

Estimated treatment effects of tight glycaemic targets in mild gestational diabetes mellitus: a multiple cut-off regression discontinuity study design.

David Song (✉ davidso@bhs.org.au)

Ballarat Base Hospital <https://orcid.org/0000-0002-8242-1268>

James C Hurley

The University of Melbourne Department of Rural Health

Maryanne Lia

Peninsula Health

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Abstract

Background

We investigated the treatment effects of tight glycaemic targets in a population universally screened according to the International Association of Diabetes and Pregnant Study Groups/World Health Organisation gestational diabetes mellitus (GDM) guidelines.

Methods

A multiple cut-off regression discontinuity study design in a retrospective observational cohort undergoing oral glucose tolerance tests ($n = 1178$). Treatment of GDM women with the targets: fasting glucose of ≤ 5.0 mmol/L and the 2-hour post-prandial glucose of ≤ 6.7 mmol/L.

Results

Treated GDM women had lower rates of large for gestational age 4.6% versus those just below diagnostic thresholds 12.6%, relative risk 0.37 (95% CI, 0.16–0.85); reduced caesarean section rates, 32.2% versus 43.0%, relative risk 0.75 (95% CI, 0.56–1.01). The subgroup analysis suggested that treatment of GDM women with $\text{BMI} \geq 30$ kg/m² drove the reduction in caesarean section rates: 32.9% versus 55.9%, relative risk 0.59 (95%CI, 0.4–0.87). Linear regression interaction term effects between non-GDM and treated GDM were significant for LGA ($p = 0.001$) and caesarean sections ($p = 0.015$).

Conclusions

Tight glycaemic targets reduced rates of large for gestational age and caesarean sections compared to a counterfactual group just below the diagnostic thresholds albeit at the expense of increased rates of neonatal hypoglycaemia, induced deliveries, and insulin usage.

Introduction

The International Association of Diabetes and Pregnancy Study Groups (IADPSG)¹ Gestational Diabetes Mellitus¹ (GDM) diagnostic thresholds, endorsed by the World Health Organisation (WHO)², are not universally accepted³. The ongoing lack of consensus reflect concerns of the increasing costs of higher GDM prevalence using the one-step universal screening with lower oral glucose tolerance test (OGTT) cut-offs and the limited evidence on the clinical effectiveness of treating milder disease⁴. Indeed, there is disagreement between those suggesting new randomised controlled trials (RCT) are required and those who believe existing RCTs, which did not use the current IADPSG/WHO guidelines, with observational studies are sufficient^{4,5}.

In centres where the IADPSG/WHO GDM guidelines have become the standard of care, RCTs comparing outcomes of new to old guidelines may be ethically difficult to perform. Moreover, RCTs for mild GDM can be challenging as the act of randomisation may reduce treatment effects by affecting the behaviour of study's controls⁶. This is salient in GDM, as the primary interventions are behavioural modification: dietary and lifestyle.

Variations in obstetric practises challenge the external validity of RCTs. For instance, the reduction of caesarean section rates is purported to be a driver of the cost-effectiveness of treating GDM⁷. Since caesarean section rates differ widely around the world⁸, results from multi-centre RCTs may not have local applicability.

We propose a new method of estimating GDM treatment effects in local observational cohorts. This multiple cut-off regression discontinuity study design is used to estimate the treatment effects of tight glycaemic targets among women proximate to the diagnostic thresholds in a population universally screened using IADPSG/WHO guidelines.

Methods

We received local ethics committee approval for this study (LNR/18/BHSSJOG/16).

Study population and sampling design

This single-centre retrospective cohort study searched records of women birthing at Ballarat Health Services (BHS) between January 1st 2017 and December 31st 2017. BHS is a regional public hospital in the state of Victoria, Australia with a population of approximately 100,000. BHS delivers approximately 70% of births in Ballarat. Additionally, women with GDM requiring intensification of therapy with medications are referred to the antenatal clinic from up to 150 km away.

We used the Australasian Diabetes in Pregnancy Society⁹ (ADIPS) guidelines, which recommends single-step universal screening for GDM by 24–28 weeks gestation using 75 g anhydrous glucose Oral Glucose Tolerance Test (OGTT). The ADIPS guidelines follow IADPSG GDM thresholds. A GDM diagnosis was based on one or more results meeting the following plasma glucose levels: fasting 5.0-6.9 mmol/L, 1-hour ≥ 10.0 mmol/L, or 2 hour 8.5–11.0 mmol/L. The pre-analytical and analytical OGTT methods were described in a study by Song D et al¹⁰.

Inclusion criteria were all singleton births at BHS between January 1st 2017 and 31st December 2017 with OGTTs.

Exclusion criteria were women with overt diabetes mellitus as defined by OGTT levels fasting glucose ≥ 7.0 mmol/L and 2-h plasma glucose of ≥ 11.1 mmol/L; and GDM women who did not receive GDM antenatal interventions at BHS. For women below the GDM diagnostic thresholds, we excluded those with

incomplete OGTTs, missing 1-hour and 2-hour plasma glucose levels; and those with OGTTs before 24 and after 28 weeks.

