Australasian Diabetes in Pregnancy Society

TOBOGM Workshop 2023:

Options for Diagnostic Approaches for Early Gestational Diabetes Mellitus

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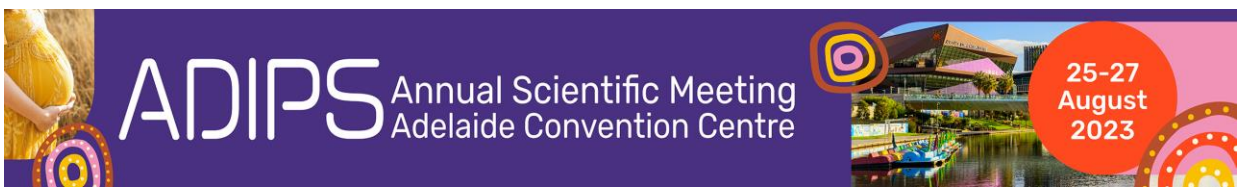

Background

Current Australasian Diabetes in Pregnancy Society (ADIPS) guidelines recommend routine testing for and treatment of gestational diabetes (GDM) with the 75-g oral glucose tolerance test (OGTT) at 24-28 weeks gestation.[1] The recommended diagnostic thresholds at 24-28 weeks align with International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations determined by a consensus approach following the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study.[2] Early testing is recommended in women at increased risk of diabetes but how this should be performed and the diagnostic thresholds for early GDM are unclear. There have been limited randomised controlled trial (RCT) data on early testing and treatment, and no RCT has evaluated the 75-g OGTT for early GDM diagnosis and treatment.

The Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial[3] was a multicentre, randomised controlled trial (RCT) assessing pregnancy outcomes in women tested and treated for GDM before 20 weeks gestation (immediate-treatment group) and in women whose diagnosis and management were deferred until the results of the 24-28 week repeat OGTT (control group). The study population comprised of women with at least one risk factor for diabetes. The diagnosis of early GDM was based on the 2-hr 75g OGTT (IADPSG/ADIPS thresholds: fasting ≥5.1 and/or 1-hr ≥10 and/or 2-hr ≥8.5 mmol/L), consistent with the 24-28 week OGTT diagnostic thresholds used. Randomisation was stratified by glucose ranges determined by thresholds associated with 1.75 (lower band) and 2.0 (higher band) odds ratios for adverse outcomes in the HAPO Study. The primary outcomes were:

- PO1: Composite of adverse neonatal outcomes (preterm birth, birth trauma, birth weight ≥4500g, respiratory distress, phototherapy, stillbirth or neonatal death, shoulder dystocia)
- PO2: Pregnancy-related hypertension
- PO3: Neonatal lean body mass

The composite adverse neonatal outcome (PO1) was significantly lower in the immediate-treatment group (24.9% vs 30.5%, adjusted [adj] difference -5.6% [95% CI -10.1 to -1.2]). PO2 and PO3 were not significantly different. Other key secondary outcomes were a reduction in 3rd-4th degree perineal injury (0.8% vs 3.6%, adj difference -2.8% [95% CI -4.1 to -1.5]) and in neonatal intensive care unit/special care unit length of stay (adj difference -0.8 [95% CI -1.3 to -0.3]) days. Quality of Life was improved at 24-28 weeks gestation (EQ5D score adj difference +0.02 [95% CI 0.01 to 0.04]). There were no differences in Caesarean section or induction of labour. Birthweight was lower (adj difference -72.1 [95% CI -127.6 to -16.6])g as was neonatal fat mass (adj difference -0.03 [95% CI -0.05 to -0.01])kg.

In secondary analyses, significant reductions in PO1 were achieved in the higher not the lower glucose band and before 14 weeks gestation. Treatment of the lower glucose band, but not the higher glucose band was associated with significantly more SGA small-for-gestational-age (SGA) offspring.

