

Alternative pathways to oral glucose tolerance test for Chinese pregnant women

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Objectives: To compare the gold standard pathway of universal second-trimester oral glucose tolerance test (OGTT) with eight alternative pathways to determine the optimal pathway that can reduce the number of OGTTs performed but still maintains high sensitivity and specificity for gestational diabetes mellitus (GDM) diagnosis in the Chinese population.

Methods: We retrospectively reviewed medical records of pregnant women who underwent an OGTT during 26+0 to 29+6 weeks of gestation between January 2021 and June 2021 at the Pamela Youde Nethersole Eastern Hospital. The gold standard pathway of universal second-trimester OGTT were compared with eight alternative pathways (which considered fasting glucose levels, a history of GDM, and/or any risk factors) in terms of the estimated percentage reduction in the number of OGTTs performed, sensitivity and specificity of detecting GDM, and estimated percentage of women with composite adverse outcomes (CAO).

Results: Of 769 women who underwent the OGTT, 96 (12.5%) had GDM. The need for an OGTT was reduced 100% in pathway 3, 87.1% in pathway 9, 84.9% in pathway 5, 80.8% in pathway 8, 78.5% in pathway 4, 46.3% in pathway 7, 41.4% in pathway 2, 4.8% in pathway 6, and 0% in pathway 1. Specificity was high (97% to 100%) for all pathways, as were negative predictive values (90% to 100%). However, sensitivity was low (20% to 59%) for all pathways, except for pathways 1 and 6 (100%). In all pathways, the estimated percentage of women with CAO was higher in true-positive groups than in false-negative groups.

Conclusion: In Chinese women, compared with the universal second-trimester OGTT, alternative pathways could reduce the number of OGTTs performed, but the detection rate of GDM was poor. Obstetricians should encourage pregnant women to undergo the OGTT to reduce maternal and neonatal complications, even in the event of pandemic. In situations when infection control measures are ineffective, pathway 3 can be considered because it detects the highest percentage of women with CAO and eliminates the need for OGTTs.

Keywords: *Diabetes, gestational; Glucose tolerance test; Infection control*

Introduction

Gestational diabetes mellitus (GDM) affects both mothers and fetuses and can complicate 9.3% to 25.5% of pregnancies¹. Poor glycaemic control increases the risks of preterm delivery, macrosomia, birth injury such as shoulder dystocia, neonatal hypoglycaemia, polycythaemia, and stillbirth. Maternal complications include hypertensive diseases and the need for labour induction and Caesarean sections. GDM is defined as a fasting plasma glucose level of ≥ 5.1 mmol/l and/or a 2-hour post-glucose load plasma glucose level of ≥ 8.5 mmol/l². Oral glucose tolerance test (OGTT) at around 28 weeks of gestation is considered standard prenatal care³. At the beginning of the COVID-19 pandemic, the OGTT was considered to have a high infection risk when unvaccinated unmasked pregnant women grouped together in an enclosed area, and some might vomit after drinking the glucose solution. Some women declined to take the OGTT, taking the risks of undiagnosed GDM and maternal and perinatal complications.

Alternative pathways for the universal OGTT have been suggested, including measurement of the fasting glucose (FG) level alone, pre-screening of a history of GDM, and selective OGTTs for high-risk women⁴⁻⁶. However, these alternative pathways greatly reduce the detection rate of GDM⁷ and may not be applicable to the Chinese population owing to their higher skeletal muscle insulin resistance. Only 26% of women with GDM have a raised FG level in Hong Kong (mainly Chinese ethnicity), whereas >70% of women with GDM have a raised FG level in Barbados (mainly Black population), Bellflower, California (mainly Hispanic population), and Providence, Rhode Island (mainly White population)¹.

We compared the gold standard pathway of universal second-trimester OGTT with eight alternative pathways to

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determine the optimal pathway that can reduce the number of OGTTs performed but still maintains high sensitivity and specificity for GDM diagnosis in the Chinese population.