Data were collected prospectively from the initial antenatal clinic visit until after delivery. The hospital's electronic records were searched for OGTT, demographic data (age, ethnicity, gravida, parity, BMI at first presentation, foetal sex), maternal outcomes (induced deliveries, caesarean sections, gestation age of delivery, diabetes mellitus diagnosis, medication use), and foetal outcomes (delivery weight, foetal length, neonatal hypoglycaemia, shoulder dystocia).

Large for gestational age (LGA) and small for gestational age (SGA) was defined as a birth weight greater than the 90th and less than the 10th percentile, for gestational age respectively, using age based standardised charts¹¹. Gestational age was based on either ultrasound reports of gestational age or the last menstrual period. Neonatal hypoglycaemia was based on documentation in the database.

Interventions

Women with GDM typically received initial group education by the diabetes educator and the dietician. Women were advised to test capillary blood glucose (CBG) at fasting, and 2 hours after the beginning of each significant meal. In subsequent appointments GDM women were given individualised advice on the recommended weight gain in pregnancy and diet, as appropriate. Recommended weight gain suggestions, for GDM and non-GDM women, in pregnancy were based on the Institute of Medicine guidelines¹²; except for those with BMI > 35, where the local consensus was for minimal further weight gain.

The standard management for GDM women included attendance at the multi-disciplinary antenatal clinic one week after the initial education, this clinic included endocrinologists, obstetricians, midwives, anaesthetists, dieticians, and diabetes educators. For those diagnosed early in pregnancy, women typically attended four weekly appointments until 28–30 weeks, thereafter, women were typically seen two weekly. Most women were encouraged to self-titrate insulin/metformin doses, within strict parameters, to reach target CBG levels.

Treatment targets

Treatment targets and thresholds for intensification were consistent with ADIPS suggestions⁹, which were fasting capillary blood glucose (CBG) \leq 5.0 mmol/L and 2 hour CBG after commencing meal \leq 6.7 mmol/L. The decision to consider intensification of treatment were based on whether there were two or more elevated CBG levels at a given time within one week, CBG pattern, ultrasound reports on estimated foetal weight/abdominal circumference, and women's preferences.

The basal insulin used was Isophane prescribed nocte. The bolus insulin used was Aspart. The metformin used was the modified-release formulation.

Subject allocation and HAPO glucose composite score

Subjects were assigned to GDM or non-GDM as per IADPSG/WHO guidelines. To further categorise subjects, all were given a HAPO glucose composite score.

HAPO glucose composite score

Each subject was scored according to their OGTT results at fasting, 1-hour, and 2-hour plasma glucose levels. As the range of fasting glucose levels in a population was narrower than the 1-hour and 2-hour levels, each subject's OGTT results were scaled according to a measure with equivalent risks of adverse outcomes – the HAPO study's glucose categories (between 1 to 7)¹³. The HAPO glucose composite score for each subject is the sum of scores of maternal plasma glucose exposure at each OGTT time point. The HAPO glucose composite score serves as the dependent variable used in linear regression analysis and the bandwidth selection of the counterfactual group. The HAPO glucose categories, from which HAPO glucose composite scores are derived, are in Fig. 2.

The range of possible HAPO glucose composite scores was from 3 (1 + 1 + 1) to the maximum of 21 (7 + 7 + 7). As the GDM diagnostic thresholds intersects category 5 at all OGTT time points, for GDM subjects the theoretical minimum HAPO glucose composite score was 7 (5 + 1 + 1). For non-GDM subjects, the maximum possible HAPO glucose composite score was 15 (5 + 5 + 5). Between GDM and non-GDM subjects, there was a possible overlap of HAPO glucose composite scores from 7 to 15.

Study Design

Our study is a regression discontinuity design structured on a composite score derived as a result of OGTT's multiple cut-offs. The composite score generates an overlap between GDM and non-GDM subjects.

Treatment effects for mild GDM were estimated by first, comparing outcomes of GDM subjects to a counterfactual group not meeting the diagnostic thresholds for GDM. Bandwidth selection for the counterfactual group was selected on the basis of HAPO glucose composite scores ≥ 9 . This threshold was selected as all GDM subjects, except five, had HAPO glucose composite score of ≥ 9 . Second, as obesity is a major independent contributor to clinical adverse GDM outcomes of LGA and caesarean Sect.¹⁴, we performed a subgroup analysis of subjects based on BMI: <30 or ≥ 30 kg/m². Third, linear regression was applied to LGA and caesarean sections, as they are known to have linear relationships to maternal glucose levels¹³.

For the linear regression, we plotted caesarean section rates and LGA versus HAPO glucose composite scores. Where there were fewer numbers of non-GDM subjects, they were pooled for HAPO glucose composite scores: 9 to 10, and 11 to 14. GDM subjects were similarly pooled at its extremes of the HAPO glucose composite score categories: 7 to 10, 15 to 19, for the purposes of the linear regressions. Where there were no LGA events in a GDM's HAPO glucose composite score, we pooled subjects with the adjacent score.