There are no RCTs comparing OGTT thresholds for early GDM diagnosis and treatment as the primary analysis. Assessment of lower and higher diagnostic thresholds at 24-28 weeks was recently addressed by the Gestational Diabetes Mellitus Trial of Diagnostic Detection Thresholds (GEMS) trial,[4] an RCT comparing pregnancy outcomes in women diagnosed with the 24-28 week 75-g OGTT using the lower glycaemic thresholds consistent with current IADPSG/ADIPS recommendations (lower glycaemic criteria group) and using the higher thresholds (fasting ≥5.5 and/or 2-hr ≥9.0 mmol/L) of the New Zealand Society for the Study of Diabetes (NZSSD) (higher glycaemic criteria group). The primary outcome was large-for-gestational age (LGA) offspring. At a population level, there was no significant difference in the rates of LGA between the two groups. In secondary analyses of treated and untreated women whose OGTT values were between the lower and higher thresholds (fasting 5.1-5.4 and/or 1-hr >10 and/or 2-hr 8.5-8.9 mmol/L), the intervention group had lower rates of LGA (6.2% vs 18.0%, relative risk [RR] 0.33 [95% CI 0.18 to 0.62]) and preeclampsia (0.5% vs 5.6%, RR 0.09 [95% CI 0.002 to 0.62]), in addition to potentially lower composite of stillbirth, neonatal death, birth trauma and shoulder dystocia (0.5% vs 3.9%, RR 0.13 [95% CI 0.003 to 1.00]). SGA (9.7% vs 3.9%, RR 2.48 [95% CI 1.07 to 5.75]) and detection of neonatal hypoglycaemia (27.2% vs 9.0%, RR 3.02 [95% CI 1.80 to 5.09]) were higher in the intervention group.

The TOBOGM Workshop

The TOBOGM Workshop was held at the ADIPS Annual Scientific Meeting on 27th August 2023 to review the results of the TOBOGM RCT and to discuss the options for testing for and treatment of early GDM. Implications and options for 24-28 week testing if early testing and treatment are implemented were also discussed. The Workshop comprised presentations from TOBOGM investigators, panel discussion with multidisciplinary healthcare and consumer representation and Workshop attendee input.

Chairs: Ian Fulcher, Alison Nankervis

Presenters: David Simmons, Wah Cheung, Chris Nolan

Panellists: David Simmons, Wah Cheung, Chris Nolan, Michael Peek, Robyn Barnes, Mugdha Joglekar, Alison Barry

The following is a summary of the options discussed.

Some issues were common to all early GDM options:

- Early GDM appears to be a more severe form of GDM in terms of pregnancy complications.
- TOBOGM is the only RCT evaluating the 75-g OGTT in early pregnancy. There are also no current RCTs comparing lower and higher glucose bands. As there are no ongoing or known upcoming trials, additional high quality evidence may not become available.
- Early diagnosis would be associated with an increase in duration of GDM
- Consumer perspectives need to be considered: Increased burden with longer time for glucose monitoring and treatment vs positive view of early opportunity to institute changes that may improve neonatal outcomes. Consumer concern that early diagnosis may exacerbate existing issues of suboptimal transition from primary care to hospital-based clinics was raised.
- Adopting early GDM screening would increase the proportion of women diagnosed with GDM unless 24-28 week GDM criteria were changed concurrently.
- Increase in number of women undergoing two OGTTs and potential risk of more women not attending their 24-28 week OGTTs
- Timing of early testing would need to balance evidence of benefit and practical considerations:
    - TOBOGM comprised women less than 20 weeks gestation. Subgroup analysis suggested greater clinical benefit in women who underwent testing and treatment at less than 14 weeks, although with potential benefits of testing and treatment also after 14 weeks. Preliminary unpublished data suggest greater cost saving.
    - Practical challenges implementing testing at less than 14 weeks due to later presentations to healthcare, resource accessibility and hyperemesis in early pregnancy. Potential for aligning with other early pregnancy risk assessments, but practice varies across states.
- No long-term data available.
- Preanalytical error concerns for all OGTTs due to glycolysis in Na-F tubes if there is delayed centrifugation +/- analysis.

