

Oxford, UK

2. **Blair Johnson Wylie**, Beth Israel Deaconess Medical Center, Boston, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Tobias Brummaier (tobias@shoklo-unit.com)

Author roles: Prüst JT: Conceptualization, Data Curation, Formal Analysis, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Brummaier T**: Conceptualization, Data Curation, Formal Analysis, Methodology, Project Administration, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Wah M**: Investigation, Writing – Review & Editing; **Yee HH**: Investigation, Writing – Review & Editing; **Win NN**: Investigation, Writing – Review & Editing; **Pimanpanarak M**: Investigation, Writing – Review & Editing; **Min AM**: Investigation, Validation, Writing – Review & Editing; **Gilder ME**: Investigation, Validation, Writing – Review & Editing; **Tun NW**: Investigation, Validation, Writing – Review & Editing; **Ilozumba O**: Supervision, Writing – Review & Editing; **Kabeer BSA**: Funding Acquisition, Writing – Review & Editing; **Terranegra A**: Funding Acquisition, Writing – Review & Editing; **Nosten F**: Funding Acquisition, Writing – Review & Editing; **Lee SJ**: Formal Analysis, Methodology, Supervision, Visualization, Writing – Review & Editing; **McGready R**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Methodology, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Wellcome [220211; assigned to Nicholas Day]; and the parent cohort was funded by Sidra Medicine, a member of the Qatar Foundation for Education, Science and Community Development [project numbers SDR400089, SDR400075 and SDR400132].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2023 Prüst JT *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Prüst JT, Brummaier T, Wah M *et al.* **Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: An observational cohort [version 2; peer review: 2 approved]** Wellcome Open Research 2023, **7**:132
https://doi.org/10.12688/wellcomeopenres.17743.2

First published: 07 Apr 2022, **7**:132 https://doi.org/10.12688/wellcomeopenres.17743.1

REVISED **Amendments from Version 1**

Version 2 of the manuscript was submitted in response to the reviewer comments on version 1. Comments and suggestions by the reviewers were considered to revise the manuscript or rebuked were appropriate (see response to reviewer comments). Most notably all references to environmental factors (i.e., seasonality of GDM diagnosis) has been removed from the manuscript. This also resulted in the removal of Figure 3a and Figure 3b from version 2 of the manuscript.

The abstract was amended to include all risk factors that were screened for the risk-factor based screening procedure. Sample size justification and a power estimation was added. Some items (e.g., Asian BMI definitions, exact nature of the risk-factor based screening or rational to include symphysis-fundal height (SFH) in the analysis) were clarified.

Table 1 was complemented with the addition of number of pregnant women presenting with a SFH ≥90th centile and figures describing gestational weight gain; how these compare between non-GDM and GDM women was also added.

Centiles for head circumference, length, and weight for length ratio, as published by the Intergrowth 21st consortium, were added to Table 2, together with the number of neonates admitted to the special care baby unit (SCBU) and number of neonates diagnosed with hypoglycaemia.

As suggested by the reviewer, a paragraph presenting results of oral glucose tolerance test (OGTT) results was added.

A sentence on historical context of GDM screening was added to the discussion and the fact the there is no international consensus on the best screening approach exists, together with the ongoing debate whether screening criteria derived from high-resource settings are applicable to low-resource settings is now discussed in more detail.

Strengths and limitations were expanded to address comments from the reviewers. Lastly, the conclusion was amended to highlight the translational impact of this analysis.

Any further responses from the reviewers can be found at the end of the article

Introduction

Gestational diabetes mellitus (GDM) is rising in tandem with obesity globally, including in South- and South-East Asia[1]. The prevalence of GDM in Thailand is estimated between 6.1% and 29.2%[1,2]. In Myanmar, there is insufficient data to provide reliable estimations of the GDM prevalence[1]. Detection of GDM is important as it is associated with neonatal macrosomia, neonatal hypoglycaemia and an increased risk for birth complications, such as shoulder dystocia and the need for caesarean section[3–5]. Furthermore, GDM is associated with an increased risk of preeclampsia, and entails a tenfold risk of developing type II diabetes and doubles the risk of cardiovascular events later in life[6,7].

In absolute numbers more women are diagnosed with GDM in low- and middle-income countries (LMIC although relative estimates are similar between LMIC and high-income countries (HIC): 13.5% and 13.4%, respectively)[8]. Within HIC, migrant women have a higher risk for GDM and associated adverse birth outcomes, but this is poorly evidenced for migrants in LMIC[9]. In South-East Asia domestic as well as international migration is a dominant feature and access to health care for migrants is problematic[10,11]. While most women receive some form of antenatal care (ANC), screening for GDM is often not available[12,13]. In addition, awareness of GDM is limited, as are adequate protocols and tools to monitor blood glucose, which hinders best-practice management[13,14].

Officially Thailand has approximately 2 million migrant workers predominantly from Myanmar, as well as an unknown number of undocumented migrants. Shoklo Malaria Research Unit (SMRU) has provided health care to both the refugee and migrant populations residing along the Thailand-Myanmar border. In the pregnant migrant population attending SMRU antenatal (ANC) clinics, the nutrition transition has been marked by a two-fold increase in first trimester overweight in just over a decade, aggravated by limited awareness of healthy diets and lifestyle[15,16]. These trends in marginalized populations are worrying given the greater risk of cardiometabolic effects occurring at lower BMI in Asians than in white Europeans[17].

In a meta-analysis, Lee *et al*. described a GDM prevalence of 11.5% in Asian women and identified the following risk factors: multiparity, previous GDM, or pregnancy-induced hypertension (PIH), a family history of GDM and an increased maternal body mass index (BMI ≥25kg/m^2)[18]. An obstetric history of preterm birth, macrosomia, stillbirth, or an infant with congenital anomalies are also recognised GDM risk factors[18].

GDM diagnosis and management improves maternal and perinatal outcomes, although this is largely evidenced from HIC[13,19]. Both universal and risk-factor-based screening are common practices, with no international consensus about best practice[2,20,21]. In 2011–2012, one of the first surveys conducted in a refugee camp reported a GDM prevalence of 10.1% (95% CI 6.2-14.0%) on the Thailand-Myanmar border with GDM being significantly associated with increased maternal age and parity, and low literacy[20]. Although the proportion of caesarean section and obesity (BMI ≥27.5kg/m^2) were higher among women with GDM, this difference was not significant[20]. In the low-resource setting of the refugee camp, the decision at that time was to commence efforts to screen for GDM based on risk factors using the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) criteria[22]. SMRU implemented this approach in all its antenatal care clinics on the border in 2018.

The study presented here aimed to evaluate the performance of two screening methods for GDM detection: risk-factor-based identification of pregnant women who were then screened by an OGTT, which was routinely used in antenatal care clinics for migrant women, to universal screening by OGTT. Within this cohort, risk factors for GDM were examined and adverse maternal and neonatal outcomes were evaluated in women with and without GDM.

Methods

Ethical approval

The study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Ethics Reference: TMEC 15–062, initial approval 1

December 2015), the Oxford Tropical Research Ethics Committee (Ethics Reference: OxTREC: 33–15, initial approval 16 December 2015) and reviewed by the local Tak Province Community Ethics Advisory Board. The study was conducted in full conformity with the Declaration of Helsinki and followed regulations of the ICH Guidelines for Good Clinical Practice.

Study design

This is a secondary analysis of data from an observational preterm birth cohort study with data collected prospectively between September 2016 and February 2019 in women enrolled in their first trimester of pregnancy (ClinicalTrials.gov Identifier: NCT02797327) with GDM screening occurring from December 2016 to November 2018.

Study setting

SMRU was established more than three decades ago and combines research and humanitarian work that serves the migrant population alongside the Thailand-Myanmar border. To be accessible within these communities, which largely depend on below minimum wage jobs, SMRU operates free-of-charge walk-in clinics offering universal antenatal care, as well as 24-hour delivery services, led by trained personnel originating from the local population.

At the same clinics, women may be invited to participate in research. The study was explained to all pregnant women attending SMRU ANC clinics in the first trimester and they were invited to participate if they met the study inclusion criteria and enrolled if consent was forthcoming. Informed consent was obtained in the form of a signature or in the event of an illiterate participant by thumbprint coupled with a confirmatory signature by an impartial literate witness.