Statistical methods

The statistical significance for baseline demographic parametric data was calculated using non-paired student t-tests and non-parametric baseline data was calculated using the Mann-Whitney test. Statistical significance for maternal and neonatal outcomes for proportions was calculated using the χ^2 test; for parametric outcome data we used unpaired student t-test. The non-parametric bootstrap method was used to determine the 2.5, 97.5 percentile reference interval for OGTT fasting plasma glucose¹⁵. Clinical outcomes were considered statistically significant at a p value of < 0.05. A linear regression of LGA and caesarean sections versus HAPO glucose composite score was undertaken and the statistical significance of interaction term effects was determined. Statistics were analysed using Minitab 18, State College, PA; and STATA 15, statacorp LLC.

Results

Study population

Among 1505 women delivering at BHS, 1178 had OGTTs (Fig. 1). There were 162 subjects with OGTT above IADPSG/WHO GDM thresholds. The prevalence of GDM was 13.5% (n = 159/1178) excluding the three subjects with overt diabetes. And after excluding a further seven subjects because they did not attend BHS GDM clinic, there were 152 GDM subjects. Between 24–28 weeks gestation, 1000 women had OGTTs; and after removal of subjects above diagnostic thresholds and incomplete OGTT (n = 4), there were 888 subjects. There were 135 subjects with HAPO glucose composite scores ≥ 9 , which are here defined as the counterfactual group.

The lower 2.5th percentile and the upper 97.5th percentile for OGTT fasting plasma glucose (n = 1178) were 3.7 mmol/L and 5.3 mmol/L, respectively.

Table 1
Baseline characteristics of the study population

Variable	GDM n = 152	Counterfactual group n = 135	All subjects with OGTTs n = 1178
Age (years)	30.5 ± 5.5 p = 0.87	30.4 ± 5.3	29.1 ± 5.4
BMI (kgm ²)	31.4 ± 8.2 p = 0.037	29.5 ± 7.3	27.7 ± 7.0
Ethnicity	Caucasian 86% South Asian 6 East Asian 3 Other 5	Caucasian 90% South Asian 4 East Asian 4 Other 2	Caucasian 91% South Asian 3 East Asian 2 Other 3
Gravida	2.8 ± 1.7 p = 0.46	2.6 ± 1.6	2.6 ± 2.3
Parity*	1.1 ± 1.2 p = 0.86	1.1 ± 1.1	0.97 ± 1.1
OGTT (mmol/L)	5.0 ± 0.4 (p < 0.001)	4.5 ± 0.3	4.3 ± 0.5
Fasting glucose	9.3 ± 1.6 (p < 0.001)	8.5 ± 0.9	7.0 ± 1.8
1 hour	7.5 ± 1.5 (p < 0.001)	7.0 ± 0.9	5.8 ± 1.4
2 hour			
HAPO glucose composite score	13# (11–13) (p = 0.001)	10# (9–11)	6# (5–9)
Values are mean ± standard deviation unless otherwise specified			
#Median and Interquartile range			
p values as compared to the counterfactual group			
*Adjusted for parity at first presentation			

The baseline population characteristics of GDM subjects, counterfactual group, and overall population with OGTTs are described in Table 1.

Table 2
Neonatal and Maternal Outcomes

Outcome	GDM treated n = 152	Counterfactual group n = 135	Relative risk (95% CI)
Maternal outcomes			
Gestational age at delivery (weeks)	38.2 ± 1.2 p < 0.001	38.8 ± 1.2	NA
Caesarean sections (%)	32.2 (n = 49) p = 0.015#	43.0 (n = 58)	0.75 (0.56–1.01)
Primary caesarean sections* (%)	24.3 (n = 33)	30.7 (n = 35)	0.79 (0.52–1.18)
Induced delivery	61.8 (n = 90)	39.3 (n = 53)	1.57 (1.18–1.9)
Neonatal outcomes			
Birth weight (g)	3224 ± 499 p < 0.001	3516 ± 509	NA
Newborn BMI (kg/m ²)	13.4 ± 1.5 p = 0.001	14.0 ± 1.4	NA
Large for gestational age (%)	4.6 (n = 7) p = 0.001#	12.6 (n = 17)	0.37 (0.16–0.85)
Small for gestational age (%)	4.6 (n = 7)	1.5 (n = 2)	3.1 (0.65–14.7)

Values are mean ± standard deviation unless otherwise specified

p values are unadjusted

NA not applicable

#p value from linear regression interactions (Fig. 2)

*Calculated as a percentage of subjects without previous caesarean sections

Outcome	GDM treated	Counterfactual group	Relative risk
	n = 152	n = 135	(95% CI)
Neonatal hypoglycaemia (%)	15.8 (n = 24)	5.9 (n = 8)	2.66 (1.23–5.73)
Admission to special care nursery (%)	19.8 (n = 30)	17.0 (n = 23)	1.15 (0.71–1.9)
Shoulder dystocia (%)	1.3 (n = 2)	0 (n = 0)	NA
Values are mean ± standard deviation unless otherwise specified			
p values are unadjusted			
NA not applicable			
#p value from linear regression interactions (Fig. 2)			
*Calculated as a percentage of subjects without previous caesarean sections			

Maternal outcomes

Compared to the counterfactual group below the diagnostic thresholds (Table 2), GDM women delivered earlier, 38.2 versus 38.8 weeks ($p < 0.001$); had higher rates of induced deliveries, 61.8% (90 out of 152) versus 39.3% (53 out of 135), RR 1.57 (95%CI, 1.18–1.9); and had lower caesarean section rates, 32.2% (49 out of 152) versus 43% (58 out 135), relative risk 0.75 (95% CI, 0.56–1.01) which did not reach statistical significance ($p = 0.06$), but the interaction effects in the linear regression were statistically significant ($p = 0.015$; Fig. 2).

