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Patient-led rapid titration of basal insulin in gestational diabetes is associated with improved glycaemic control and lower birthweight

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Abstract

Aims: Elevated fasting blood glucose in gestational diabetes (GDM) is a key predictor of high birthweight babies and adverse pregnancy outcomes but is hard to treat. We implemented a simple, patient-led, insulin dose titration algorithm aiming to improve fasting glycaemic control in GDM.

Methods: In women with GDM, initiating basal insulin, we recommended a daily four-unit dose increase after every fasting glucose value ≥5.0 mmol/mol (90 mg/dl). This approach augmented our pre-existing intensive (weekly) specialist nursing input. Using a before-and-after retrospective observational study design, we examined insulin doses and glucose values at 36 weeks gestation and maternal and neonatal outcomes in 105 women completing pregnancy before and 93 women after the intervention.

Results: The baseline characteristics of women in the before and after groups were the same. Women initiated on insulin after implementation ($n = 30$ before, $n = 43$ after) achieved substantially higher doses at 36 weeks (53 vs. 36 units/day; 0.56 vs. 0.37 units/kg/day; $p = 0.027$). 36-week mean fasting glucose was lower in those on insulin after implementation (4.6 vs. 5.1 mmol/L [83 vs. 92 mg/dl]; $p = 0.031$). Birthweight was significantly reduced (birthweight Z-scores 0.34 vs. 0.92; $p = 0.005$). There was no significant difference in macrosomia (after; 2% vs. before; 17% $p = 0.078$) or caesarean sections (after; 33% vs. before; 47%; $p = 0.116$). No women experienced severe hypoglycaemia. There were no outcome differences before versus after intervention in women not treated with insulin.

Conclusions: Patient-led daily insulin titration in gestational diabetes leads to higher insulin dose use lower fasting glucose and is associated with lower birthweight without causing significant hypoglycaemia.

KEYWORDS
algorithms, birth weight, blood glucose, diabetes, gestational, hyperglycemia, insulin, self-management

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy.[1] GDM is estimated to complicate around 17% of pregnancies globally although there is large regional variation (9%–25%) due to differences in obesity levels, ethnicity, screening strategies and other factors.[2,3] Multiple adverse pregnancy outcomes are associated with GDM, including macrosomia and babies that are large for gestational age; maternal and infant birth trauma; the greater need for obstetric intervention at delivery (caesarean section or assisted vaginal delivery); neonatal hypoglycaemia, jaundice, and respiratory problems; and perinatal mortality.[4–6] Longer-term, in utero exposure to hyperglycaemia is associated with subsequent childhood obesity and insulin resistance.[7,8] The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) observational study of 23,316 pregnancies demonstrated that fasting glucose is associated with high birthweight across the whole continuum of glucose values; the lower the fasting glucose the lower the risk for high birthweight with no lower threshold for risk identified.[4]

Treatment of GDM with diet and lifestyle advice, and pharmacological therapy when required, reduces birthweight and GDM-associated complications.[6,9] In the UK, GDM treatment targets are defined by the National Institute for Health and Clinical Excellence (NICE) as; a fasting capillary plasma glucose of <5.3 mmol/L (95 mg/dl) and either a 1-h post-meal glucose of <7.8 mmol/L (140 mg/dl) or 2-h post meal <6.4 mmol/L (115 mg/dl). Similar targets are recommended by the American Diabetes Association (ADA), American College of Obstetricians and Gynecologists (ACOG).[10,11] Metformin and insulin are the mainstay of pharmacological treatments.[10,12]

Despite clear treatment guidelines, glucose remains above target in the latter part of pregnancy in a large proportion of women.[13–15] As screening for GDM is usually performed between 24 and 28 weeks gestation,[11,12,16,17] there is only a short window in which to instigate and optimise treatment. Given that many women with GDM are overweight, and therefore have a degree of insulin resistance, treatment with insulin is often required for GDM. However, there are no recommended approaches to insulin titration in GDM in current guidelines. In our clinic, we found that women with GDM were slow to reach glycaemic targets when using an approach of weekly physician or nurse-led insulin dose titration, and targets were not reached by the end of pregnancy in a third of women. Data from observational studies suggest this is a widespread difficulty.[13–15] We, therefore, devised a method to achieve rapid glycaemic control in GDM using a simple algorithm which enables women to adjust their own insulin doses. We present the pregnancy outcomes of women with GDM in our clinic before and after the implementation of this approach.