Methods

In accordance with the World Health Organization recommendations², pregnant women attending antenatal care in our hospital were screened for GDM using the OGTT. Women with a high risk of GDM would undergo an OGTT at the early second trimester, whereas women without a high risk of GDM and women with normal early OGTT results would undergo an OGTT at around 28 weeks of gestation. We retrospectively reviewed medical records of pregnant women who underwent an OGTT during 26+0 to 29+6 weeks of gestation between January 2021 and June 2021 at the Pamela Youde Nethersole Eastern Hospital. Women with multiple pregnancy, incomplete OGTT records, or non-Chinese ethnicity were excluded. Data collected included baseline characteristics, pre-existing risk factors, OGTT results, and delivery outcomes.

The gold standard pathway of universal second-trimester OGTT were compared with eight alternative pathways in terms of specificity and sensitivity, positive and negative predictive values, and the percentage reduction in the number of OGTTs performed. Pathway

1 is the gold standard universal second-trimester OGTT. Pathway 2 provides the OGTT only to women with any risk factors. Pathway 3 is the universal screening of the FG level alone. Pathway 4 is the universal screening of the FG level and then provides the OGTT only to women with an FG level of 4.5 to 5.1 mmol/l, based on the Australasian Diabetes in Pregnancy Society recommendations during the COVID-19 pandemic⁶. Pathway 5 is the universal screening of the FG level and then provides the OGTT only to women with an FG level of 4.5 to 5.1 mmol/l plus any risk factors. Pathways 6 to 9 assume that women with a history of GDM have GDM and provide the OGTT only to women with no history of GDM, women with no history of GDM plus any risk factors, women with no history of GDM plus an FG level of 4.5 to 5.1 mmol/l, and women with no history of GDM plus any risk factors plus an FG level of 4.5-5.1 mmol/l, respectively (Figure 1). The optimal pathway that can reduce the number of OGTTs performed but still maintains high sensitivity and specificity for GDM diagnosis was determined.

Similar pathways have been studied in a French population in 2021⁸. In accordance with the Hong Kong College of Obstetricians and Gynecologists⁹, high-risk women were defined as those with any risk factors of maternal age ≥ 35 years, body mass index ≥ 25 kg/m² before