Decreases in the primary caesarean rates for GDM women 24.3% (33 out of 152) from 30.7% (35 out of 135) did not reached significance, RR 0.79 (95%CI, 0.52–1.18). The study centre's overall rate of caesarean births for women with OGTT at BHS was 27.8% ($n = 328/1178$).

Neonatal Outcomes

GDM treated neonates had lower mean birth weight (Table 2), 3224 g vs 3516 g ($p < 0.001$), lower neonatal mean BMI 13.4 versus 14.0 kgm^2 ($p = 0.001$). GDM subjects had lower rates of LGA (4.6% versus 12.6%), RR 0.37 (95%CI, 0.16–0.85). Increases in SGA rates did not reach statistical significance. We note that 5 of the 6 subjects with SGA were from GDM women managed with diet/lifestyle only.

Neonatal hypoglycaemia increased in GDM subjects 15.8% versus 5.9%, RR 2.66 (95% CI, 1.23–5.73) but with no difference in the admissions to the special care nursery (Table 2).

Table 3
Subgroup analysis: maternal and neonatal outcomes stratified by BMI \geq 30, BMI < 30.

Outcome	GDM BMI \geq 30 n = 79	Counterfactual group BMI \geq 30 n = 59	Relative risk 95% CI	GDM BMI < 30 n = 73	Counterfactual group BMI < 30 n = 76	Relative risk 95% CI
Caesarean sections (%)	32.9 (n = 26)	55.9 (n = 33)	0.59 (0.4–0.87)	31.5 (n = 23)	32.9 (n = 25)	0.96 (0.6–1.15)
Primary caesarean sections* (%)	26.4 (n = 19)	45.8 (n = 22)	0.58 (0.35–0.94)	20.6 (n = 13)	20.3 (n = 13)	1.02 (0.51–2.0)
Large for gestational age (%)	5.1 (n = 4)	13.6 (n = 8)	0.37 (0.12–1.18)	4.1 (n = 3)	11.8 (n = 9)	0.35 (0.1–1.23)
Small for gestational age (%)	6.3 (n = 5)	0 (n = 0)	NA	2.7 (n = 2)	2.6 (n = 2)	1.04 (0.15–7.2)
CI, confidence interval						
NA, not applicable						
* Calculated as a percentage of subjects without previous caesarean sections						

Subgroup analysis

The GDM women with BMI \geq 30 had reduced absolute caesarean section rates (32.9% versus 55.9%), RR 0.59 (95% CI, 0.4–0.87); and primary caesarean section rates (26.4% versus 45.8%), RR 0.58 (95%CI, 0.35–0.94) when compared to the counterfactual group with BMI \geq 30. For women with BMI < 30, there were no statistically significant differences in total and primary caesarean section rates (Table 3).

Linear regression

Figure 2 demonstrates a change in the gradient suggesting discontinuity for GDM treated compared to non-GDM subjects for LGA and caesarean sections. Linear regression interaction term effects were significant for LGA ($p = 0.001$) and caesarean section ($p = 0.015$).

The management of GDM subjects

Table 4
GDM management

Interventions	n (%)
Diet and lifestyle only	52 (34.2%)
Metformin only	7 (4.6%)
Insulin (basal, bolus, with metformin)	93 (61.1%)
	Subtype:
	basal 91 (59.9%)
	median dose 16 units (IQR 8–26)
	maximum dose 190 units
	bolus 43 (28.3%)
	median dose* 10 units (IQR 4–18)
	maximum dose* 230 units
	metformin 11 (7.2%)
IQR, interquartile range	
*total daily dose	

Discussion

Study design

Regression discontinuity studies use variations in assignment methods to emulate random treatment assignment, analogous to RCTs¹⁶. For instance, when diagnostic tests are used to assign subjects, random analytical/pre-analytical variations of test results around the threshold acts to quasi-randomise subjects to an intervention¹⁶. This quasi-random allocation of subjects based on OGTT is pertinent given the poor reproducibility of OGTT for individuals¹⁷; nonetheless, there are robust correlations of GDM outcomes to OGTT plasma glucose for a population¹³.

Regression discontinuity studies assumes that there is a continuous relationship between outcome variables¹⁶ such as rates of LGA, caesarean sections and the dependent variable, the HAPO glucose composite scores. We demonstrate a linear continuous relationship between LGA and caesarean sections and HAPO glucose composite scores in non-GDM subjects (Fig. 2).

Regression discontinuity studies typically estimates treatment effects proximate to the diagnostic cut-off¹⁶. However, the diagnosis of GDM is unusual in having multiple diagnostic cut-offs at OGTT fasting, 1 hour, and 2 hour plasma glucose. Furthermore, the heterogeneity of OGTT plasma glucose trajectories

with multiple cut-offs resulted in overlaps in the HAPO glucose composite scores, between GDM and non-GDM subjects. This allowed inference of treatment effects to wider bandwidths than other forms of regression discontinuity study designs. Nevertheless, the counterfactuals represent those with milder GDM.

