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What's new?

- Optimal glycaemic targets for gestational diabetes mellitus (GDM) are controversial because there are no randomized trials comparing targets and pregnancy outcomes.
- In this large observational study of two healthcare networks, the service with tight targets had greater insulin use and obstetric interventions than the service with standard targets.
- Tight targets were associated with no difference in primary birthweight or maternal outcomes, with decreased hypoglycaemia, jaundice and respiratory distress, but lower Apgar scores. Whether mixed observations relate to targets or obstetric practice variation is unclear.
- Clinical variation in obstetric practice was significant and insulin use alone was not a good marker of neonatal risk.
- Interventional studies are needed to define glycaemic targets for optimizing pregnancy outcomes.

Abstract

Aim With no current randomized trials, we explored the impact of tight compared with standard treatment targets on pregnancy outcomes in gestational diabetes mellitus (GDM).

Methods This cohort study of singleton births ≥ 28 weeks' gestation was conducted at two major Australian maternity services (2009–2013). Standardized maternal, neonatal and birth outcomes were examined using routine healthcare data and compared for women with GDM at Service One ($n = 2885$) and Service Two ($n = 1887$). Services applied different treatment targets: Service One (standard targets, reference group) fasting < 5.5 mmol/l, 2-h postprandial < 7.0 mmol/l; Service Two (tight targets) fasting < 5.0 mmol/l, 2-h postprandial

< 6.7 mmol/l. Multivariable regression with propensity score adjustment was used to examine associations between targets and outcomes.

Results GDM prevalence and insulin use were 7.9% and 31% at Service One, and 5.7% and 46% at Service Two. There were no differences in primary outcomes: birthweight > 90th centile [adjusted odds ratio (OR) 1.06, 95% confidence interval (CI) 0.87–1.30] and < 10th centile (OR 0.84, 95% CI 0.70–1.01), or secondary outcomes gestational hypertension, pre-eclampsia, shoulder dystocia or a perinatal composite. Service Two with tight targets had increased induction of labour (OR 3.63, 95% CI 3.17–4.16), elective Caesarean section (OR 1.75, 95% CI 1.37–2.23) and Apgar scores < 7 at 5 min (OR 1.54, 95% CI 1.05–2.25), decreased hypoglycaemia (OR 0.76, 95% CI 0.61–0.94), jaundice (OR 0.47, 95% CI 0.35–0.63) and respiratory distress (OR 0.68, 95% CI 0.47–0.98).

Conclusions Tight GDM treatment targets were associated with greater insulin use and no difference in primary birthweight outcomes. The service with tight targets had higher obstetric intervention, lower rates of reported hypoglycaemia, jaundice, respiratory distress and lower Apgar scores. High-quality interventional data are required before tight treatment targets can be implemented.

<H1>Introduction

Gestational diabetes mellitus (GDM) is a condition of glucose intolerance with onset or first recognition in pregnancy [1]. The prevalence of GDM is increasing, particularly with application of the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria with universal single step screening, lowering of the fasting glucose threshold and addition of a 1 h threshold for diagnosis [1]. These criteria were developed based on an odds ratio (OR) of 1.75 times the risk of adverse outcomes seen at mean glucose levels in the multinational observational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [2]. Prevalence of GDM in this study ranged from 9.3% to 25.5% using IADPSG criteria [3]. HAPO showed a continuous relationship between maternal glucose and neonatal outcomes; however, there was no clear glucose inflection point for increased risk and criteria have been controversial with a lack of interventional data [2]. Further, there are no randomized trials comparing treatment targets in GDM and these continued to be debated.

Two randomized controlled trials (RCTs) have reported that GDM treatment reduced adverse outcomes including large for gestational age (LGA) and pre-eclampsia. However, these studies used different diagnostic criteria, treatment targets and thresholds for insulin

commencement [4,5]. In the Australian Carbohydrate Intolerance Study (ACHOIS), 20% of intervention women were prescribed insulin if two or more glucose levels/week exceeded thresholds (fasting 5.5 mmol/l and 2-h postprandial 7.0 mmol/l) [4]. In the U.S. Maternal–Fetal Medicine Unit (MFMU) study, 7.6% of intervention women received insulin when the majority of thresholds were exceeded (fasting 5.3 mmol/l, 2-h postprandial 6.7 mmol/l) [5]. The MFMU study found lower Caesarean section and shoulder dystocia rates, whereas ACHOIS found a reduction in a composite perinatal outcome, but increased induction of labour and nursery admissions [4,5].