A. Options for Early Testing

Option 1: No screening for early GDM

Pros:

- No change to current models of care required
- No increase in resource utilisation for testing or of antenatal care services
- No change to the burden for women of GDM diagnosis and treatment

Cons:

- Missed opportunity to diagnose and treat early GDM, thus foregoing the multiple benefits demonstrated by TOBOGM (clinical, economic, consumer, potentially staff with less workload under some options)
- Inconsistency in the approach to early screening and treatment will remain
- Arguments over numbers diagnosed with current approach at 24-28 weeks continue

Issues:

- Status quo

Option 2: Screen for early GDM using 75-g OGTT with the current ADIPS glycaemic criteria ("lower band" HAPO OR 1.75: fasting ≥5.1 and/or 1-hr ≥10 and/or 2-hr ≥8.5 mmol/L) among women with risk factors as per TOBOGM

Pros:

- Aligns with TOBOGM's primary analysis showing reduction in composite adverse neonatal outcomes (PO1)
- Benefits in RCT secondary outcomes including reduction in neonatal intensive care bed length of stay, 3rd-4th degree perineal tear, quality of life benefit
- Cost saving overall (preliminary data)
- Consistent with current criteria for the 24-28 week OGTT

Cons:

- Increase in GDM diagnosis overall
- Composite adverse neonatal outcome (PO1) benefit significant in higher but not lower glycaemic band in TOBOGM secondary analyses
- Potential harm of early diagnosis and treatment for women in the lower glycaemic band, with increased SGA offspring in TOBOGM secondary analyses.
- Cost increment with early testing and treatment in the lower band (preliminary data)

Issues:

- Risk factor-based screening would lead to missed diagnosis, although no RCT of treating early GDM in those with no risk factors. Rates of missed early GDM unknown
- Revising clinical practice based on one high quality RCT
- Implications for the workforce of increased GDM diagnosis and more women changing to higher risk models of care. Current structures of care models may need to be revised to facilitate review of larger numbers of women for longer duration
- Challenges of increased resource demands and accessibility particularly for rural/remote sites

Option 2.1: As Option 2 but with Universal Early Screening

Pros:

- No missed diagnoses

Cons:

- As above but generally more (eg resource requirements)
- No RCTs reported among those with no risk factors (although TOBOGM included a majority of those identifying as ethnic groups other than European without other risk factors)

Option 3: Screen for early GDM using 75-g OGTT with higher glycaemic criteria ("higher band" HAPO OR 2.0: fasting ≥5.3 and/or 1-hr ≥10.6 and/or 2-hr ≥9.0 mmol/L) among women with risk factors

Pros:

- Aligns with TOBOGM's secondary analyses demonstrating significant benefit in PO1 for women diagnosed in the higher band and treated
- Cost saving of early testing and treatment for women in the higher band in contrast to a cost increment for the lower band (preliminary data)
- Reduced number of GDM diagnosis compared to using lower band and thus less impact for workforce and models of care
- Used already in Canada for the 24-28 weeks OGTT

Cons:

- Not based on TOBOGM's primary analysis but on subgroup analysis.
- Challenges adopting new diagnostic criteria in clinical practice and potential for confusion for women and healthcare providers
- Not aligned with current recommended criteria for the 24-28 week OGTT (see Part B below).

Issues:

- Aligning early and 24-28 week diagnostic criteria (see Part B)
- As for Option 2: Revising clinical practice based on one RCT, missed diagnosis with risk factor-based early screening, implications for workforce particularly for rural/remote sites

Option 3.1: As Option 3 but with Universal Early Screening

Pros:

- No missed diagnoses

Cons:

- As above but generally more (eg resource requirements)
- No RCTs reported among those with no risk factors (although TOBOGM included a majority of those identifying as ethnic groups other than European without other risk factors)

Option 4: Screen for early GDM using 75-g OGTT with hybrid glycaemic criteria (fasting ≥5.3 and/or 1-hr ≥10 and/or 2-hr ≥8.5 mmol/L)

Pros:

- Aligns with fasting, 1-hr and 2-hr thresholds of Carpenter and Coustan criteria on 100g OGTT
- Reduced number of GDM diagnosis compared to using lower band

Cons:

- Not based on primary or secondary analyses of TOBOGM data.
- As per Options 3 and 3.1

Issues:

- Absence of any trial data supporting these criteria
- As per Options 3 and 3.1

Option 5: Screen for early GDM using 75-g OGTT with fasting and 1-hr values

Pros:

- Reduces time, resource and blood collection burden by removing the 2-hr collection timepoint
- Unpublished but presented TOBOGM secondary analyses suggest greater neonatal outcome benefit of early diagnosis and treatment for women diagnosed based on elevated 1-hr level than women diagnosed based on elevated 2-hr level only
- Reduction in GDM diagnosis compared to using 2-hr OGTT (12% of GDM in HAPO due to elevated 2-hr only, 9% of GDM in TOBOGM due to elevated 2-hr only)