Sample size

A detailed description of the study protocol and SMRU routine ANC procedures are available elsewhere[23]. Briefly, women were followed fortnightly throughout pregnancy, at delivery, and in the postpartum period. The planned sample size of 400 in the original cohort study was based on estimated preterm birth rates (of approximately 8%) and on the following inclusion criteria: a viable, singleton first trimester pregnancy and an unremarkable medical and obstetric history e.g., no history of caesarean section. For this secondary analysis of the original cohort to determine appropriateness of GDM risk-factor-based screening, additional exclusion criteria were miscarriage prior to GDM screening, maternal death, lost to follow-up, withdrawal of consent (primary cohort), and if OGTT was performed late (gestational age (GA) ≥33 weeks) or not done at all. Women who did not complete follow-up to delivery were replaced as permitted in the original protocol. At an expected GDM rate of 10%, a sample size of 400 is expected to be sufficient to determine population prevalence[20].

Study variables

Baseline characteristics, regular prenatal symphysis-fundal height (SFH) measurements, blood pressure, weight, and assessment of gestation by ultrasound, as well as birth outcomes, were collected by trained ANC staff and midwives in accordance with the study protocol. GA was estimated by crown rump length measured by first trimester ultrasound[24]. Body-mass index (BMI) definitions followed recommendations for Asian BMI groups: underweight <18.5 kg/m^2; normal weight 18.5 to <23 kg/ m^2; overweight 23 to <27.5 kg/m^2; obese ≥27.5 kg/m^2[17].

While the study protocol specified GDM screening with OGTT at 24–26 weeks of gestation, the HAPO study target time for testing was at 28 weeks (24–32 weeks)[22]. Therefore, OGTTs to 32 weeks of gestation were included in this analysis. In women with a history of GDM, an OGTT was performed as early as possible in pregnancy and repeated at 24–26 weeks if previously negative. GDM diagnosis was based on HAPO trial cut-offs: a fasting capillary blood glucose measurement of ≥92mg/dL, ≥180mg/dL one hour or ≥153mg/dL two hours after ingestion of 75g glucose were considered positive[22].

Risk-factor based screening

In 2018, risk-factor-based screening for GDM commenced at SMRU clinics. The risk factors were based on a survey in Karen and Burmese women in a SMRU refugee clinic screened at 24-28 weeks with a 75-gram OGTT using the HAPO trial cut-offs, where prevalence was 10.1% (95% CI 6.1-14.0). Risk factors in positive cases and review of recommendations from UK and Australia, both of which have populations of South-East Asian women, and Thailand resulted in the final list[20]. The risk factors for GDM screening required at least one positive finding among the following 10 criteria: (i) age ≥30 years, (ii) obesity (BMI ≥27.5kg/m^2, the WHO definition for Asian populations)[17], (iii) GDM in a previous pregnancy, (iv) family history (1st degree relative) of diabetes mellitus (although this is of reduced sensitivity in LMIC as access to diabetes screening is limited), (v) previous macrosomia (≥4kg), (vi) previous stillbirth, (vii) SFH ≥90th percentile, (viii) previous caesarean section regardless of birth-weight, (ix) 2+/3+ glucose on a urine dipstick test, or (x) polycystic ovarian syndrome (PCOS). The following criteria were not included in the analysis: women with a previous caesarean section, as they were excluded from the original study protocol, PCOS, as it was not encountered, and glucosuria, as there was no routine screening, leaving seven criteria.

Maternal and Neonatal Outcomes

In resource-limited settings, assessment of the uterus size by SFH measurement as a proxy for fetal size has been suggested as a first level screening tool for fetal growth assessment. SFH measurement is a straightforward and inexpensive method, but its precision is controversial[3]. A previously published bespoke SFH growth curve has been in use for more than 10 years in the pregnant population along the Thailand-Myanmar border[25]; however, whether increased SFH using this local growth curve is a useful addition to the identification of GDM (macrosomia is a common adverse effect of GDM) has not been assessed.

Serial SFH measurements were included from 16 weeks of gestation on a two-weekly basis and data was examined using both, local population and international centiles[25,26].

Gestational weight gain was defined as the final maternal weight measured not more than four weeks prior to birth, minus the weight measured at the first antenatal visit. For women with a normal BMI at enrolment (between 18.50 and 24.99kg/m^2), Intergrowth-21st standard percentiles for each weight measurement from ≥26 weeks and ≤40 weeks of gestation were calculated[27].

Neonatal anthropometry (i.e., birthweight, head circumference, and length) were only considered if measured within 72 hours of birth. If women gave birth at SMRU, the neonate was weighed on a digital SECA 354 scale (precision 5g) with weekly calibration. Percentiles and z-scores for neonatal anthropometry were calculated using standards as published by the Intergrowth-21st Project[28]. Born too small or large for GA (SGA, LGA) were defined as ≤10th and ≥90th percentile, respectively.

Standard management of infants admitted to the special care baby unit included measurement of blood glucose and treatment for neonates with blood glucose below 45 mg/dL

GDM management

If GDM was diagnosed, all women were counselled about lifestyle modification (e.g., diet and exercise) and, due to the unavailability of glucose self-monitoring in the population, the status of GDM control was monitored weekly or every two weeks at the clinic. Monitoring was as follows: women with GDM were asked to attend fasting and blood glucose was checked on arrival; then women ate a typical meal and were retested after one hour (post-prandial) with the desired value of <90 mg/dL (fasting) and <140 mg/dL (after one hour) for satisfactory control. Treatment was provided either directly or if non-pharmacologic interventions led to insufficient glucose control, with metformin as the first choice and glibenclamide as an additional oral agent. Due to the lack of home-based glucose monitoring options and the absence of adequate storage facilities, insulin is rarely prescribed in this population.

Statistical analysis

Data were analysed using Stata, version 17.0 (TX, USA) (Stata, RRID:SCR_012763, https://www.stata.com/). Normally distributed continuous data were presented as means with standard deviation (SD) and non-normally distributed data as medians with interquartile range (IQR). Baseline characteristics as well as birth outcomes were compared between women with and without GDM. For continuous variables, the Student's t-test or Mann-Whitney U test were used, and categorical variables were compared using the Fisher's exact or Chi-square test. Univariate associations were quantified using logistic regression. To evaluate the predictive ability of the risk factors used in the current screening approach to identify women with GDM, all risk factors were combined into one logistic regression model, using GDM as the outcome. The sensitivity and specificity of risk-factor-based screening criteria was calculated using OGTT as the gold standard. An *any positive* test principle (i.e., if any of the GDM risk factors stated above were positive, an OGTT was performed) was the basis for this assessment. For further in-depth analysis and to identify risks and potential risk groups for GDM in this population, age (30 or older, vs. all others), smoking (yes/no), ethnicity (Karen and Burman), and BMI groups underweight, normal weight (reference group) and overweight/obese were explored using interaction terms and logistic regression modelling.

Results

Following exclusions, 87.4% (374/428) of pregnant women from the original cohort were available for analysis (Figure 1). Of these, 13.4% (50/374, 95% CI 10.3-17.2), were diagnosed with GDM by OGTT. The median number of antenatal care visits was 16 (IQR 15-17). Baseline maternal characteristics of women with and without GDM were compared (Table 1). Women with GDM were significantly more likely to have had previous GDM (4.0% vs. 0, p<0.001) and postpartum hypertension (4.0% vs. 0.3%, p=0.006) and less likely to have had previous preterm labour (0% vs. 7.41%, p=0.047). A family history of diabetes was rarely reported (n=6) by women irrespective of GDM status.

Overall, 23 women (6.1%) were obese (BMI ≥27.5kg/m^2). In the group of women who self-identified as being of Burman descent the GDM prevalence was 17.4% (19/109) compared to 11.7% (29/247) in women of Karen descent and 11.1% (2/18) in women of other ethnicities. Burman women accounted for 29.1% of the cohort population, but 38.0% of GDM cases (Table 1). There were more women with GDM with an SFH ≥90th centile during pregnancy with gestational week ≥24, 68.0% vs. 52.8%, p=0.044 (Table 2). In particular, from about 224 days (32 weeks) onwards, women with GDM appeared to have larger SFH when compared with women without GDM (Figure 2).