Novelty statement

What is already known?

- Elevated fasting blood glucose in gestational diabetes (GDM) is associated with high birthweight and adverse pregnancy outcomes.
- Achieving the swift glucose reduction needed in pregnancy can be difficult.

What this study has found?

- Women with GDM can be successfully enabled to rapidly titrate their own basal insulin using a simple algorithm.
- This low-cost intervention resulted in the use of higher insulin doses even compared to intense specialist diabetes nurse-led titration.
- The approach was associated with improved glucose control and lower birthweight
- There were no severe hypoglycaemia events experienced.

What are the implications of the study?

- Wider adoption of this approach could reduce complications in GDM pregnancies at no additional cost.

2 | METHODS

We performed a retrospective before-and-after observational study to assess the impact of introducing a simple algorithm designed to support women with GDM to titrate their own insulin.

2.1 | Population and setting

Our centre, in the South-West of England, uses the national criteria for the diagnosis of GDM outlined by NICE; a fasting plasma glucose level of ≥5.6 mmol/L (101 mg/dl) or a 2-h plasma glucose level of 7.8 mmol/L (140 mg/dl) during a 75 g oral glucose tolerance test (OGTT).[12] We care for approximately 100 women with GDM annually.

We follow NICE recommendations for the treatment of GDM[12] with diet and lifestyle advice provided by specialist diabetes dietitians and nurses following a GDM diagnosis to all women. We recommend glucose testing four times daily; with fasting and 2-h post-prandial measurements and recording of results in a paper diary. The glucose meter in use in our clinic at the time was the Accu-Check Aviva. Women with GDM are reviewed regularly in a joint clinic by the obstetric and diabetes teams. Between clinic visits, women have weekly blood glucose reviews via email and telephone by our diabetes specialist nurse team. These clinic and remote reviews are used to initiate and up-titrate pharmacological therapy when required.

All women with GDM referred to our centre in the year prior (2016) to the implementation of our algorithm and in the year after (2018) were eligible for inclusion. We did not include women with GDM referred during the implementation year (2017) as many women were exposed to the intervention only for part of their pregnancy. Women were only excluded from the study if they were lost to follow-up, had multiple pregnancies, or there were missing data on treatment at 36 weeks or the end of pregnancy (whichever was first).

We retrospectively reviewed the clinical notes for all women and collected data on patient demographics and pregnancy outcomes. Data collection was completed in December 2019 to allow sufficient time for the after-intervention group to complete their pregnancies and for all outcomes to be recorded. Demographic and baseline data collected comprised, maternal age at conception, ethnicity (categorised as white, Asian, other, or not recorded), pre-pregnancy weight, pre-pregnancy body mass index (BMI), smoking status, and OGTT results.

2.1.1 | Intervention and control groups

Women with GDM were divided into two groups for analysis; those who required treatment with basal insulin and those who did not. The insulin titration algorithm we implemented was only relevant to women using basal insulin and therefore these women formed the intervention group. Baseline characteristics and treatment outcomes were compared in those before and after the intervention.

Those who did not require basal insulin were used as a control group. As with the treatment group, baseline characteristics and outcomes were compared in those before and after the intervention. Any systematic changes in care resulting in changed GDM outcomes over the study period should be apparent in both the intervention and control groups. We assume that changes occurring only in the intervention group were potentially related to the intervention. This control group included a small number of women who were on mealtime insulin without basal insulin.

2.2 | Intervention

Prior to the implementation of our algorithm, we observed that a proportion of our women with GDM were not achieving glycaemic targets towards the latter part of pregnancy. Even with intensive (weekly) insulin dose up-titration by specialist nurses, women with GDM frequently did not attain high enough insulin doses to achieve glucose targets. We, therefore, decided to incorporate a simple patient-led daily insulin titration algorithm (Figure 1) into our standard practice. All diabetes specialist doctors and specialist nurses within our service were educated on this approach. As described in Figure 1, we initiated basal insulin as a first-line treatment in women with elevated fasting glucose, metformin or mealtime insulin was initiated for elevated post-prandial glucose according to patient preference.