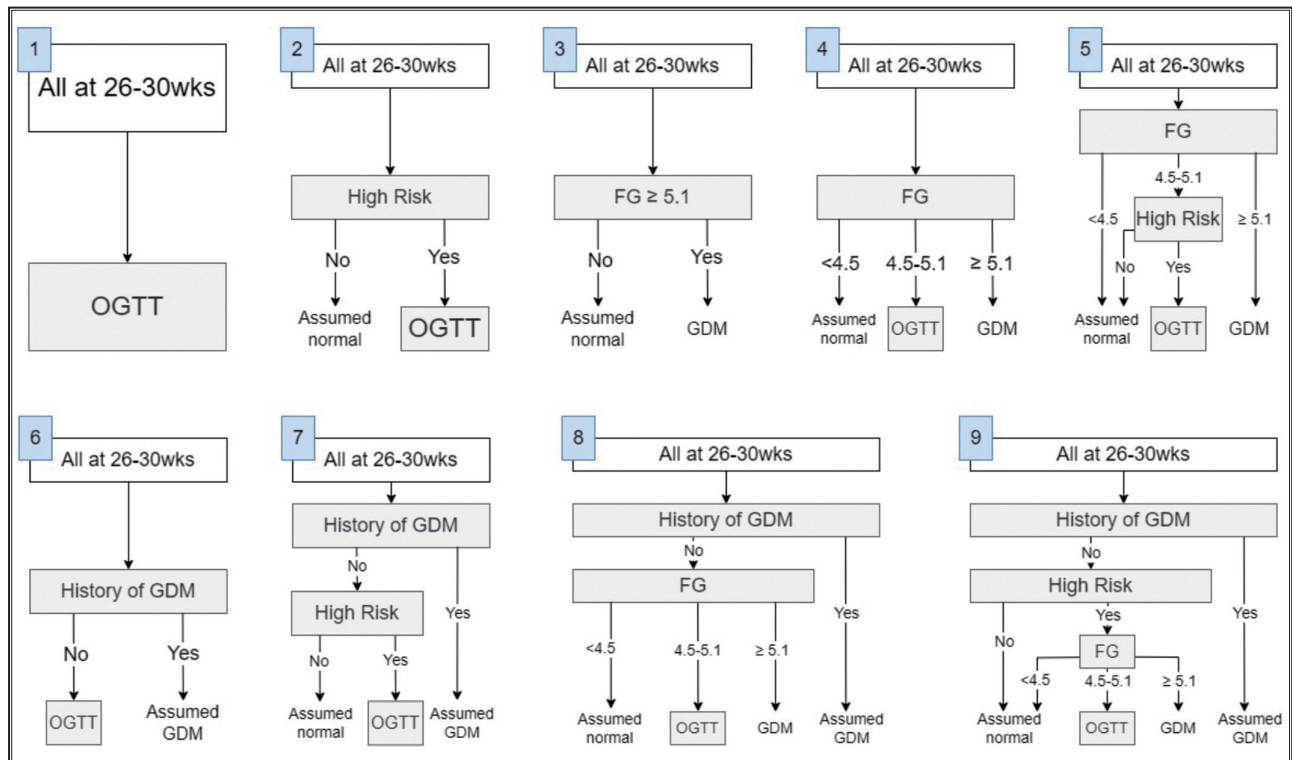


Figure 1. The nine pathways of oral glucose tolerance test (OGTT) with or without consideration of fasting glucose (FG) levels, a history of gestational diabetes mellitus (GDM), and/or any risk factors

pregnancy or in the first trimester, family history of diabetes in first-degree relatives, polycystic ovarian syndrome, autoimmune disease, chronic hypertension, long-term use of diabetogenic medications (such as corticosteroids), history of macrosomia (≥ 4 kg), and history of GDM. Although Asian ethnicity was considered a risk factor by the National Institute for Health and Care Excellence and the American College of Obstetricians and Gynecologists^{10,11}, we did not consider Asian ethnicity as a risk factor, because most of our population are Asian, and this makes it difficult to differentiate high- and low-risk groups.

Preterm delivery was defined as birth before 34 weeks. Birthweight was adjusted by gestational age according to Hong Kong specific reference ranges¹². Appropriate for gestational age was defined as those within the 10th to 90th percentiles. Hypertensive diseases in pregnancy included eclampsia, pre-eclampsia, and pregnancy-induced hypertension. Shoulder dystocia was defined as the head-to-shoulder delivery time of >1 minute¹³ and the use of an additional manoeuvre (eg, McRoberts manoeuvre, suprapubic pressure, rotational manoeuvres, removal of posterior arm)¹⁴. Neonatal complications included hypoglycaemia and clavicular fracture. Composite adverse outcomes (CAO) comprised preterm birth, large for gestational age, hypertensive diseases in pregnancy, shoulder dystocia, and neonatal complications.

Women with or without GDM were compared using the analysis of variance for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. A *p* value of <0.05 was considered statistically significant.

Results

Of 834 women who underwent an OGTT during the study period, 65 were excluded because of multiple pregnancies ($n=12$), non-Chinese ethnicity ($n=52$), or incompleteness of OGTT owing to sepsis ($n=1$). Of 769 women included in analysis, 96 (12.5%) had GDM. Women with or without GDM were comparable in terms of all baseline characteristics and the rate of CAO, except that a higher proportion of women with GDM, as expected, had a higher body mass index at the first visit, a history of GDM, a history of macrosomia, a higher FG level, and a higher 2-hour plasma glucose level (Table 1).

The need for an OGTT was reduced 100% in pathway 3, 87.1% in pathway 9, 84.9% in pathway 5, 80.8% in pathway 8, 78.5% in pathway 4, 46.3% in pathway 7, 41.4% in pathway 2, 4.8% in pathway 6, and 0% in pathway 1 (Table 2). Specificity was high (97% to 100%)

for all pathways, as were negative predictive values (90% to 100%). However, sensitivity was low (20% to 59%) for all pathways, except for pathways 1 and 6 (100%).

In total, 538 delivery records were available for analysis. Figure 2 shows the estimated rates of CAO in each pathway in terms of true-positive, false-negative, true-negative, and false-negative groups. The true-positive group of pathway 3 had the highest rate of CAO at 31.3%.