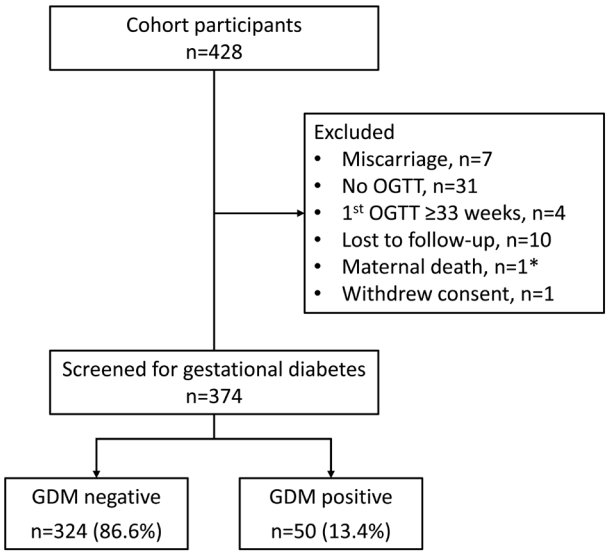

Figure 1. Flow diagram of participant selection. Abbreviations: GDM gestational diabetes mellitus, OGTT oral glucose tolerance test. * Sudden death due to mixed mitral valve disease at seven months gestation.

Table 1. Demographic enrolment characteristics of women without and with GDM diagnosed by OGTT.

Characteristics	Total	Without GDM	With GDM	p-value
N	374	324	50	
Age (years), median [IQR]	25 [21, 30]	25 [21, 30]	24 [22, 28]	0.899
Age 30 and older, n (%)†	99 (26.5%)	87 (26.9%)	12 (24.0%)	0.671
Ethnicity*, n (%)				0.333
Karen	247 (66.0%)	218 (67.3%)	29 (58.0%)	
Burman	109 (29.1%)	90 (27.8%)	19 (38.0%)	
Other	18 (4.8%)	16 (4.9%)	2 (4.0%)	
Gravidity, n (%)				0.935
Nulligravida	99 (26.5%)	86 (26.5%)	13 (26.0%)	
Multigravida	275 (73.5%)	238 (73.5%)	37 (74.0%)	
GA at enrolment (weeks), median [IQR]	9.6 [8.1, 11.6]	9.5 [8.0, 11.6]	9.9 [8.6, 11.7]	0.211
Literate, n (%)	240 (64.2%)	210 (64.8%)	30 (60.0%)	0.509
Smoking, n (%)	27 (7.2%)	21 (6.5%)	6 (12.0%)	0.161
BMI (kg/m^2), median [IQR]	20.6 [18.9, 23.3]	20.5 [19.0, 23.1]	21.0 [18.5, 24.4]	0.586
BMI ≥27.5kg/m^2, n (%)†	23 (6.1%)	19 (5.9%)	4 (8.0%)	0.558
BMI <18.5kg/m^2, n (%)	73 (19.5%)	61 (18.8%)	12 (24.0%)	0.390
Height (cm), mean ± SD	151.8 ± 4.8	151.7 ± 4.8	152.4 ± 4.7	0.369
MUAC (cm), median [IQR]	25.9 [23.8, 28.3]	25.9 [23.9, 28.3]	25.4 [23.6, 28.9]	0.793
HIV, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Syphilis, n (%)	6 (1.6%)	6 (1.9%)	0 (0.0%)	0.331
HepBsAg positive, n (%)	21 (5.6%)	17 (5.2%)	4 (8.0%)	0.431
Obstetric history, n (%)				
GDM†	2 (0.5%)	0 (0.0%)	2 (4.0%)	<0.001
Vacuum delivery	3 (0.8%)	3 (0.9%)	0 (0.0%)	0.495
Macrosomia†	2 (0.5%)	1 (0.3%)	1 (2.0%)	0.127
Stillbirth†	6 (1.6%)	6 (1.9%)	0 (0.0%)	0.332
Miscarriage	93 (24.9%)	82 (25.3%)	11 (22.0%)	0.614
Previous preterm Labour	24 (6.4%)	24 (7.4%)	0 (0.0%)	0.047
Pregnancy Induced Hypertension	2 (0.5%)	2 (0.6%)	0 (0.0%)	0.577
Hypertension postpartum	3 (0.8%)	1 (0.3%)	2 (4.0%)	0.006
Family history of diabetes†	6 (1.6%)	5 (1.5%)	1 (2.0%)	0.811
During Pregnancy				
SFH ≥90th centile (GA ≥24), n (%)**†	205/374 (54.8%)	171/324 (52.8%)	34/50 (68.0%)	0.044
Gestational weight gain (kg), median [IQR]	10 [7, 12]	10 [7, 12]	10 [7, 12]	0.982
Weight gain ≥90th centile	43/367 (11.7%)	38/319 (11.9%)	5/48 (10.4%)	0.764

Abbreviations (alphabetic order): Ag antigen, BMI body mass index, GA gestational age, GDM gestational diabetes mellitus, IQR interquartile range, HepBsAg hepatitis B surface antigen, HIV human immunodeficiency virus, MUAC mid-upper arm circumference, SD standard deviation.

† Included in list of risk-factor based screening

*Other includes Mon (n=8), Pa Oh (n=5), Rakhine (n=2), Shan (n=1), Ka Main (n=1), one patient self-identified as Muslim (n=1)

** at least once from 24 weeks onward

Table 2. Birth outcomes and neonatal anthropometry of women without and with GDM diagnosed by OGTT.

Birth outcomes and neonatal anthropometry	Total	Without GDM	With GDM	p-value
N	374	324	50	
GA at delivery (weeks), median [IQR]	39.6 [38.7, 40.1]	39.6 [38.8, 40.3]	39.1 [38.3, 39.9]	0.068
Gestational weight gain (kg), median [IQR]	10 [7, 12]	10 [7, 12]	10 [7, 12]	0.982
Weight gain ≥90th centile	43/367 (11.7%)	38/319 (11.9%)	5/48 (10.4%)	0.764
SFH ≥90th centile (GA ≥24), n (%)	205/374 (54.8%)	171/324 (52.8%)	34/50 (68.0%)	0.044
Preterm birth, n (%)	18/374 (4.8%)	17/324 (5.2%)	1/50 (2.0%)	0.318
Stillbirth, n (%)	4/374 (1.1%)	4/324 (1.2%)	0/50 (0.0%)	1.000
Mode of delivery				
Vaginal delivery, n (%)	352/374 (94.1%)	304/324 (93.8%)	48/50 (96.0%)	0.543
Caesarean Section, n (%)	20/374 (5.3%)	18/324 (5.6%)	2/50 (4.0%)	0.649
Place of labour				0.905
SMRU clinic, n (%)	301/374 (80.5%)	259/324 (79.9%)	42/50 (84.0%)	
Home, n (%)	27/374 (7.2%)	25/324 (7.7%)	2/50 (4.0%)	
Hospital, n (%)	37/374 (9.9%)	32/324 (9.9%)	5/50 (10.0%)	
Other, n (%)	9/374 (2.4%)	8/324 (2.5%)	1/50 (2.0%)	
Induction of labour, n (%)	25/373 (6.7%)	22/323 (6.8%)	3/50 (6.0%)	0.831
Augmentation of labour, n (%)	36/373 (9.7%)	31/323 (9.6%)	5/50 (10.0%)	0.929
Length of ROM (min), median [IQR]	36 [5, 160]	35 (5, 156)	65 (7, 217)	0.287
Postpartum haemorrhage‡, n(%)	19/352 (5.4%)	18/304 (5.9%)	1/48 (2.1%)	0.274
Perineum				0.604
Intact, n (%)	160/303 (52.8%)	136/261 (52.1%)	24/42 (57.1%)	
1st or 2nd degree tear, n (%)	134/303 (44.2%)	116/261 (44.4%)	18/42 (42.9%)	
Episiotomy, n (%)	9/303 (3.0%)	9/261 (3.4%)	0/42 (0.0%)	
Infant sex (male), n (%)	181/373(48.5%)	155/323 (48.0%)	26/50 (52.0%)	0.597
Median Apgar score [IQR] at one min	9 [9, 9]	9 [9, 9]	9 [9, 9]	0.825
Median Apgar score [IQR] at five min	10 [10, 10]	10 [10, 10]	10 [10, 10]	0.620
Neonatal resuscitation, n (%)	8/361 (2.2%)	8/313 (2.6%)	0/48 (0.0%)	0.263
Abnormal newborn exam, n (%)	4/373 (1.1%)	4/323 (1.2%)	0/50 (0.0%)	1.00
Infant weight (g), mean ± SD	2972 ± 402	2952 ± 398	3096 ± 408	0.019
Large for GA (>p90), n (%)	7/346 (2.0%)	4/297 (1.3%)	3/49 (6.1%)	0.028
Small for GA (<P10), n (%)	75/346 (21.7%)	68/297 (22.9%)	7/49 (14.3%)	0.175
Percentile*, median [IQR]	24.8 [11.6, 47.6]	23.2 [11.2, 43.9]	40.5 [16.3, 61.0]	0.004
Head circumference, mean ± SD	32.8 ± 1.3	32.7 ± 1.3	33.3 ± 1.3	0.005
Percentile, median [IQR]	19.9 [7.54, 40.4]†	19.3 [6.69, 37.6]§	30.6 [12.8, 60.5]$	0.002