GDM treatment targets remain contentious and there are no RCTs comparing different treatment targets with regard to birthweights and pregnancy outcomes. The HAPO observational study and normative glucose data in pregnancy have led to proposed tighter treatment targets [6,7]. Internationally, guidelines vary, rely largely on consensus opinion and continually cite a lack of high-quality evidence and a need for greater research into potential benefits, risks and costs [1,8–10]. In the interim, recommendations with potential to affect a large population of women are promulgated with vast implications for increased insulin use, costs and service provision. In this large epidemiological study, we aimed to inform debate regarding the impact of different treatment targets on birthweight and pregnancy outcomes.

<H1>Methods

<H2>Design and study population

A cohort study was conducted of singleton births ≥ 28 weeks' gestation attending public antenatal clinics and delivering at one of two major maternity services in Victoria, Australia from 2009 to 2013. Service One had ~ 7500 births/year and Service Two had ~ 6800/year during the study. Data were integrated from two routinely collected pregnancy data sets GE Healthcare and the Birthing Outcomes System, containing mandatory statutory data for Victorian perinatal records. Data sets were de-identified, cleaned, validated and merged by a clinician author with input from a biostatistician and data manager.

Data were collected prospectively by midwives from the booking antenatal visit until delivery and hospital discharge. Maternal demographics, medical and obstetric history, and birthing outcomes were compared for women with GDM at Service One and Service Two. Women with known pre-existing Type 1 or 2 diabetes were excluded. Each service used the same two-step diagnostic process for GDM according to Australasian Diabetes in Pregnancy

Society (ADIPS) 1998 recommendations [11]: a screening 1-h glucose challenge (≥ 8.0 mmol/l) and 2-h 75 g oral glucose tolerance test (OGTT) at 24–28 weeks (fasting plasma glucose ≥ 5.5 mmol/l and/or 2-h ≥ 8.0 mmol/l). Both services used a similar dietary and diabetes nurse educator intervention. Women were asked to monitor fasting glucose and 2-h postprandial glucose after every meal. Clinicians initiated first-line insulin if two or more glucose levels per time point exceeded targets in one week despite dietary intervention. However, the services applied different treatment targets: Service One applied standard targets of fasting < 5.5 mmol/l and 2-h postprandial < 7.0 mmol/l (aligned with ADIPS 1998 [11] and ACHOIS [4]); Service Two applied tight targets of fasting < 5.0 mmol/l and 2-h postprandial < 6.7 mmol/l (aligned with ADIPS 2014 and IADPSG suggestions [10]). An assumption of compliance to targets was made as no objective glucose data were recorded aligned with past randomized controlled trials in the field.

<H2>Process and outcomes

Outcomes were standardized and defined according to Victorian perinatal data (ICD-10 codes), which have been validated [12]. Rigorous processes were used by clinician authors to determine clinically relevant outcomes *a priori*, informed by prior studies in GDM [2,4,5], and alignment of core outcomes for diabetes in pregnancy [13].

Gestational age was determined by ultrasound or date of last menstrual period if unavailable. BMI was measured at first antenatal visit. Primary neonatal outcomes were birthweight > 90 th centile and < 10 th centile for gestational age and sex based on Australian birthweight percentiles [14]. Adjustments were not made for ethnicity with birthweights shown to be identical across groups in the absence of maternal or fetal pathology [15].

Secondary neonatal outcomes included hypoglycaemia (< 2.6 mmol/l), jaundice requiring phototherapy, respiratory distress and Apgar score < 7 at 5 min. Neonates were routinely checked for hypoglycaemia at both services. Shoulder dystocia (impacted anterior shoulder preventing pelvic descent) was reported for vaginal deliveries. A composite perinatal outcome was used as per the ACHOIS trial (perinatal death, shoulder dystocia, bone fracture and nerve palsy) [4].