The sensitivity was almost 100% when the FG cutoff level of <3.7 mmol/l was used. The sensitivity reduced gradually as the FG cutoff level increased. The sensitivity was about 50% when the FG cutoff level was 4.5 mmol/l. The estimated percentage reduction in the number of OGTTs performed was 100% when the FG cutoff level was 5.1 mmol/l, which was the pathway 3 (Figure 3).

In future pandemics, pathway 3 can be used, because it completely eliminated the need for an OGTT and could detect the highest rate (31.3%) of CAO. However, if the risk of infection can be controlled, the universal OGTT (pathway 1) is still recommended, because alternative pathways had poor sensitivity in detecting GDM.

Discussion

The prevalence of GDM in our patients was 12.5%. This is comparable to the 14.4% in a Hong Kong population¹ and the 11.9% in a pooled Chinese population¹⁵. The alternative pathways could reduce the number of OGTTs performed, but the sensitivity in detecting GDM decreased to 20% to 59%.

In pathway 3, when universal screening of FG level was used, OGTTs could be eliminated, but the sensitivity was poor at 20%, which is worse than the 49% reported in a French population⁸. In the Hyperglycemia and Adverse Pregnancy Outcome Study, the post-glucose load level had a higher detection rate of GDM, compared with the FG level, in Chinese populations¹. In pathway 6, when an OGTT was provided only to women without a history of GDM, the sensitivity was 100%, but only 4.8% of OGTTs were avoided. Although the universal OGTT is recommended by the World Health Organization, some centres provide OGTTs to high-risk women only, probably owing to limited resources. Pathway 2 had a 59% sensitivity, meaning that 41% of women with GDM had no personal or family history risk factors of GDM. In pathways 4 and 5, when the FG cutoff level of 4.5-5.1 mmol/l was used to triage OGTTs, the sensitivity was poor (47% and 38%, respectively), although the estimated percentage reduction

Table 1. Baseline characteristics of women with or without gestational diabetes mellitus (GDM)

Characteristic	GDM (n=96)*	No GDM (n=673)*	p Value
Age at delivery (estimated), y	33.7±3.9	33.4±4.2	0.51
No. of parities	0.7±1.1	0.5±0.7	0.11
First pregnancy	50 (52.1)	372 (55.3)	0.59
Chinese ethnicity	96 (100)	673 (100)	-
Body weight at first visit, kg	57.9±9.4	56.3±8.5	0.09
Body mass index at first visit, kg/m ²	22.9±3.4	22.2±3.0	0.05
Relevant medical history	5 (5.2)	27 (4.0)	0.58
Family history of diabetes	16 (16.7)	133 (19.8)	0.49
History of GDM	19 (41.3)	19 (6.3)	<0.001
History of macrosomia	3 (6.5)	2 (0.7)	0.005
History of hypertensive diseases in pregnancy	0	10 (3.3)	0.38
High-risk group	57 (59.4)	393 (58.4)	0.91
Gestation at oral glucose tolerance test, wk	27.7±0.6	27.7±0.6	0.44
Fasting plasma glucose level, mmol/l	4.6±0.6	4.2±0.3	<0.001
2-hour plasma glucose level after oral glucose tolerance test, mmol/l	9.2±1.2	6.5±1.0	<0.001
Delivery records available	69 (71.9)	469 (69.7)	0.72
Gestation at delivery, wk	38.4±1.2	38.6±1.6	0.11
Preterm delivery <34 weeks	0	5 (1.1)	0.39
Induction of labour	24 (34.8)	133 (28.4)	0.32
Mode of delivery			0.93
Normal vaginal delivery	42 (60.9)	300 (64)	
Vacuum extraction	5 (7.3)	40 (8.5)	
Forceps delivery	1 (1.5)	6 (1.3)	
Elective Caesarean section	14 (20.3)	75 (16.0)	
Emergency Caesarean section	7 (10.1)	48 (10.2)	
Birthweight, g	3051.4±433.6	3069.6±421.8	0.74
Small for gestational age	9 (13.0)	47 (10.0)	0.34
Appropriate for gestational age	55 (79.7)	403 (85.9)	
Large of gestational age	5 (7.3)	19 (4.1)	
Hypertensive disorders of pregnancy	3 (4.4)	18 (3.8)	0.74
Shoulder dystocia	0	1 (0.3)	-
Neonatal complications	3 (4.3)	17 (3.6)	0.73
Intrauterine death/neonatal death	0	3 (0.6)	-
Composite adverse outcome	11 (15.9)	50 (10.7)	0.22