Birth outcomes and neonatal anthropometry	Total	Without GDM	With GDM	p-value
Length[28], mean ± SD	48.2 ± 2.0	48.1 ± 2.0	48.4 ± 1.8	0.358
Percentile, median [IQR]	27.5 [13.2, 50.4]†	26.5 [13.0, 49.3]§	33.1 [15.6, 59.8]$	0.182
Weight-length ratio (%), mean ± SD	6.2 ± 0.7	6.1 ± 0.7	6.4 ± 0.7	0.010
Percentile, median [IQR]	0.96 [0.61, 1.72]†	0.91 [0.60, 1.62]§	1.17 [0.91, 1.92]$	0.030
Admitted special care baby unit, n (%)	73/374 (19.5%)	65 (20.1%)	8 (16.0%)	0.500
Hypoglycaemic, n (%)	2/73 (2.74%)	2/65 (3.08%)	0/8	0.615

Abbreviations (alphabetic order): GA gestational age, GDM gestational diabetes mellitus, IQR interquartile range, min minutes, ROM rupture of membranes, SD standard deviation, SFH symphysis fundal height, SMRU Shoklo Malaria Research Unit.

*birth weight for GA and sex, ‡ >500ml blood loss, † n=345, § n=296, $ n=49

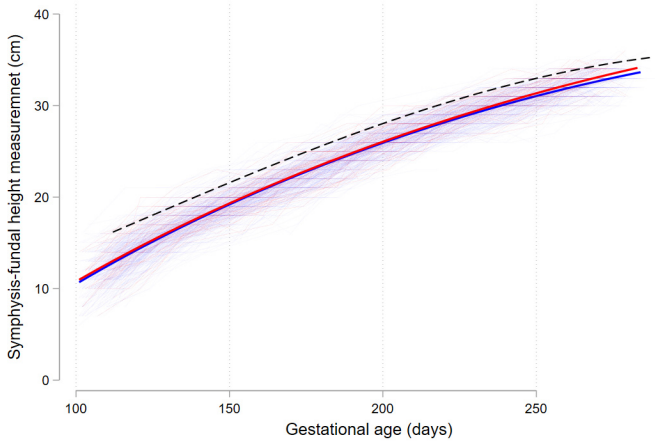

Figure 2. Symphysis-fundal height trajectories throughout pregnancy. Red lines indicate women with GDM (13.4%, n=50), blue lines women without GDM (86.6%, n=324). Dashed black line indicates the 90th centile. Heavy red and blue lines represent fractional polynomial fit from individual measurements. Abbreviations: GDM gestational diabetes mellitus.

Red lines indicate women with GDM (13.4%, n=50), blue lines women without GDM (86.6%, n=324). Dashed black line indicates the 90th centile. Heavy red and blue lines represent fractional polynomial fit from individual measurements. Abbreviations: GDM gestational diabetes mellitus.

Birth outcomes

Newborns from mothers with GDM were heavier (mean birthweight (SD): 3096g (408) vs. 2952g (398), p=0.019), and nearly five times more likely to be born large for gestational age (6.1% (3/49) vs. 1.3% (4/297), OR 4.78, 95% CI 1.04-22.1) (Table 2). They were also more likely to be in a higher percentile for birthweight and head circumference, adjusted for GA and sex: median [IQR]: 40.5 [16.3, 61.0] vs. 23.2 [11.2, 43.9], p=0.004), and 30.6 [12.8, 60.5] vs. 19.3 [6.69, 37.6], p=0.002 respectively. Infants born to mothers with GDM had a higher weight-length ratio (mean (SD): 6.4% WLR (0.7) vs. 6.1% w/l (0.7), p=0.010), Table 2. Overall, the proportion of SGA was relatively high (21.7%, 75/346) with a lower proportion of SGA in the GDM positive group which was not statistically significant (14.3% (7/49) vs. 22.9% (68/297, p=0.175). Other adverse birth complications such as stillbirth (0%, 0/50 of GDM positive; 1.2%, 4/324 of GDM negative), and preterm birth (2.0%, 1/50 in GDM positive; 5.2%, 17/324 in GDM negative) were low.

OGTT test results

As expected, the absolute blood sugar levels (BSL) levels were higher in the GDM positive group (Table 3). Of the women with GDM, 88.0% (44/50) had only one of the three glucose measurements above the cut-off, 10% (5/50) had two of three glucose measurements above the defined threshold and in only one study participant (1/50, 2.0%) all three measurements were above the defined limits. Screening with fasting and two-hour results, as performed in some institutions to reduce costs, would result in only 66% (33/50) of the GDM cases being detected in this study population (Table 3).

Risk-factor-based screening for GDM

There were 37 women in the GDM positive group and 234 women in the GDM negative group who had at least one risk factor, translating into an overall proportion of 72.5% (271/374) (Table 1). Of the 50 OGTT positive cases, 37 were correctly identified by risk factors alone, resulting in a sensitivity of 74.0% (59.7%-85.4%). Specificity was low, with 90 of 324 being correctly identified as negative for GDM using risk-factor-based screening: 27.8% (23.0%-33.0%). The positive and negative predictive values were 13.7% (9.8%-18.3%) and 87.4% (79.4%-93.1%), respectively.

Of the seven risk-factor-based screening items included in this analysis, a history of GDM and previous stillbirth could not be included in a multivariable model due to zero counts. None of the risk-factor-based screening criteria significantly predicted GDM status in this migrant population. History of

Table 3. Details of OGTT test result and GDM treatment.

OGTT test results and GDM treatment	Total	Without GDM	With GDM	p-value
N	374	324	50	
GA (weeks) at OGTT, median [IQR]	26.6 [25.7, 27.6]	26.6 [25.7, 27.6]	26.6 [25.9, 27.4]	0.949
OGTT* results (mg/dL), median [IQR]				
BSL fasting	79 [74, 84]	78 [73, 83]	86 [81, 96]	<0.001
BSL one hour	132 [114, 154]	129 [112, 147]	173 [142, 191]	<0.001
BSL two hours	111 [97, 127]	110 [96, 123]	129 [113, 157]	<0.001
Proportion of positivity at each OGTT timepoint				
Fasting only			17 (34%)	
One hour only			17 (34%)	
Two hours only			10 (20%)	
Fasting and one hour			2 (4%)	
Fasting and two hours			0 (0%)	
One hour and two hours			3 (6%)	
All three			1 (2%)	
GDM treatment, n (%)				
Diet and exercise only			18 (36%)	
Diet & metformin			27 (54%)	
Metformin and glibenclamide			4 (8%)	
Metformin and insulin			1 (2%)	

Abbreviations (alphabetic order): BSL blood sugar level, GA gestational age, GDM gestational diabetes mellitus, HAPO Hyperglycaemia and Adverse Pregnancy Outcomes, IQR interquartile range, OGTT oral glucose tolerance test.