Secondary maternal outcomes were gestational hypertension (new onset hypertension from 20 weeks with systolic and/or diastolic BP $\geq 140/90$ mmHg) and pre-eclampsia (hypertension

with proteinuria > 300 mg/24 h, spot urine protein : creatinine ratio ≥ 0.03 g/mmol and/or other system involvement).

Practice-based outcomes included mode of birth: induction of labour, Caesarean section and preterm birth (< 37 weeks). Newborns were admitted to the special care nursery (SCN) if requiring specialized observation or neonatal intensive care unit (NICU) for potentially life-threatening conditions, with similar protocols for both services. However, given the degree of variation in care across the services for these outcomes, these are described separately under 'practice-related outcomes'.

<H2>Statistical analyses

Maternal characteristics were compared using descriptive statistics. Categorical data were analysed using the Pearson chi-square test. Continuous data were presented as mean and standard deviation (SD) or median and interquartile range (i.q.r.), and compared using Student's *t*-tests or Mann–Whitney *U*-tests as appropriate.

There were higher rates of induction and elective Caesarean section at Service Two compared with Service One which may influence neonatal outcomes. These outcomes are also influenced by gestation at birth. Propensity score analysis was conducted in an attempt to adjust for variation in obstetric practice and gestation at birth. A propensity score, or probability of being assigned to a treatment given a set of observed covariates, was calculated for each outcome based on mode of birth (induction and/or Caesarean section) and gestation. The propensity score was then applied within a multivariable logistic regression model to calculate odds ratios (OR) and 95% confidence intervals (CI) for outcomes in women treated with tight targets compared with standard targets (reference category). Models were adjusted for covariates: age, BMI, parity, smoking status and country of birth. Statistical significance was conveyed by a two-sided *P*-value of 0.05. Analyses were performed using Stata version 12 (StataCorp, College Station TX, USA).

<H2>Ethics approval

The study was approved by the respective Human Research Ethics Committees in 2014.

<H1>Results

<H2>Study population

There were 36 617 women with a singleton pregnancy at Service One, of whom 2891 (7.9%) developed GDM. At Service Two there were 33 069 women with a singleton pregnancy, of whom 1894 (5.7%) developed GDM. Insulin therapy was required in 31% of women with GDM at Service One (standard targets) and 46% at Service Two (tight targets). This analysis includes women with GDM with singleton births ≥ 28 weeks' gestation ($n = 2885$ Service One, $n = 1887$ Service Two). There were no differences in age or BMI between women with GDM at each service, but there were differences in parity, smoking and country of birth (Table 1).

Babies of women at Service Two with tight targets were born earlier (median 38.0 vs. 39.1 weeks, $P < 0.001$) with no difference in birthweight z -score compared with Service One with standard targets (Table 2).

<H2>Primary and secondary outcomes

Tight targets at Service Two were not associated with a difference in the primary outcomes birthweight > 90 th centile (adjusted OR 1.06, 95% CI 0.87–1.30) or birthweight < 10 th centile (adjusted OR 0.84, 95% CI 0.71–1.01) compared with standard targets at Service One (Table 3).

After propensity scoring, there were no difference in risk of gestational hypertension, pre-eclampsia, shoulder dystocia, or the composite perinatal outcome (Table 2). Babies of women with tight targets had decreased risk of hypoglycaemia (adjusted OR 0.76, 95% CI 0.61–0.94), jaundice (adjusted OR 0.47, 95% CI 0.35–0.63) and respiratory distress (adjusted OR 0.68, 95% CI 0.47–0.98), but increased risk of Apgar scores < 7 at 5 min (adjusted OR 1.54, 95% CI 1.05–2.25) compared with standard targets (Table 3).