Population characteristics

The overall GDM prevalence and OGTT glucose levels were similar to HAPO centres¹⁸. GDM subjects compared to the counterfactual group had higher BMI. Expectedly, as OGTT were used to determine diagnosis, GDM subjects had higher OGTT plasma glucose levels. As covariates associated with adverse outcomes were higher for GDM subjects, the interventions had to overcome these selection biases to show improved outcomes.

Our centre's overall caesarean section rate of 27.8% is similar to the Organisation for Economic Co-operation and Development rate of 27.9%¹⁹; but below the Australian rate of 34%¹⁹.

Capillary blood glucose targets and treatment intensification thresholds

Presumably, higher maternal glucose levels are the driver of adverse clinical outcomes in GDM¹³ and that moderating elevated maternal glucose levels improves outcomes. Therefore it is important to discuss clinical outcomes with the understanding of treatment targets and thresholds for treatment intensification. ADIPS⁹ suggested treatment targets were fasting CBG ≤ 5.0 mmol/L and the post-prandial ≤ 6.7 mmol/L. Ostensibly the aim was to have maternal CBG levels within the reference range of a healthy population⁹. This is tighter than RCT CBG targets in the Australian Carbohydrate Intolerance Study (ACHOIS)²⁰: fasting ≤ 5.5 mmol/L, and 2 hour post-prandial of ≤ 7.0 mmol/L; and the Maternal-Fetal Medicine Unit study (MFMU)²¹: fasting ≤ 5.3 mmol/L, and 2 hour post-prandial of ≤ 6.7 mmol/L.

The threshold for intensifying treatment will also impact medication usage. ADIPS⁹ suggested intensification if ≥ 2 out of 7 results (29%) were above target; in comparison, the MFMU study²¹ intensified treatment if more than 50% of CBG were above target. Glucometer imprecision will affect treatment intensification; the median coefficient of variation (CV) among of 18 commercial glucometers in recent survey was 9.3%²². To illustrate this point, take a theoretical woman with 'true' consistent fasting CBG levels within recommended levels at 5.0 mmol/L, but due to glucometer imprecision 95% (2 sd or 2CV) of results would be between 4.1 to 5.9 mmol/L, of which half would be > 5.0 mmol/L. Therefore it is probable that more than 29% of fasting CBG will be above 5.0 mmol/L, necessitating treatment intensification.

Notwithstanding glucometer imprecision issues, our population's upper reference interval (97.5th percentile) of OGTT fasting plasma glucose was 5.3 mmol/L. Our OGTTs were collected using sodium fluoride collected at room temperature and batched centrifuged¹⁰. This pre-analytical method has been recently documented, via the process of glycolysis, to lower reported OGTT fasting glucose levels by

approximately 10%^{10,23}. Therefore the adjusted lower and upper reference level of fasting glucose should be 10% higher – approximately 4.1 to 5.8 mmol/L. A fasting glucose target of 5.0 mmol/L is well within our population's reference intervals.

Clinical outcomes

Treated GDM subjects had a relative risk of LGA of 0.37, reducing the absolute risk from 12.6 to 4.6%. The RCTs, ACHOIS²⁰ and MFMU²¹, reported a decrease in LGA rates from 22 to 13%, 13–7.1%, respectively. As our CBG targets were lower it was not surprising that our rates of foetal overgrowth were also lower.

The relative risk for caesarean sections for GDM as compared to the counterfactual group was 0.75, the absolute risk reduced from 43.0 to 32.3%. Subgroup analysis suggests the reduction of caesarean section rates were driven by women with BMI ≥ 30 , where the relative risk was 0.58 compared to counterfactual group with BMI ≥ 30 . The absolute risk decreased from 55.9–32.9%. In contrast, GDM women with BMI < 30 did not demonstrate a reduction in caesarean section rates. Our study suggests the treatment response upon caesarean section rates is modified by obesity.

The two randomised led trials of GDM had shown contrasting caesarean section rates. ACHOIS²⁰, showed no effect of treatment on caesarean section rates, but in the MFMU study²¹, treatment resulted in a relative risk of 0.79 ($p = 0.02$). Although these studies differed in treatment targets and selection of subjects, our BMI subgroup analysis may partly explain the differences in caesarean section outcomes. The baseline BMI of subjects differed between these two RCTs, the trial not showing caesarean rate reduction had lower median BMI of 26.8²⁰, the other had a mean BMI of 30.1 kgm²²¹.

Apart from tighter treatment targets, another factor that may have contributed to the larger absolute and relative caesarean risk reduction seen in our study compared to the RCTs is the marked differences in the baseline risks of caesarean sections. Our counterfactual group had caesarean section rate of 43.0%, driven primarily by women with BMI ≥ 30 ; this is in the context of the overall study centre rate of 27.8%. In contrast, the RCTs had rather muted untreated GDM (control) caesarean section rates of 32% and 33.8%. This is in the context of national caesarean section rates in Australia (2004)²⁴ of 29.4% and the United States (2005)²⁵ of 30.3%. We note the established linear correlation of caesarean section rates with increasing maternal plasma glucose¹³. Therefore in women with very high maternal plasma glucose levels, as in untreated GDM, we would have expected much higher caesarean section rates than the centre or national levels. In our study, obesity was a strong driver of higher caesarean section rates; and our rates for the counterfactual group are consistent with the odds ratios seen in a meta-analysis investigating obesity's impact on caesarean sections: 2.05 and 2.89 for obese and severely obese women, respectively²⁶.