*HAPO cut points in GDM: fasting, one hour and two hours BSL are ≥92, ≥180 and ≥153mg/dL, respectively.

macrosomia had a positive (wide confidence interval) and non-significant association due to the small number of cases (6.59, 95% CI 0.41-107.1, p=0.185). All other risk factors were not significant at p>0.20.

GDM management and treatment

Approximately two out of three women, 64% (32/50), were medicated for their GDM (Table 3). Most received metformin only (54% (27/50)), with a smaller proportion receiving metformin plus glibenclamide (8.0% (4/50)), and only one patient (2.0%) received insulin due to metformin failure at 27+3 weeks of gestation. This case required referral to the government hospital.

GDM risk in Burman and Karen ethnic groups

Risk factors for GDM were examined separately for the two main ethnic groups in the population by multivariate analysis (Table 4). After adjustment, overweight or obese Burman women were at a five-fold higher risk of GDM. A different relationship between BMI and GDM was apparent for Karen women where the risks were similarly elevated (non-significant) for both underweight and overweight or obese women (Table 4).

Discussion

The most consequential early GDM definition was published by O´Sullivan and Mahan in 1964[29]. Their criteria were then tried and adapted over decades with the culmination in the HAPO trial[30,31]. Currently there is no consensus on the optimal screening approach with Europe leaning more to risk-factor based screening and USA towards glucose challenge tests; and it is not entirely clear whether criteria derived from high-resource settings are adequate for institutions in low-resource settings[30,32]. Hence, as the main objective of this manuscript was to assess the performance of the risk-factor-based screening used in routine clinical practice and draw conclusions of its fitness, the presented cohort was explored by an *any positive* approach. This was possible because all women had data on the relevant risk-factors collected, and as they were part of a preterm birth study cohort,

Table 4. Risk factors for GDM diagnosed by OGTT in Karen and Burman women.

Risk factors	Karen n=247				Burman n=109			
	No GDM, n=218	GDM, n=29	Adjusted Odd Ratio (95% CI)	p-value	No GDM, n=90	GDM, n=19	Adjusted Odd Ratio (95% CI)	P-value
Age 30 and older, n (%)	56 (25.7)	6 (20.7)	0.52 (0.18-1.52)	0.231	24 (26.7)	5 (26.3)	0.54 (0.15-1.92)	0.343
Smoker, n (%)	19 (8.72)	5 (17.2)	3.09 (0.92-10.39)	0.069	2 (2.22)	1 (5.26)	5.27 (0.39-71.88)	0.213
BMI, kg/m^2*								
Normal (18.50-22.99)	126 (57.8)	11 (38.0)	reference		46 (51.1)	6 (31.6)	reference	
Underweight (≤18.5)	31 (14.2)	7 (24.1)	2.41 (0.85-6.79)	0.097	26 (28.9)	4 (21.1)	1.20 (0.30-4.73)	0.704
Overweight / obese (≥23)	61 (28.0)	11 (37.9)	2.36 (0.95-5.89)	0.064	18 (20.0)	9 (47.4)	**5.03 (1.43-17.64)**	**0.012**

Data are shown in n (%) unless otherwise indicated. Abbreviations (alphabetic order): BMI body mass index, GDM gestational diabetes mellitus.

* BMI definitions followed recommendations for Asian BMI groups.

all women had an OGTT done. The analysis identified the shortcomings of current clinical practice as almost one in four women with GDM would have been missed based on risk-factor-based selection for screening when compared with universal screening by 75g OGTT.

While the risk-factor-based screening had a sensitivity of 74.0% (95% CI 59.7-85.4), it lacked specificity 27.8% (95% CI 23.0-33.0) and resulted in an inadequate positive predictive value of 13.7% (95% CI 9.8-18.3). Reasons for this underperformance could be related to the limited size of the cohort; due to exclusion of women with a previous caesarean section (potentially due to undiagnosed GDM) from the original cohort; or that risk-factor-based screening is inherently weak for GDM diagnosis in South-East Asian women. The low incidence of reported prior history of GDM or family history of diabetes, most likely results from the limited extent of testing in this population that has limited access to health care[33].

At least one in seven 'healthy' migrant women presenting to antenatal care in this study cohort had GDM based on the 75g OGTT and thus identifying GDM as a significant health problem in Burman and Karen migrants on the Thailand-Myanmar border. These findings are similar to other migrant populations globally who have to make food choices based on limited expenditure[34]. The BMI-related differences in risk factors observed on regression analysis for GDM in Karen and Burman women may relate to different diets and smoking habits between these ethnic groups. A more detailed dietary analysis based on quantitative 24-hour food recall is currently under evaluation. The similar odds for GDM in underweight and overweight/obese Karen women may be related to the thin-type II diabetic phenotype where individuals are at increased risk at a lower BMI[35]. Gujral *et al.* and Rajakramikan *et al.* have proposed pathogenic mechanisms including impaired insulin secretion, *in utero* undernutrition, or epigenetic alterations, to explain thin-type II diabetes[36,37]. Of greatest concern is the propensity for this group of patients with undernutrition to have worse diabetes. Ethnohistorical Burman and Karen are distinct populations with their own pheno- and genotypic peculiarities[38]. As the slightly different GDM risk-profile is based on a small sample size, these findings must be confirmed in larger cohorts.

In this analysis, there was a positive association between GDM and higher percentiles for infant birthweight, larger head circumference and weight-length ratio composition but no difference was seen in mode of delivery, postpartum haemorrhage, perineal damage or Apgar score by GDM status[39–41]. Given that pregnant women with an unremarkable medical and obstetric history were prioritized in the cohort and women with GDM received treatment following the abnormal OGTT result, the low rate of adverse birth outcomes is not unexpected. The high rate of small for gestational age (one in five) newborns has been reported previously and highlights the double burden of nutrition in this population but may also signal a risk for thin-type II diabetes[15,35]. Data from other South-East Asian populations suggest that obese women with GDM have a higher risk of adverse outcome when compared to normal weight pregnant women with GDM[42]. However, considering a significant increase in perinatal morbidity in women with uncontrolled GDM compared to women with adequately treated GDM, different strategies of GDM management for obese and non-obese pregnant women does not seem appropriate at this point[43].

Early detection of GDM may prevent the need for caesarean section, which limits total expenditure per pregnancy. While the cost for an individual OGTT is small (i.e., approximately 18 THB (0.54 USD) for one glucose test strip, 7.5 THB (0.22 USD) for 75g glucose powder), costs add up if thousands of pregnant women are universally screened each year. Considering the average cost for caesarean section in 2020 for migrant women was 27,695 THB (approximately 824 USD) when referred to the public hospital

system, one averted caesarean section would be equivalent to 1,539 glucose test strips – enough for OGTTs in 500 women. Mo *et al*. concluded that cost effectiveness of universal GDM screening is likely favourable over screening of targeted high-risk populations in a meta-analysis in mostly HIC, while others suggest that universal screening is not useful[44,45]. Since access to adequate diabetes monitoring and pharmacological intervention is severely limited outside of pregnancy in resource-limited settings, there may be added benefit to universal screening in LMIC. The counselling women receive during pregnancy about their GDM may be the first and only information provided on lifestyle modification to prevent the development of type II diabetes later in life[46]. Reducing from three (fasting, one hour, two hours) to two (fasting, two hours) tests to bring down costs is not a useful alternative in this population as nearly nine in 10 were positive at a single timepoint distributed across all three time points. As the majority (68.7%) of GDM positive women in this study used oral hypoglycaemic agents, there is a need for a better understanding of effective lifestyle interventions in this marginalized group[2,16,47].

The findings on the usefulness of SFH contributes to the ongoing debate on the use of international vs. local centiles. The proportion of pregnant women presenting with a SFH ≥90th centile using local centiles differs markedly compared to the proportion when using international centiles. Using international standards for SFH, most GDM positive women would not be signalled as women with a problem in this population[26]. This most likely arises from maternal anthropometric differences (e.g., the greater than 10cm difference in maternal height) between the populations participating to the cohorts for centile curve calculation.