<H2>Practice-related outcomes

Increased induction of labour (adjusted OR 3.63, 95% CI 3.17–4.16) and Caesarean section (adjusted OR 1.17, 95% CI 1.03–1.33) were seen at Service Two. Elective Caesarean section was increased at Service Two compared with Service One (adjusted OR 1.75, 95% CI 1.37–2.23). Babies of women with GDM at Service Two had lower risk of SCN admission (adjusted OR 0.32, 95% CI 0.26–0.38). There was no difference in preterm birth or NICU admission (Table 3).

<H1>Discussion

The prevalence of GDM is increasing and causes a significant healthcare burden. This is the largest epidemiological study to date on GDM treatment targets, reporting the association between different glycaemic targets, birthweight and health outcomes in 4772 singleton pregnancies with GDM. There were no differences in the primary outcomes of birthweight > 90th or < 10th centile with tight targets (fasting < 5.0 mmol/l, 2-h postprandial < 6.7 mmol/l) compared with standard targets (< 5.5 mmol/l and < 7.0 mmol/l). Tight targets were associated with higher insulin use. The service applying tight targets also had higher rates of obstetric interventions and earlier birth compared with the service applying standard targets. This variation in care was observed despite similar protocols across both services and limits interpretation of associations between treatment targets and secondary neonatal and maternal outcomes. Propensity score analysis was conducted to minimize the impact of variation in care around obstetric interventions and gestation differences between services, although the authors cannot fully adjust for such differences. It appears that the services have similar risks of gestational hypertension, pre-eclampsia, shoulder dystocia and perinatal composite outcomes. In the service with tight targets, there was lower risk of hypoglycaemia, jaundice and respiratory distress, yet 5-min Apgar scores appeared lower. It is not possible to clearly attribute these to differences in treatment targets, given the variation observed in care.

Optimal GDM treatment targets to reduce adverse pregnancy outcomes remain unclear. Tightening targets may improve neonatal outcomes but may increase risks for the mother [16]. Historically, the goal has been to mimic glycaemic patterns in normal pregnancy to 'normalize' outcomes [17]. The Fifth International Workshop on GDM recommended targets of fasting < 5.3 mmol/l and 2-h postprandial < 6.7 mmol/l based on observational data and rates of macrosomia [18]. Some organizations suggest a lower fasting target of < 5.0 mmol/l to align with new diagnostic criteria [10]. However, a recent meta-analysis found low-quality evidence to recommend a fasting target and insufficient evidence for postprandial targets [19]. Here, we contribute novel data on this major evidence gap by comparing cohorts where tight and standard treatment targets were applied. Our results highlight not only no difference in primary outcomes, but also the complexity of research in pregnancy where variation in care can be substantive and can impact significantly on clinical outcomes independent of the practice under study.

Diagnosis of GDM prompts increased fetal surveillance, earlier induction of labour and Caesarean delivery. Induction may increase Caesarean sections [20,21], although Sutton *et al.* did not find an increase in mild GDM before 40 weeks [22]. ACHOIS reported no increase in

Caesarean sections, despite increased induction of labour [4]. Insulin use can influence practice potentially prompting increased intervention and earlier delivery. Given the higher rate of insulin use in Service Two to attain tighter targets, this may have impacted on practice. Our research indicates that insulin use is not a good marker of neonatal risks, with no difference in birthweight or emergency Caesarean sections between services. We therefore suggest that decisions regarding mode of birth and delivery timing should be based around maternal glucose control, rather than insulin use per se, and other indicators of maternal and fetal health.

In this study of two large pregnancy services, we found practice differences in GDM with higher rates of induction of labour (57% vs. 31%) and Caesarean section (39% vs. 34%) with earlier births (38 vs. 39 weeks) at Service Two compared with Service One (Table 1 and 2). Likewise, in women without GDM, there were also higher rates of induction of labour (51% vs. 20%, $P < 0.001$), Caesarean section (29% vs. 26%, $P < 0.001$) and earlier birth (39 vs. 40 weeks, $P < 0.001$) at Service Two suggesting a more active approach to obstetric intervention (data not shown). In GDM, there were fewer SCN admissions (12% vs. 28%) but no significant difference in NICU admissions after adjustment (6% vs. 4%), despite similar written SCN and NICU admission policies (Table 2). Differences in neonatal admission were also seen for babies in women without GDM (Service Two compared with Service One: 7% vs. 16%, $P < 0.001$ for SCN and 4% vs. 2%, $P < 0.001$ for NICU) and hence we postulate that they largely relate to variation in practice rather than to neonatal morbidity. Thus, clinical variation in obstetric practice was significant and may warrant cross-sectional or longitudinal benchmarking across services in relation to outcomes.