In RCTs, the act of randomisation⁶ and subject selection processes may have recruited women with better baseline prognoses relative to the target population²⁷. RCTs selects for particular types of willing participants²⁷. Moreover, inclusion in a study may have affected the behaviour of subjects, especially as

the primary interventions in GDM are behavioural change. This may have resulted in RCTs lowering adverse outcomes in comparator controls thereby attenuating the treatment response.

As our counterfactual group represents those borderline for GDM, we likely understated the overall treatment response. If the counterfactual group were to represent untreated GDM, mild and severe, they would have been higher baseline adverse outcomes. Linear regression (Fig. 2) visualises treatment effects beyond mild OGTT maternal plasma glucose levels.

GDM women had the relative risk of neonatal hypoglycaemia of 2.66. This may be the result of detection bias. The local protocol mandates screening for neonatal hypoglycaemia of all GDM women and neonates with a birth weight > 4000 g. In a study of neonates with no risk factors of hypoglycaemia, close serial monitoring within the 24 hours showed a neonatal hypoglycaemia rate, as defined by < 2.6 mmol/L, of 14%, which is similar to our rate of 15.8%²⁸.

Increased rates of induced deliveries and consequently lower birth gestational age of GDM subjects is perhaps due to clinicians' perception of higher risk for GDM women.

Medication usage

Of GDM women, 61.1% were treated with insulin (Table 4). Nearly all of those on insulin were on Isophane insulin, aimed to treat elevated fasting CBG. Our usage of insulin is higher than reported in randomised control studies: ACHOIS²⁰ of 20%, and MFMU²¹ of 7.6%. ADIPS treatment targets were tighter and so were the thresholds for the intensification of therapy. Moreover, as the effective treatment target for the fasting CBG level was well within our population's reference intervals the extent of basal insulin usage was unsurprising.

Limitations and strengths

Our method may not be suitable for centres using the currently recommended citrate tubes for OGTT plasma glucose. Samples using citrate tubes would report fasting glucose levels of approximately 10% higher²³. The HAPO glucose categories will no longer represent equivalent risks of adverse outcomes, as the HAPO study did not use citrate tubes¹⁰. Furthermore, quasi-randomisation partially relies on variations in pre-analytical handling, which would be reduced with citrate tubes.

Our study has limitations. As a retrospective design we did not have complete data on GDM risk factors such as family history of diabetes mellitus, smoking; in addition to data on maternal weight gain, and maternal hypertension. We did not record adherence to therapy with records of CBG but the high medication usage rate indicate that our GDM subjects were treated to ADIPS suggestions. We did not search for maternal hypoglycaemia in the database, but as the author was also the clinician involved there was no recollection of severe hypoglycaemia.

As a single centre study design with a predominately Caucasian population our results may not be applicable to all centres. Obstetric practices such as rates of caesarean section may vary between and

within countries⁸ and therefore our risk reduction of caesarean sections may not be able to be extrapolated.

LGA/SGA outcomes relied on age standardised growth charts not adjusted for ethnic composition. However, as our population was predominately Caucasian there would have been marginal impact.

Our study may have been underpowered to determine differences in incidence rates for some less common end points such as shoulder dystocia.

We expect the loss of subjects by birthing at other centres to be rare, as our hospital is a referral centre for high-risk pregnancies for smaller regional hospitals. The closest hospital able to deliver high-risk pregnancies is more than 90 km from BHS. We did not see women expected to deliver at the local private hospital.

Subjects was analysed on an intention-to-treat basis irrespective of the adherence to therapy. Since our subjects were treated contemporaneously and by the same group of health professionals, our study is unlikely to be confounded by evolving medical practises.

It is our view that our study design is particularly suited to the study of GDM. This method, which can be performed in retrospective and prospective cohorts, will allow other centres with differing populations and obstetric practices to assess the local effectiveness of GDM treatments. Furthermore, this quasi-experimental design may be suitable to evaluate the effects GDM interventions on childhood adiposity and glucose tolerance.

Conclusion

Treatment of GDM women screened using IADPSG/WHO guidelines with tight treatment target reduces LGA outcomes, and caesarean section rates when compared to non-GDM subjects just below the diagnostic thresholds. The treatment response upon caesarean section rates appear to be modified by obesity with GDM women with BMI ≥ 30 kgm² having reductions in rates but there was no suggested benefit in GDM women with BMI < 30 kgm². This is at the expense of slightly earlier gestational age at delivery, and increases in induced deliveries, notations of neonatal hypoglycaemia, and medication usage.

We believe this multiple cut-off regression discontinuity study design is an ideal method to investigate the treatment effects upon mild GDM when RCTs are impractical. This design is uniquely suitable for the investigation for GDM due to the unusual feature of GDM: a continuous linear relationship between maternal plasma glucose and clinical outcomes.