From 24 weeks EGA there was a significantly higher proportion of women in the GDM positive group with a SFH above the 90th centile compared to women without GDM. While this suggests that SFH may have a role, the fact that more than half (52,8%) the women with no GDM had at least one SFH measurement ≥90th centile renders SFH for GDM as rather unspecific. In addition, the timeframe of detection of increased SFH (32 weeks) is later than when an OGTT identifies GDM.

Strengths of this study

The strengths of this study include first trimester enrolment and ultrasound dating allowing accurate assessment of neonatal anthropometry based on gestation. The risk of information bias is reduced by the prospective cohort design with minimal missing data. There was also close monitoring throughout pregnancy with a high number of antenatal care visits (median 16, IQR 15-17). Furthermore, weight and SFH were measured with calibrated instruments and by well-trained personnel. In addition, this analysis has had a direct local impact resulting in the implementation of universal GDM screening for all women with a two-step approach; with the first step being a glucose challenge test (i.e., 50 g non-fasting oral glucose load, followed by a 1-hour glucose measurement) with 1-hour levels of ≥200 mg/dL being diagnostic of GDM and values 140–199 mg/dL requiring a 2nd step, namely a complete OGTT. This pragmatic choice to increase the number of women screened and minimize the burden of a full OGTT in all women follows the recommendation of the American College of Obstetricians and Gynecologists.

Potential study limitations

Women with a complicated obstetric or medical history were excluded from the original study. As SMRU does not perform caesarean sections in their clinics, women thought to be at risk of this pregnancy complication were excluded from the original study as they were predicted to not be able to provide a complete set of samples. This was a selection bias for healthier pregnant women, potentially leading to an underestimate of the GDM prevalence in this border population, i.e., the study likely presents the minimum GDM rate in the community of pregnant women. With the selection bias and treatment for all GDM positive women there was a low number of complications; among 37 risk-factor positive cases (vs 17 risk-factor negative cases), there were seven complications overall (preterm (n=1), stillbirths (n=0), caesarean section (n=2), postpartum haemorrhage (n=1), and LGA (n=3)). The study design did not allow exploration of whether those identified in the high-risk group were also the same women who are likely to have complications from GDM.

Due to the relatively small sample, the suggestion of differences in the risk of GDM between the two major ethnic groups requires further verification.

Conclusions

These findings imply that GDM is a problem at the Thailand-Myanmar border with Burman women who are overweight/obese being at the highest risk. GDM determined by risk-factor-based screening performed sub-optimally in this rural, resource-constrained pregnant population. Access to universal screening for GDM can potentially reduce negative impacts for an individual pregnancy but also provide an opportunity to sensitize people in marginalized populations of their potential increased risk for type II diabetes later in life. Considering that additional costs for universal screening appear limited, this is the preferred policy in this population.

Data availability

Underlying data

Oxford University Research Archives: MSP COHORT GDM SCREEN.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Reporting guidelines

Figshare: STARD checklist for ‘ Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: an observational cohort’. https://doi.org/10.6084/m9.figshare.19382624[48].

Acknowledgments

We are immensely grateful to all women in the cohort and for the efforts of local healthcare workers in the recruitment centres to participate in patient management and study data collection.

References

1. Nguyen CL, Pham NM, Binns CW, *et al.*: **Prevalence of Gestational Diabetes Mellitus in Eastern and Southeastern Asia: A Systematic Review and Meta-Analysis.** *J Diabetes Res.* 2018; **2018**: 6536974.
PubMed Abstract | Publisher Full Text | Free Full Text
2. Kunasegaran T, Balasubramaniam VRMT, Arasoo VJT, *et al.*: **Gestational Diabetes Mellitus in Southeast Asia: A Scoping Review.** *Int J Environ Res Public Health.* 2021; **18**(3): 1272.
PubMed Abstract | Publisher Full Text | Free Full Text
3. Goto E: **Symphysis-fundal height to identify large-for-gestational-age and macrosomia: a meta-analysis.** *J Obstet Gynaecol.* 2020; **40**(7): 929–935.
PubMed Abstract | Publisher Full Text
4. Plows JF, Stanley JL, Baker PN, *et al.*: **The Pathophysiology of Gestational Diabetes Mellitus.** *Int J Mol Sci.* 2018; **19**(11): 3342.
PubMed Abstract | Publisher Full Text | Free Full Text
5. Tieu J, McPhee AJ, Crowther CA, *et al.*: **Screening for gestational diabetes mellitus based on different risk profiles and settings for improving maternal and infant health.** *Cochrane Database Syst Rev.* 2017; **8**(8): CD007222.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Vounzoulaki E, Khunti K, Abner SC, *et al.*: **Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis.** *BMJ.* 2020; **369**: m1361.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Paschou SA, Sydney GI, Ioakim KJ, *et al.*: **Comment on the systematic review and meta-analysis titled "Gestational diabetes and the risk of cardiovascular disease in women".** *Hormones (Athens).* 2020; **19**(3): 447–448.
PubMed Abstract | Publisher Full Text
8. Guariguata L, Linnenkamp U, Beagley J, *et al.*: **Global estimates of the prevalence of hyperglycaemia in pregnancy.** *Diabetes Res Clin Pract.* 2014; **103**(2): 176–185.
PubMed Abstract | Publisher Full Text
9. Seghieri G, Di Cianni G, Seghieri M, *et al.*: **Risk and adverse outcomes of gestational diabetes in migrants: A population cohort study.** *Diabetes Res Clin Pract.* 2020; **163**: 108128.
PubMed Abstract | Publisher Full Text
10. **World Migration Report 2020.**
Reference Source
11. International Labour Organization: **Thailand (April - June 2019).** In: *Triangle in ASEAN Quarterly Briefing Note*. Bangkok, Thailand: International Labour Organization; 2019.
Reference Source
12. MOHS, ICF: **Myanmar Demographic and Health Survey 2015-16**. Nay Pyi Taw, Myanmar: Ministry of Health and Sports and ICF, 2017.
Reference Source
13. Nielsen KK, de Courten M, Kapur A: **Health system and societal barriers for gestational diabetes mellitus (GDM) services - lessons from World Diabetes Foundation supported GDM projects.** *BMC Int Health Hum Rights.* 2012; **12**: 33.
PubMed Abstract | Publisher Full Text | Free Full Text
14. Lorga T, Srithong K, Manokulanan P, *et al.*: **Public knowledge of diabetes in Karen Ethnic rural residents: a community-based questionnaires study in the far north-west of Thailand.** *Int J Gen Med.* 2012; **5**: 799–804.
PubMed Abstract | Publisher Full Text | Free Full Text
15. Hashmi AH, Solomon N, Lee SJ, *et al.*: **Nutrition in transition: historical cohort analysis summarising trends in under- and over-nutrition among pregnant women in a marginalised population along the Thailand-Myanmar border from 1986 to 2016.** *Br J Nutr.* 2019; **121**(12): 1413–1423.
PubMed Abstract | Publisher Full Text
16. Hashmi AH, Paw MK, Nosten S, *et al.*: **'Because the baby asks for it': a mixed-methods study on local perceptions toward nutrition during pregnancy among marginalised migrant women along the Myanmar-Thailand border.** *Glob Health Action.* 2018; **11**(1): 1473104.
PubMed Abstract | Publisher Full Text | Free Full Text
17. WHO expert consultation: **Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.** *Lancet.* 2004; **363**(9403): 157–163.
PubMed Abstract | Publisher Full Text
18. Lee KW, Ching SM, Ramachandran V, *et al.*: **Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis.** *BMC Pregnancy Childbirth.* 2018; **18**(1): 494.
PubMed Abstract | Publisher Full Text | Free Full Text
19. Farrar D, Simmonds M, Bryant M, *et al.*: **Treatments for gestational diabetes: a systematic review and meta-analysis.** *BMJ Open.* 2017; **7**(6): e015557.
PubMed Abstract | Publisher Full Text | Free Full Text
20. Gilder ME, Zin TW, Wai NS, *et al.*: **Gestational diabetes mellitus prevalence in Maela refugee camp on the Thai-Myanmar border: a clinical report.** *Glob Health Action.* 2014; **7**: 23887.
PubMed Abstract | Publisher Full Text | Free Full Text
21. Rani PR, Begum J: **Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand.** *J Clin Diagn Res.* 2016; **10**(4): QE01–04.
PubMed Abstract | Publisher Full Text | Free Full Text
22. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, *et al.*: **Hyperglycemia and adverse pregnancy outcomes.** *N Engl J Med.* 2008; **358**(19): 1991–2002.
PubMed Abstract | Publisher Full Text
23. Brummaier T, Syed Ahamed Kabeer B, Lindow S, *et al.*: **A prospective cohort for the investigation of alteration in temporal transcriptional and microbiome trajectories preceding preterm birth: a study protocol.** *BMJ Open.* 2019; **9**(1): e023417.
PubMed Abstract | Publisher Full Text | Free Full Text
24. Rijken MJ, Mulder EJ, Papageorghiou AT, *et al.*: **Quality of ultrasound biometry obtained by local health workers in a refugee camp on the Thai-Burmese border.** *Ultrasound Obstet Gynecol.* 2012; **40**(2): 151–157.
PubMed Abstract | Publisher Full Text | Free Full Text
25. White LJ, Lee SJ, Stepniewska K, *et al.*: **Estimation of gestational age from fundal height: a solution for resource-poor settings.** *J R Soc Interface.* 2012; **9**(68): 503–510.
PubMed Abstract | Publisher Full Text | Free Full Text
26. Papageorghiou AT, Ohuma EO, Gravett MG, *et al.*: **International standards for symphysis-fundal height based on serial measurements from the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: prospective cohort study in eight countries.** *BMJ.* 2016; **355**: i5662.
PubMed Abstract | Publisher Full Text | Free Full Text
27. Cheikh Ismail L, Bishop DC, Pang R, *et al.*: **Gestational weight gain standards based on women enrolled in the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project: a prospective longitudinal cohort study.** *BMJ.* 2016; **352**: i555.
PubMed Abstract | Publisher Full Text | Free Full Text
28. Villar J, Cheikh Ismail L, Victora CG, *et al.*: **International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.** *Lancet.* 2014; **384**(9946): 857–868.
PubMed Abstract | Publisher Full Text
29. O'Sullivan JB, Mahan CM: **Criteria for the oral glucose tolerance test in pregnancy.** *Diabetes.* 1964; **13**: 278–285.
PubMed Abstract
30. McIntyre HD, Catalano P, Zhang C, *et al.*: **Gestational diabetes mellitus.** *Nat Rev Dis Primers.* 2019; **5**(1): **47**.
PubMed Abstract | Publisher Full Text
31. HAPO Study Cooperative Research Group: **The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study.** *Int J Gynaecol Obstet.* 2002; **78**(1): 69–77.
PubMed Abstract | Publisher Full Text
32. Mishra S, Rao CR, Shetty A: **Trends in the Diagnosis of Gestational Diabetes Mellitus.** *Scientifica (Cairo).* 2016; **2016**: 5489015.
PubMed Abstract | Publisher Full Text | Free Full Text
33. Saito M, Keereevijit A, San TD, *et al.*: **Challenges to primary healthcare services in the management of non-communicable diseases in marginalised populations on the Thailand-Myanmar border: a pilot survey.** *Trop Doct.* 2018; **48**(4): 273–277.
PubMed Abstract | Publisher Full Text
34. Pottie K, Hadi A, Chen J, *et al.*: **Realist review to understand the efficacy of culturally appropriate diabetes education programmes.** *Diabet Med.* 2013; **30**(9): 1017–1025.
PubMed Abstract | Publisher Full Text