* Data are presented as mean±standard deviation or No. (%) of participants

in the number of OGTTs was high (78.5% and 84.9%, respectively). However, 15.1% to 21.5% of women would need to be tested twice: first for the FG level and second for an OGTT. This may lead to a higher non-compliance rate of OGTTs. In pathways 7 to 9, the OGTT was provided only to women with no history of GDM with or without

any risk factors. Triage based on the FG level of 4.5-5.1 mmol/l with or without any risk factor resulted in a higher percentage reduction in the number of OGTTs performed but a lower sensitivity; 2.5% of women with a history of GDM were falsely labelled as having GDM and received unnecessary intervention, although their OGTT result was actually normal.

Table 2. Estimated percentage reduction in the number of oral glucose tolerance tests (OGTTs) performed and sensitivity in detecting gestational diabetes mellitus (GDM) in the nine pathways with or without consideration of fasting glucose (FG) levels, a history of GDM, and/or any risk factors

Pathway	No. of OGTTs performed	Estimated % reduction in the No. of OGTTs performed	Sensitivity, %
1: Universal OGTT	769	0	100
2: OGTT for high-risk group	451	41.4	59
3: Universal FG alone	0	100.0	20
4: Universal FG then OGTT for FG level of 4.5-5.1 mmol/l	165	78.5	47
5: Universal FG then OGTT for FG level of 4.5-5.1 mmol/l + high risk	116	84.9	38
6: OGTT for no history of GDM	732	4.8	100
7: OGTT for no history of GDM + high risk	413	46.3	59
8: OGTT for no history of GDM + FG level of 4.5-5.1 mmol/l	148	80.8	54
9: OGTT for no history of GDM + high risk + FG level of 4.5-5.1 mmol/l	99	87.1	42