Abbreviations

ACHOIS

Australian Carbohydrate Intolerance Study
ADIPS
Australasian Diabetes in Pregnancy Society
BHS
Ballarat Health Services
BMI
body mass index
CBG
capillary blood glucose
CI
confidence interval
CV
coefficient of variation
GDM
gestational diabetes mellitus
HAPO
Hyperglycaemia and Adverse Pregnancy Outcome study
IADPSG
International Association of Diabetes and Pregnant Study Groups
IQR
interquartile range
MFMU
Maternal-Fetal Medicine Unit study
OGTT
oral glucose tolerance tests
RR
relative risk
RCT
randomised controlled trials
sd
standard deviation
SGA
small for gestational age
WHO
World Health Organisation

Declarations

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Author information: David Song^{1,2,3}, James C Hurley^{1,4}, Maryanne Lia⁵

Dr David Song^{1,2,3} (0000-0002-8242-1268), endocrinologist, general physician, chemical pathologist, and senior clinical lecturer.

Address: Internal Medicine Service, Ballarat Base Hospital, Ballarat, Victoria 3350, Australia.

Associate Professor James C Hurley^{1,4} (0000-0002-5885-2084), staff physician.

Address: Department of Rural Health | Melbourne Medical School, University of Melbourne, Ballarat, Victoria.

Dr Maryanne Lia⁵, resident doctor.

Address: Peninsula Health, Frankston, Melbourne, Victoria, Australia

Affiliations

Author's affiliations:

1. Ballarat Base Hospital, Ballarat, Victoria, Australia
2. Dorevitch Pathology, Melbourne, Victoria, Australia
3. Deakin University, Geelong, Victoria, Australia
4. University of Melbourne, Department of Rural Health
5. Peninsula Health, Melbourne, Victoria, Australia

Contributions

DS is the corresponding author. DS, JCH and ML contributed to the study concept. DS and ML had full access to all the data in the study and takes responsibility for the integrity of the data. DS developed the methodology. DS and JCH contributed to the statistical analysis and figure development. DS and ML contributed to the data collection development. DS wrote the manuscript with contributions from JCH and ML. All the authors contributed to the critical revision of the article. DS is the guarantor for this article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have read and approved the manuscript

Corresponding author

Dr David Song, Ballarat Base Hospital, Ballarat, Victoria 3350, Australia

davidso@bhs.org.au

Ethics approval and consent to participate

Ballarat Health Services and St John of God Healthcare Human Research Ethics Committee (LNR/18/BHSSJOG/16).

Consent for publicatio

As a retrospective observational study no patient consent was required for publication. In addition, there were no identifiable information disclosed.

Availability of data and materials

The ethics committee has not allowed any sharing of data.

Competing interests

The authors declare that they have no competing interests.

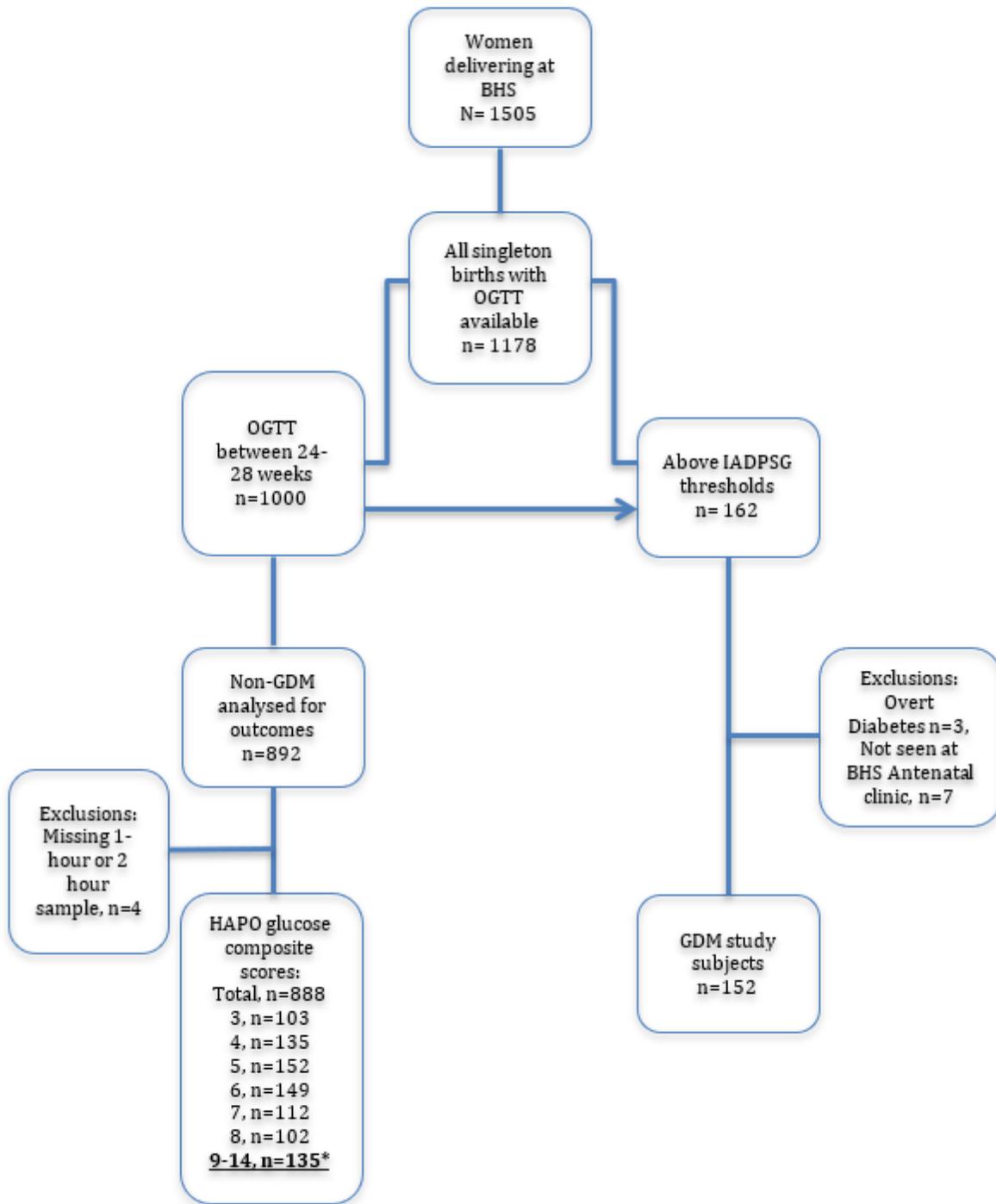
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Figures