35. Gujral UP, Weber MB, Staimez LR, *et al.*: **Diabetes Among Non-Overweight Individuals: an Emerging Public Health Challenge.** *Curr Diab Rep.* 2018; **18**(8): 60.
PubMed Abstract | Publisher Full Text

36. Gujral UP, Pradeepa R, Weber MB, *et al.*: **Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations.** *Ann N Y Acad Sci.* 2013; **1281**(1): 51–63.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Rajamanickam A, Munisankar S, Dolla CK, *et al.*: **Impact of malnutrition on systemic immune and metabolic profiles in type 2 diabetes.** *BMC Endocr Disord.* 2020; **20**(1): 168.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Bancone G, Gilder ME, Chowwiwat N, *et al.*: **Prevalences of inherited red blood cell disorders in pregnant women of different ethnicities living along the Thailand-Myanmar border [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2017; **2**: 72.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Logan KM, Gale C, Hyde MJ, *et al.*: **Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis.** *Arch Dis Child Fetal Neonatal Ed.* 2017; **102**(1): F65–F72.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Villar J, Puglia FA, Fenton TR, *et al.*: **Body composition at birth and its relationship with neonatal anthropometric ratios: the newborn body composition study of the INTERGROWTH-21st project.** *Pediatr Res.* 2017; **82**(2): 305–316.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Yau KI, Chang MH: **Weight to length ratio--a good parameter for determining nutritional status in preterm and full-term newborns.** *Acta Paediatr.* 1993; **82**(5): 427–429.
PubMed Abstract | Publisher Full Text

42. Yue S, Thi VTK, Dung LP, *et al.*: **Clinical consequences of gestational diabetes mellitus and maternal obesity as defined by asian BMI thresholds in Viet Nam: a prospective, hospital-based, cohort study.** *BMC Pregnancy Childbirth.* 2022; **22**(1): 195.
PubMed Abstract | Publisher Full Text | Free Full Text

43. Langer O, Yogev Y, Most O, *et al.*: **Gestational diabetes: the consequences of not treating.** *Am J Obstet Gynecol.* 2005; **192**(4): 989–997.
PubMed Abstract | Publisher Full Text

44. Mo X, Gai Tobe R, Takahashi Y, *et al.*: **Economic Evaluations of Gestational Diabetes Mellitus Screening: A Systematic Review.** *J Epidemiol.* 2021; **31**(3): 220–230.
PubMed Abstract | Publisher Full Text | Free Full Text

45. Fitria N, van Asselt ADI, Postma MJ: **Cost-effectiveness of controlling gestational diabetes mellitus: a systematic review.** *Eur J Health Econ.* 2019; **20**(3): 407–417.
PubMed Abstract | Publisher Full Text | Free Full Text

46. Hashmi AH, Nyein PB, Pilaseng K, *et al.*: **Feeding practices and risk factors for chronic infant undernutrition among refugees and migrants along the Thailand-Myanmar border: a mixed-methods study.** *BMC Public Health.* 2019; **19**(1): 1586.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Martis R, Crowther CA, Shepherd E, *et al.*: **Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews.** *Cochrane Database Syst Rev.* 2018; **8**(8): CD012327.
PubMed Abstract | Publisher Full Text | Free Full Text

48. Brummaier T: **STARD checklist for Risk factor-based screening compared to universal screening for gestational diabetes mellitus in marginalized Burman and Karen populations on the Thailand-Myanmar border: an observational cohort.** figshare. Edited by Journal contribution, 2022.
http://www.doi.org/10.6084/m9.figshare.19382624.v1

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 22 February 2023

https://doi.org/10.21956/wellcomeopenres.20890.r54240

© **2023 Wylie B.** This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

✔ **Blair Johnson Wylie**
Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA

These changes are acceptable to me. I approve the revisions

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 21 February 2023

https://doi.org/10.21956/wellcomeopenres.20890.r54239

© **2023 Hirst J.** This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

✔ **Jane E. Hirst**
Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK

Thank you for the opportunity to look at this revision. The paper addresses a topic that has not previously been well described in this population. It is well written and presented and I have no further comments for the authors and recommend indexing.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 23 September 2022

https://doi.org/10.21956/wellcomeopenres.19636.r52286

© **2022 Wylie B.** This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

?