Fetal overgrowth and associated complications are primary concerns in GDM. In the ACHOIS and MFMU RCTs, treatment of GDM reduced LGA [4,5]. In the Metformin in GDM (MiG) trial, risk of LGA increased across glycaemic tertiles [23]. Although earlier induction of labour may mitigate fetal overgrowth and related adverse outcomes [5], we saw no difference in birthweight > 90th centile with tight compared with standard targets, questioning a key rationale for tight targets. Importantly, birthweight < 10th centile was not increased. Potentially, greater monitoring in women on insulin, earlier birth and intervention with tight targets may reduce risk of lower birthweight.

In our large observational study, tight targets were associated with no difference in secondary maternal outcomes and mixed results for secondary neonatal outcomes. These results differ

from that of previous studies in GDM. Pre-eclampsia was reduced in the ACHOIS and MFMU RCTs [4,5], and increased with glycaemia in the MiG trial [23], however we found comparably low rates of pre-eclampsia and no association with tight targets. GDM treatment in ACHOIS reduced the composite perinatal outcome, with no difference in shoulder dystocia, hypoglycaemia, jaundice or respiratory distress, despite reduced LGA using identical targets to Service One [4]. Although the MFMU trial found a reduction in LGA and shoulder dystocia, there was no difference in hypoglycaemia, jaundice or respiratory distress [5]. Interestingly, despite no difference in the primary outcome birthweight > 90th centile, we found lower risk of secondary outcomes hypoglycaemia, jaundice and respiratory distress after adjustment for practice differences in the service with tight targets. This appears to suggest fetal metabolic benefits in the tight target group; however, the observational nature of the data and practice variations make it difficult to attribute these differences entirely to treatment targets. There was no difference in shoulder dystocia or the composite outcome in the service with tight targets. More significant glucose differences may be required to see a difference in these outcomes, however even small differences in targets resulted in 50% higher rates of insulin use, with associated more intense clinical care and costs. More Apgar scores < 7 at 5 min in the tight target group may be of concern; however, the nature of our data does not allow us to further draw clinical associations here between glycaemic targets and Apgar scores.

In the future, risk stratification of targets based on maternal diabetes phenotype, glucose, fetal growth trajectory, BMI and risk of adverse outcomes may be more appropriate. Randomized trials may provide further insights, however variation in care across sites will continue to challenge interpretation of outcomes. Overall, we propose more research is needed, with attempts made to reduce variation in obstetric care where possible, before routine implementation of tight targets with associated increased costs and service demands for insulin use and potentially for obstetric interventions [24,25].

Our study has limitations. It was conducted across two sites where we cannot fully account for variation in practice which may confound our secondary endpoint analysis. We have integrated statistical approaches in an attempt to limit these influences with careful methodology and statistical analysis, yet acknowledge this cannot fully address the impact of practice differences. Country of birth rather than ethnicity was recorded. This is a common feature of perinatal data sets and previous research suggests this would not influence results [26]. Socio-economic status is not routinely recorded in the database. Gestational weight gain

was not measured, another common limitation of perinatal data sets. OGTT data were not available for all women in the study and hence were not analysed. Blood glucose data to confirm achievement of glucose targets were not captured, yet these data are generally lacking in studies of GDM treatment including an RCT [4] and review [19]. Despite this, clinicians at each service adhere to the same management principles for insulin initiation in women failing to achieve targets. Future prospective data should report both planned and achieved glucose targets. Early screening for GDM is performed in women at high risk, and the nature of our data set does not allow us to quantify this at each service. Lastly, GDM was diagnosed by ADIPS 1998 criteria [11] rather than IADPSG criteria [6] used in the ADIPS 2014 guidelines [10]. However, we feel that differences in outcome with new criteria are less likely given potentially milder GDM detected.