- Counterfactual group

Figure 1

Subject selection and allocation

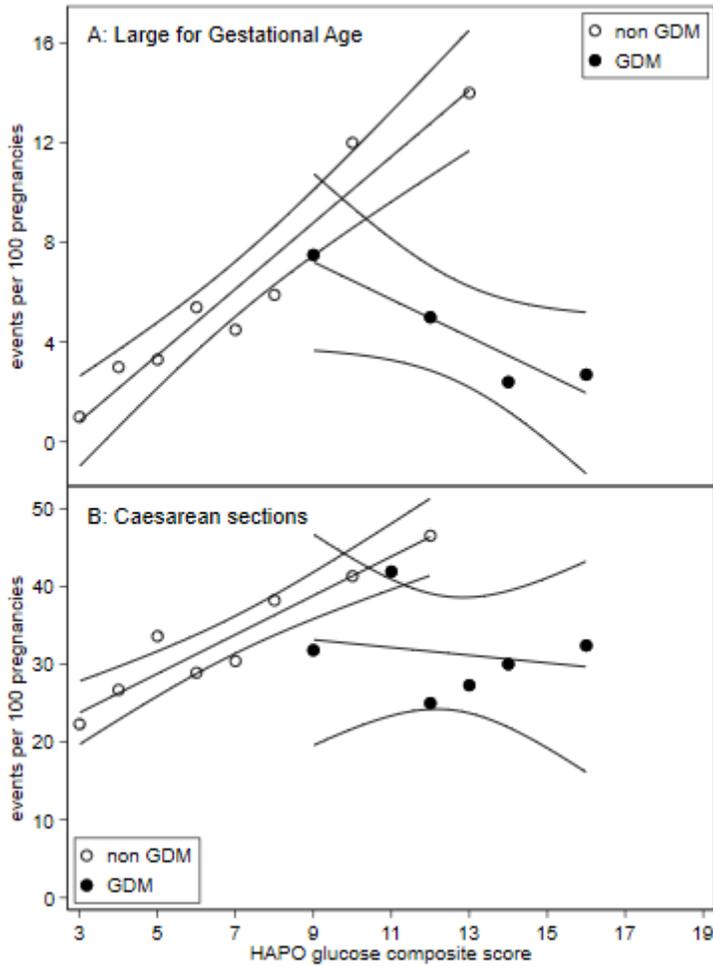


Figure 3

Frequency of (A) large for gestation age (birth weight >90th percentile) and (B) caesarean sections across HAPO glucose composite scores with 95% confidence intervals. HAPO glucose composite scores were calculated by adding the HAPO glucose categories for fasting, 1-hour, and 2-hour plasma glucose. HAPO glucose categories, fasting plasma glucose: category 1, <4.2 mmol/L; category 2, 4.2 to 4.4; category 3, 4.5 to 4.7 mmol/L; category 4, 4.8 to 4.9 mmol/L, category 5, 5.0 to 5.2 mmol/L; category 6, 5.3 to 5.5 mmol/L; category 7, 5.6 to 7.0 mmol/L. 1-hour plasma glucose: category 1, \leq 5.8 mmol/L; category 2, 5.9 to 7.3 mmol/L; category 3, 7.4 to 8.6 mmol/L; category 4, 8.7 to 9.5 mmol/L; category 5, 9.7 to 10.7 mmol/L; category 6, 10.8 to 11.7 mmol/L; category 7, \geq 11.8 mmol/L. 2-hour plasma glucose: category 1, \leq 5.0 mmol/L; category 2, 5.1 to 6.0 mmol/L; category 3, 6.1 to 6.9 mmol/L; category 4, 7.0-7.7 mmol/L; category 5, 7.8 to 8.7 mmol/L; category 6, 8.8 to 9.8 mmol/L; category 7, 9.9 to 11.0 mmol/L.