Blair Johnson Wylie
[1] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA
[2] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA

The authors should be commended for tackling the issue of GDM in a vulnerable and marginalized population of migrants/refugees on the Thai-Myanmar border. Much of the evidence underlying practice recommendations for GDM comes from high-resource populations. The title suggests the analysis will focus on the comparison of risk factors vs universal GDM screening; this was a question posed in HIC in the not-too-distant past with evidence/practice moving to universal screening. Addressing this question in this population is novel. However, the data presented cover a number of GDM-related topics. As presented though, it is a bit challenging for the reader to pull out the key questions and conclusions.

From my reading of the manuscript, there are a number of questions being posed:

- Prevalence of GDM (with universal screening)
- What are the risk factors for GDM in this population
- Comparison of risk factor-based approach (risk factors identified prior to this study) with universal screening (test performance characteristics)
- Association of GDM with adverse pregnancy outcomes
- Seasonality of GDM diagnoses
- Serial SFH and GDM

I think the overarching scientific question is whether in this population GDM should be evaluated and screened for like it is in high-income settings. Data may not be sufficient to answer this.

Main criticism/suggestion - clarify the specific question(s) being posed in the manuscript. Some of the topics may need to be saved (and extended) in separate manuscripts. In particular, the seasonality of GDM diagnosis, while intriguing, seems misplaced and not fully developed. The serial SFH analysis also seems perhaps unnecessary (at least in the figure).

Specific suggestions:

1. Is this a secondary analysis of a prospective cohort constructed for another purpose (this was unclear in the abstract and methods)?

2. Remove “etc” from the abstract.

3. Clarify if this was a “homegrown” risk factor-based approach or not.

4. Why was obesity defined as BMI greater than 27.5?

5. Better clarification is needed about the analysis of risk factor exploration for GDM and how this is distinct from the risk factor-based screening.

6. The first sentence of the second paragraph is confusing as written; the prevalence same, but more people living in LMICs so the overall number is higher.

7. The introduction is a bit long and may not need to be. The connection with malnutrition in the introduction is not entirely clear. The paragraph on SFH seems extraneous. The paragraph on GDM and the environment is interesting but a little off-topic in the manuscript.

8. Intro sentence that states “adequate diagnosis and mgmt. improves outcomes in GDM”—is this known for LMICs or migrant populations? It might not improve outcomes—this article helps contributes to that literature but is not sufficient to answer the question.

9. Methods section detailing screening using HAPO criteria— sixth paragraph— seems to reference #24 twice in the same sentence.

10. Sample size calculations unclear—likely as unclear as written the purpose of the primary cohort.

11. Exclusion criteria—one is listed as miscarriage. Is this history of miscarriage or pregnancy loss before glucose screening in this population?

12. Methods—could eliminate some of the details of SFH measurements and reference prior work by this group.

13. Details of newborn anthropometry measurements—some could be relegated to a supplement to simplify the manuscript.

14. How define LGA? Based on INTERGROWTH?

15. Details of analytic plan and modeling insufficient—why is a multivariable model needed? As comparing the RF-based approach (1 RF buys you screening) rather than creating a prediction model to model the probability of GDM diagnosis. The model may be overfitted.

16. Why interaction terms? What effect modification is being explored?

17. P-values to 3 decimal places probably can be taken to only 1 or 2 places based on journal guidelines.

18. Consider eliminating Figure 2.

19. The % of LGA is remarkably small in this population—this is a worth finding worth highlighting. Are the risks of GDM therefore the same in a population with less LGA and less maternal overweight?

20. Consider adding some historical context of literature from HIC and the switch from RF-based screening to universal.

21. Consider adding some historical context of the debate around whether to screen for GDM at all—expensive, onerous, does it meaningfully improve outcomes? Have we yet answered this for LMICs?

22. What proportion of women have at least one risk factor— would it be almost universal?

23. The paragraph on SFH in conclusions is a bit hard to understand.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 10 August 2022

https://doi.org/10.21956/wellcomeopenres.19636.r51816

© 2022 Hirst J. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jane E. Hirst
[1] Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK
[2] Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK

Thank you for this interesting article. I have raised a few points below to clarify the objective of the paper and the interpretation. Overall, the study would be stronger if it were framed as an exploratory study to understand the clinical picture and patterns of GDM in this population. This would make the seasonality data more obviously relevant.

Points to address:

Abstract:

1. In the abstract, it states "From the prospective cohort...", this is confusing as it implies another study. It would be clearer to state the study design was an observational cohort study to study preterm birth and this was a secondary analysis. It would be helpful to define "Healthy" for this study: does this mean women without prior or current medical complications?

2. Please list the 10 risk factors as it is unclear with just the top most well-known RF what the others are.

3. It seems strange to report the non-significant association between GDM and underweight and overweight/obese Karen women. I question whether this is helpful in the results.

4. The conclusion states that risk factors screening was not sufficiently sensitive or specific, however, these rates are similar to what is used in many higher-income countries, including the UK. The question should be whether those identified in the high-risk group are also the same women who are likely to have complications from GDM, thus warranting treatment.

Introduction

1. The introduction is quite long, making the narrative of the paper difficult to discern for a busy reader. The section on the environment, for example, it is unclear how it directly relates to what you present here.

Methods

1. Sample size: Whilst you give a rationale for the wider cohort study sample and describe pragmatically within this sample how many women were included, you do not give any indication as to whether this study was adequately powered to determine population prevalence or not.

2. Here you state that only seven criteria were used for risk factor screening. This should be corrected in the abstract.

3. Did you collect variables on any other complications associated with GDM other than the newborn size at birth, e.g. neonatal hypoglycaemia, primary CS, stillbirth? I note that BMI is defined in the results using Asian centiles. This should be specified in the methods.

4. GDM management: Was the weekly or fortnightly monitoring of glucose fasting post-

prandial or random?

Results

1. You report non-significant differences in baseline characteristics, which is confusing to the reader. It would be clearer to state there were no significant differences observed in those variables, or alternately that a null association cannot be excluded.

2. Again, be careful reporting non-significant trends in the difference in prevalence between ethnic groups.

3. Figure 2: The lines seem pretty much the same to me. Is this a significant difference? It would be useful to articulate this in cm difference if it is clinically relevant.

4. When reporting the birth outcomes, it is important to know gestational age at delivery as the difference in birth weight may be gestation related.

5. The CI for LGA is very large indicating not many babies were LGA. It would be helpful for the reader to have the absolute number of non-GDM and GDM LGA babies in the text. The fact that so many more GDM babies are SGA should also be highlighted here.

6. In the risk factors-based screening for GDM section, you start by reporting the sensitivity of the different tests in the OGTT. This should have been pre-empted in the methods and would be better under a subheading about OGTT (relating to Table 3).

7. I am a bit confused as you report risk factor screening has 74% sensitivity and 27.8% specificity, however, in the results, you then state none of the risk factors was associated with the outcome (GDM). Does this mean that women with GDM had more than one risk factor and this was the difference? What was your definition of a risk factor for the calculation of sensitivity and specificity? If you are using the OGTT values themselves, doesn't that defeat the purpose of risk factor-based screening?

8. Table 4: I worry that you are splitting your sample size and with multiple testing, it is not surprising that eventually one of your tests came up positive. There is no discussion of how you will handle false detection rates in the methods.

9. The information on seasonality is interesting, although it is unclear how it relates to the study objective. Did you include seasonality as a risk factor?

Discussion

1. I disagree that the risk factors-based screening was "grossly inadequate", although as per my comments above I am confused as to what the risk factors were that were included in your screening tests. You did not show any great changes in perinatal outcomes, other than a slight increase in the birthweight of babies, which in a setting with such high rates of LGA may not be a bad thing in itself.

2. The value of screening and treating GDM in non-obese Asian populations has been questioned (see Yue *et al.,* BMC Pregnancy and Childbirth, 2022[1]). Whilst I appreciate that an everted CS will save a lot of money, the question that arises from this is with such low CS

rates (around 5% overall), how much can you extrapolate from data from HAPO derived in very differently resource settings?

References

1. Yue S, Thi VTK, Dung LP, Nhu BTH, et al.: Clinical consequences of gestational diabetes mellitus and maternal obesity as defined by asian BMI thresholds in Viet Nam: a prospective, hospital-based, cohort study.*BMC Pregnancy Childbirth*. 2022; **22** (1): 195 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetrics, diabetes in pregnancy, global health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.