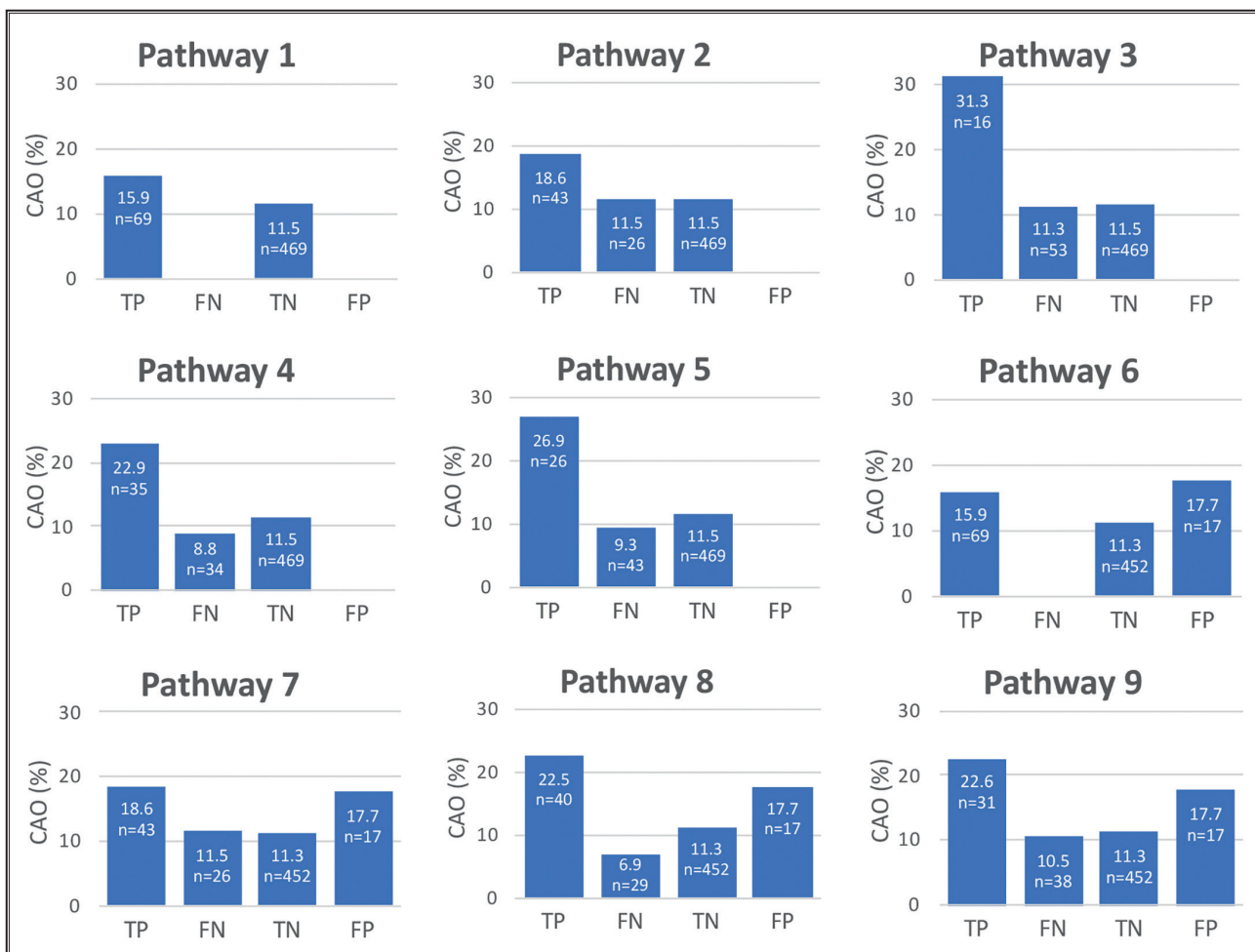


Figure 2. Estimated percentages of women with composite adverse outcome (CAO) in terms of the true-positive (TP), false-negative (FN), true-negative (TN), and false-positive (FP) groups in the nine pathways

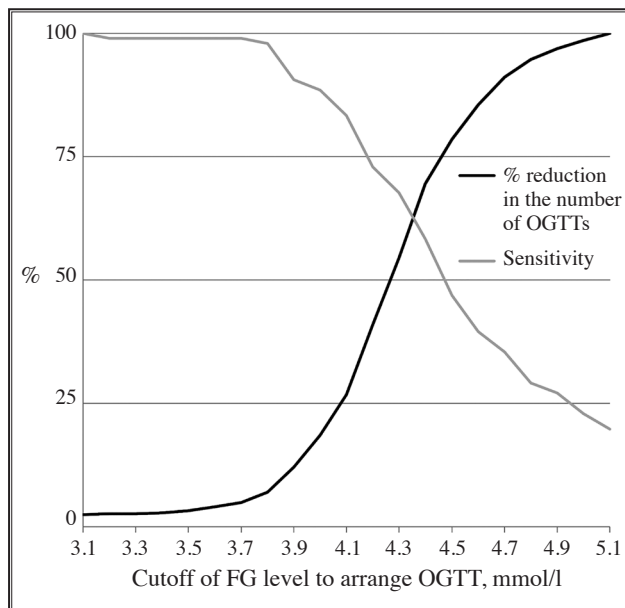


Figure 3. Relationship of estimated percentage reduction in the number of oral glucose tolerance tests (OGTTs) performed and sensitivity of fasting glucose (FG) level in detection of gestational diabetes mellitus (GDM)

In the Hyperglycemia and Adverse Pregnancy Outcome Study, only 24% of patients with GDM had an abnormal FG level in a Bangkok population. A Japanese study¹⁶ presented similar problems based on the Japanese COVID guideline, which was adapted from the guidelines of The Royal College of Obstetricians and Gynaecologists and the Australasian Diabetes in Pregnancy Society^{4,6}. At an FG cutoff level of 5.1 mmol/l, most GDM diagnoses were made based on postprandial plasma glucose levels. The Japanese COVID guideline missed 60% of GDM cases. This difference in ethnicity is important for provision of optimal clinical care in various ethnic groups, especially during a pandemic with strict infection control measures.