Cons:

- Not based on primary analysis of TOBOGM data
- As per Options 3 and 3.1

Issues:

- Lower band vs higher band vs other glycaemic band criteria for fasting and 1-hr
- As per Options 3 and 3.1

B. Options for 24-28 week OGTT if performing early OGTT

Option 1: 75-g OGTT with current ADIPS criteria (HAPO OR 1.75: fasting ≥5.1 and/or 1-hr ≥10 and/or 2-hr ≥8.5 mmol/L)

Pros:

- No change to current clinical practice at 24-28 weeks
- Aligns with diagnostic criteria used for TOBOGM
- Lower odds ratio for adverse outcomes such as LGA and neonatal hypoglycaemia than using higher thresholds (HAPO)
- GEMS secondary analysis of women whose OGTT results were between the lower and higher thresholds (ie fasting 5.1-5.4 and/or 1-hr >10 and/or 2-hr 8.5-8.9 mmol/L) showed benefit in outcomes (such as lower rates of LGA and preeclampsia), suggesting that using thresholds as low as the current ADIPS criteria may be beneficial

Cons:

- Increased number of GDM diagnosis compared to using HAPO OR 2.0 (50% increased diagnosis in HAPO)
- GEMS primary analysis demonstrated no difference in the primary outcome of LGA on a total obstetric population level between using HAPO OR 1.75 criteria and the NZSSD 5.5/9.0 criteria.

Issues:

- Aligning early and 24-28 week OGTT criteria: Complexity and potential confusion for women and healthcare providers if not using the same criteria for early and 24-28 week OGTTs

Option 2: 75-g OGTT with change to higher glycaemic band (HAPO OR 2.0: fasting ≥5.3 and/or 1-hr ≥10.6 and/or 2-hr ≥9.0)

Pros:

- Reduced GDM diagnosis compared to current criteria

- Would facilitate alignment of early and 24-28 week OGTTs using the higher glycaemic band in which TOBOGM subgroup analysis demonstrated greatest benefit

Cons:

- Lack of RCT data
- Higher odds ratio for adverse outcomes (HAPO). However, early testing and diagnosis would lead to a lower risk population undergoing 24-28 week OGTT. Thus absolute risk difference of using the higher glycaemic band compared to the low band may be low.
- Challenges adopting new diagnostic criteria in clinical practice and potential for confusion for women and healthcare providers

Issues:

- Revising current recommendations without new high quality data using HAPO OR 2.0 thresholds at 24-28 weeks
- GEMS secondary analysis suggested benefit in diagnosing and treating women whose OGTT results were between lower and higher GEMS criteria (ie fasting 5.1-5.4 and/or 1-hr >10 and/or 2-hr 8.5-8.9 mmol/L).
- Linear association between glucose and HAPO outcomes, with divided opinion on thresholds

Option 3: 75-g OGTT with change to an alternative glycaemic band guided by GEMS secondary analysis (fasting 5.1-5.4 and/or 1-hr >10 and/or 2-hr 8.5-8.9 mmol/L)

Pros:

- Evidence from RCT secondary analysis

Cons:

- Lack of RCT data
- No guidance on the alternative thresholds (within the GEMS secondary analysis ranges) and divided opinion

Issues:

- Revising current recommendations based on secondary analysis of one RCT
- Aligning early and 24-28 week OGTT criteria: Need additional analyses of TOBOGM data to assess the effect on a subgroup defined by an alternative glycaemic band

Option 4: No 75-g OGTT at 24-28 weeks (OGTT once in early pregnancy)

Pros:

- Reduced GDM diagnosis
- Reduced burden for women and pathology collection centres
- Unpublished but presented TOBOGM data suggest women with GDM on 24-28 week but not early OGTT are a lower risk group. Women detected only on 24-28 week OGTT did not have increased composite adverse neonatal outcomes, birth centiles, neonatal hypoglycaemia or preterm birth compared to those with normal early and 24-28 week OGTT. However, this lack of difference could relate to effective treatment in women with GDM detected at 24-28 weeks.