Strengths of our study include our large cohort, standardized and validated outcome measures, and adjustment for confounders. Studies in GDM are frequently limited by ill-defined, heterogeneous outcome definitions [13]. Outcomes studied are representative of international literature to ensure validity and comparability of future research [13]. Our multicultural cohort is derived from two of the largest Australian maternity services in a universal public health system with high healthcare engagement, increasing relevance of findings. We identified differences in practice that did not influence primary outcomes, but may have influenced secondary outcomes. We have attempted to statistically account for these.

This comprehensive large-scale cohort study found no attributable benefit of tight GDM treatment targets on the primary outcomes of birthweight > 90th centile or < 10th centile or on maternal secondary outcomes. Insulin use was significantly higher with tight targets. Obstetric intervention and earlier delivery were increased with tight compared with standard targets. Although this is likely to be multifactorial, given the lack of differences in birthweight or emergency Caesarean sections, this suggests that insulin use does not accurately reflect neonatal risk, and may not be appropriate to guide mode of birth and delivery timing. In applying propensity scores to attempt to account for variation in practice and earlier delivery, tight targets appear to be associated with reduced hypoglycaemia, jaundice and respiratory distress, yet lower Apgar scores, compared with standard targets. Whether these relate to other practice differences or targets is unclear. Here, we highlight the complexity of research in pregnancy, where variation in care can be substantive and can impact significantly on clinical outcomes independent of the intervention under study. These

results should prompt review of current obstetric practice with increased insulin use, mode and timing of delivery, the role of insulin use in influencing practice and the associated healthcare burden and costs. If future interventional studies do justify tight targets, unintended consequences such as higher birth interventions need to be considered and addressed. This study highlights the need for interventional studies incorporating objective glucose data and examining glucose targets with respect to pregnancy outcomes before implementation of tight targets in routine clinical practice.

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Competing interests

None declared.

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Table 1 Baseline characteristics of women with GDM and neonates at each service

Variable	Service One (n = 2885)	Service Two (n = 1887)	P-value
Age, years; mean (SD)	31.8 (5.1)	32.1 (5.2)	0.07*
BMI kg/m ² ; median (i.q.r.)	25.8 (22.7–30.8)	25.9 (22.8–30.5)	0.65†
Primiparous, n (%)	1207 (41.8)	934 (49.5)	< 0.001
Smoker, n (%)	272 (9.4)	93 (5.0)	< 0.001
Pre-existing hypertension, n (%)	68 (2.4)	48 (2.5)	0.68
Country of birth by region, n (%)			
Australia	871 (30.2)	599 (31.7)	0.26
Europe and America	174 (6.0)	123 (6.5)	0.50
Africa	169 (5.9)	264 (14.0)	< 0.001
Southeast and Northeast Asia	778 (27.0)	455 (24.1)	0.03
Southern and Central Asia	893 (31.0)	446 (23.6)	< 0.001

Data reported are count (proportion) for categorical variables.

P-values were calculated with the chi-squared test. Continuous variables are reported as mean (SD) or median (i.q.r.) with P-values calculated using *Student's t-test or †Mann–Whitney U-test as appropriate.

Table 2. Neonatal characteristics of babies born to women with GDM at each service

Variable	Service One (n = 2885)	Service Two (n = 1887)	P-value
Gestation weeks; median (i.q.r.)	39.1 (38.2–40.0)	38 (38–39)	< 0.001*
Birthweight, g; mean (SD)	3322 (582)	3222 (594)	< 0.001†
Birthweight z-score; mean (SD)	-0.10 (1.17)	-0.05 (1.14)	0.200
Male sex, n (%)	1506 (52.2)	1029 (54.5)	0.12

Data reported are count (proportion) for categorical variables.