When the universal OGTT is non-expendable, different logistics may be applied during a pandemic. Ideally, each pregnant woman should undergo the OGTT individually in a negative-pressure room with disinfection before and after use. If the single-room setting is not feasible, seating with replaceable plastic sheeting, anti-virus coating, and an ultraviolet-C disinfection unit that integrates a portable pump and a high-efficiency particulate air filter should be used¹⁷. Social distancing can be improved by reducing the number of bookings in each time slot and by increasing the number of time slots throughout the week. In our centre, a negative rapid test result on the morning before arrival to hospital for the OGTT was

necessary. Straws were provided for the women to take the glucose load with the mask on. Women were asked to raise their hands and be escorted to isolated areas when there was a need to vomit.

All alternative pathways were able to identify women at the highest risk of GDM. The estimated rate of CAO in all pathways were higher in the true-positive groups than in the false-negative groups. This suggests that the selection criteria (any high-risk factor, higher FG level, and a history of GDM) individually and jointly prognosticate adverse outcomes of GDM. Pathway 3 (using the FG level alone) could detect the highest percentage of women with CAO, suggesting that, although the FG level was not sensitive for diagnosis of GDM in a Chinese population, elevated FG levels could be associated with higher maternal and neonatal complications.

For pathways 6 to 9, 2.5% of women with a history of GDM were falsely labelled as having GDM and received unnecessary monitoring and intervention, although their OGTT results were normal. The rate of CAO in these women was 17%, which was higher than that in the true negative groups (ie, women without GDM), consistent with one study⁸. It is postulated that higher FG levels (although not beyond the cutoff) might correlate with more adverse outcomes, and that women with a history of GDM might have hidden risk factors that could result in the higher rate of CAO.

Our study had several limitations. Although the sample size was 769, about 30% of the delivery records were not available for analysis, because of delivery in private hospitals. Subgroup analysis was not possible because there were few cases of complications such as shoulder dystocia, intrauterine fetal demise, or neonatal death. Only historical risk factors and FG levels were collected for analysis. The Royal College of Obstetricians and Gynaecologists advocated using the glycated haemoglobin (HbA1c) level of 5.7% as a substitute for the second-trimester OGTT during the COVID-19 pandemic⁴. Measurement of HbA1c levels requires no fasting or consumption of a glucose load. Although the HbA1c level was not used for diagnosis of GDM in our study, all women with GDM had their HbA1c level checked a few days after diagnosis. If a HbA1c level of 5.7% were used, we would have missed 88% of GDM cases. In a study of 19000 pregnant women who underwent second-trimester OGTT and HbA1c measurement together, the HbA1c level was only weakly correlated with OGTT results; a cutoff of 5.0% yielded a sensitivity of 60%¹⁸. Other alternative pathways such as random measurement

of glucose levels, personalised risk calculators, and a combination of these parameters may be assessed in future studies.

Women with the highest risk of GDM who had already been diagnosed in an early OGTT were not included in the analysis. This reduced the sensitivity in all pathways tested. The false-negative groups were actually managed as having GDM in real life. Hence, the estimated rate of CAO would underestimate the true rate of CAO if the women did not receive treatment. However, the estimated rate of CAO for false-negative groups in pathways 2 to 9 was similar to that for true-negative groups. This suggests that interventions such as advice from a dietitian, regular self-monitoring of blood glucose levels, and additional counselling and monitoring can help reduce the rate of CAO to the level similar to true-negative groups. The false-negative groups were at lower risk than the true-positive groups, because both groups received the same intervention, but the false-negative groups had a consistently lower rate of CAO. Our cohort was affected by the COVID-19 pandemic; the prevalence of GDM and adverse outcomes were reported to increase during the pandemic. A historical cohort without the effects of the COVID-19 pandemic may be used to compare with our cohort to detect any differences.

Conclusion

In Chinese women, compared with the universal second-trimester OGTT, alternative pathways could reduce the number of OGTTs performed, but the detection rate of GDM was poor. Obstetricians should encourage pregnant women to undergo the OGTT to reduce maternal and

neonatal complications, even in the event of pandemic. In situations when infection control measures are ineffective, pathway 3 can be considered because it could detect the highest rate of CAO and eliminated the need for OGTTs.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Central Institutional Review Board of the Hospital Authority (reference: CIRB-2023-072-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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