Cons:

- Lack of RCT data
- There will be missed diagnosis and thus potential for increased adverse outcomes as many women with GDM on 24-28 week are still at increased risk

Issues:

- Forego 24-28 week OGTT in all women with normal early OGTT vs forego only in selected women determined to be at lower risk
- No data yet to support this approach

C. Non-OGTT options for early screening with or without a follow on OGTT

Option 1: Biomarker-based early screening

Potential glycaemic markers: Fasting glucose, random glucose, HbA1c, fructosamine, glycated albumin, glycated CD59, 1,5 anhydroglucitol (1,5 AG). These have all been investigated.

Potential non-glycaemic markers: Triglycerides, miRNA

Pros:

- Time saving and less burden for women and pathology collection staff
- Some tests (eg fasting glucose) are low cost and readily available
- Some tests are medium cost, non-fasting and readily available (eg HbA1c)
- Avoid the pre-analytical concerns of glucose measurement from collections in Na-F tubes

Cons:

- Lack of RCT data supporting their use
- Most (including HbA1c, glycated albumin) are poor predictors of GDM and neonatal outcomes
- Fasting glucose: sensitivity issues particularly in many high risk populations (eg Asians) increasing disparities
- Loss to follow-up if confirmatory test needed (eg OGTT)
- Triglyceride: correlation with OGTT results is greatest at 9-12 weeks gestation, but then rises during pregnancy
- Most of the biomarkers are not readily commercially available and/or are relatively expensive

Issues:

- Variability of tests, particularly due to effects of physiological and pathophysiological changes during pregnancy such as decrease in serum albumin, increase in eGFR, blood cell turnover, iron deficiency: eg lower fructosamine in pregnancy, lower 1,5AG
- Non-glucose biomarkers represent glycaemic control over varying timeframes whereas glucose-related tests such as OGTT provide a real-time indication

Option 2: Continuous glucose monitoring (CGM)

Pros:

- Avoid burden of performing early OGTT
- Real-time measure of glucose over a longer timeframe

Cons:

- Lack of RCT data supporting their use
- Insufficient evidence to guide cut-offs
- Expensive and no subsidy available for this purpose
- Potential inaccuracies
- Increased workload for the healthcare provider to interpret CGM data

Issues:

- Consensus on CGM parameters for GDM diagnosis needed. Early pregnancy vs later pregnancy parameters
- Use throughout pregnancy vs during defined 1-2 week periods
- Awaiting results of MAGIC and GO MOMS,[5,6] prospective observational studies using CGM to assess pregnancy glycaemic profile and association with GDM diagnosis and pregnancy outcomes

Option 3: Combination/risk engine approach

Pros:

- Combination of multiple markers to improve prediction of GDM and outcomes

Cons:

- Expensive

Issues:

- Lack of RCT data supporting their use and no data on optimal combination

At the conclusion of the TOBOGM Workshop, a vote on the discussed options was held among the Workshop attendees. **Performing early testing using the higher glycaemic band (HAPO OR 2.0: fasting ≥5.3 and/or 1-hr ≥10.6 and/or 2-hr ≥9.0 mmol/L) and aligning the 24-28 week OGTT with this higher band was the majority preference.** Some attendees preferred to defer until further discussion with additional analyses.

Note: The 50-g challenge and 3-hr 100-g OGTT options were not discussed as this approach is not used in Australia and New Zealand.

Summary

The TOBOGM Workshop facilitated discussion of the TOBOGM study with multidisciplinary and consumer representation. The benefit of early GDM diagnosis and treatment on adverse neonatal outcomes and on several secondary outcomes was recognised, with likely greater treatment effect in specific subgroups such as women diagnosed before 14 weeks gestation and in the higher glucose band. The Workshop panellists and attendees raised concerns for increased burden for pregnant women, impact on the workforce and healthcare resources particularly in rural and remote settings, and the challenges of developing and implementing a standardised approach if adoption of early testing was not offset by changes in diagnostic criteria.

Possible options for early testing for GDM and the implications for the 24-28 week OGTT were discussed, with the pros, cons and issues of each option detailed. There was agreement that a clear, consistent approach to early and subsequent testing for GDM should be sought, but further discussion incorporating ongoing secondary analyses of TOBOGM and wider stakeholder input is needed to reach a consensus on the approach to early testing and treatment and how this will be implemented in clinical practice.

References

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