P-values were calculated with the chi-squared test. Continuous variables are reported as mean (SD) or median (i.q.r.) with P-values calculated using *Mann–Whitney U-test or †Student's t-test or as appropriate.

Table 3. Risk of adverse outcomes for women with GDM at Service Two (tight targets) compared with Service One (standard targets).

Outcome	Service One*	Service Two N (%)	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)†	P-value
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	N (%)					
Birthweight > 90th centile	324 (11.2)	217 (11.5)	1.03 (0.86–1.23)	0.77	1.06 (0.87–1.30)	0.54
Birthweight < 10th centile	422 (14.6)	238 (12.6)	0.84 (0.71–1.00)	0.05	0.84 (0.70–1.01)	0.06
Gestational hypertension	81 (2.8)	65 (3.4)	1.23 (0.89–1.72)	0.21	1.19 (0.84–1.69)	0.32
Pre-eclampsia	98 (3.4)	85 (4.5)	1.34 (1.00–1.80)	0.05	1.31 (0.96–1.79)	0.09
Neonatal hypoglycaemia*	285 (9.9)	174 (9.2)	0.93 (0.76–1.13)	0.45	0.76 (0.61–0.94)	0.01
Shoulder dystocia†	62 (3.3)	32 (2.8)	0.86 (0.56–1.32)	0.49	1.01 (0.64–1.60)	0.96
Jaundice*	229 (7.9)	124 (6.6)	0.82 (0.65–1.02)	0.08	0.47 (0.35–0.63)	< 0.001
Respiratory distress	103 (3.6)	77 (4.1)	1.15 (0.85–1.55)	0.37	0.68 (0.47–0.98)	0.04
Apgar score < 7 at 5 min*	56 (1.9)	71 (3.8)	1.98 (1.39–2.82)	< 0.001	1.54 (1.05–2.25)	0.03
Composite outcomes‡	78 (2.7)	65 (3.4)	1.28 (0.92–1.79)	0.14	1.24 (0.87–1.76)	0.23

Induction of labour	883 (30.6)	1071 (56.8)	2.98 (2.64–3.36)	< 0.001	3.63 (3.17–4.16)	< 0.001
Caesarean section	976 (33.8)	743 (39.4)	1.27 (1.12–1.43)	< 0.001	1.17 (1.03–1.33)	0.02
Elective Caesarean section	431 (14.9)	379 (20.1)	1.32 (1.09–1.59)	0.01	1.75 (1.37–2.23)	< 0.001
Emergency Caesarean section	545 (18.9)	364 (19.3)	1.03 (0.89–1.19)	0.73	0.87 (0.74–1.02)	0.09
Preterm birth	239 (8.3)	202 (10.7)	1.33 (1.09–1.62)	0.01	1.19 (0.97–1.47)	0.10
Special care nursery admission	779 (27.8)	210 (11.8)	0.35 (0.29–0.41)	< 0.001	0.32 (0.26–0.38)	< 0.001
Neonatal intensive care admission	76 (3.6)	102 (6.1)	1.74 (1.27–2.37)	0.001	1.30 (0.93–1.81)	0.13

Results show number (percentage) of women with each outcome and the odds ratio (OR) and 95% confidence interval (CI) for each outcome comparing tight targets to standard targets in both univariable and multivariable regression models. In the multivariable regression (adjusted) models, propensity scores were computed for each outcome using the probability of treatment assignment based on the following covariates: gestation for induction and Caesarean section (C-section); C-section for preterm birth; C-section for special care nursery and neonatal intensive care unit; C-section for birthweight > 90th and < 10th centile; C-section and gestation for neonatal hypoglycaemia, jaundice, respiratory distress, Apgar score < 7 at 5 min, perinatal death and the composite outcome.

*Reference category.

†All outcomes adjusted for age, BMI, parity (nulliparous, parous), country of birth (Australia, Europe and America, Africa, South and Northeast Asia, Southern and Central Asia), smoking status (yes, no).

‡Shoulder dystocia is for vaginal deliveries only.

§ Composite outcome = perinatal deaths (stillbirth and neonatal death), shoulder dystocia, bone fracture and nerve palsy.

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