In all patients who were initiated on basal insulin (Insuman basal 14 units at night), we advised them to increase their basal insulin dose by 4 units every day where their fasting glucose that morning had been ≥5.0 mmol/L (90 mg/dl). We asked them to continue to do this daily until their fasting glucose was consistently below 5.0 mmol/L (90 mg/dl). We selected 5.0 mmol/L (90 mg/dl) as a dose escalation threshold to ensure that women rapidly and consistently achieved fasting glucose values below the NICE fasting glucose target of <5.3 mmol/L (<95 mg/dl). We counselled our patients about possible symptomatic hypoglycaemia and advised them to consider reducing their insulin dose if they experienced a glucose value below 4.0 mmol/L (72 mg/dl) which was associated with hypoglycaemia symptoms. Whilst we consider a glucose level of ≥3.5 mmol/L (63 mg/dl) as being within target for pregnancy in line with recent consensus guidelines,[18] we have selected this higher dose de-escalation threshold to allow for variability in capillary blood glucose readings (including variability arising from the inherent inaccuracies in capillary glucose meter readings). We continued performing weekly specialist nurse reviews of the patient's glucose diaries, as had been conducted before the intervention.

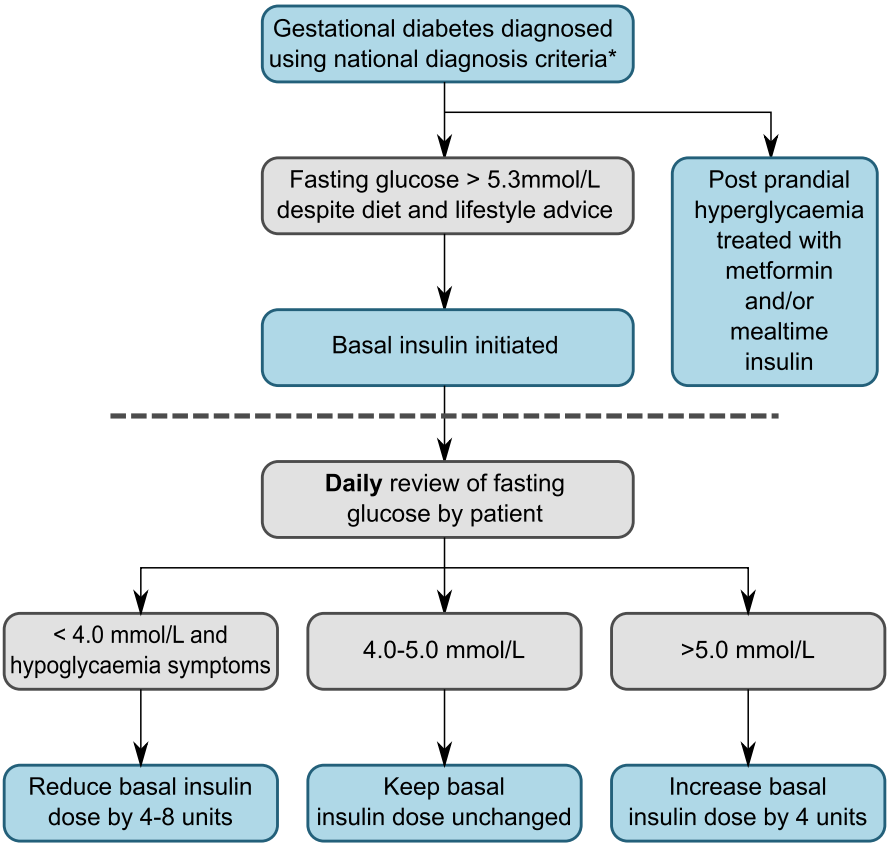

FIGURE 1 The GDM treatment process adopted in our centre. The patient-led daily insulin intensification algorithm is described in the section below the dotted line. *National criteria used for diagnosis in our clinic are those recommended by NICE (NICE guideline NG3).[12]

Our selected insulin starting dose of 14 units of intermediate-acting insulin is consistent with expert recommendations[19] and equates to a dose of 0.2 units/kg for women at the lower end of the pre-pregnancy weight distribution in our clinic (lower quartile 73.5 kg).

2.3 | Outcomes assessed

We collected outcome data on diabetes management towards the end of pregnancy (at 36 weeks) and on pregnancy outcomes. All outcomes assessed were decided a priori.

2.3.1 | Diabetes management outcomes

Our primary diabetes management outcomes were; total daily insulin dose per kilogram at 36 weeks gestation and mean fasting glucose at 36 weeks gestation. The last week prior to term (36 weeks) was selected for these outcomes to provide a measure of glucose control towards the end of pregnancy. We collected data on background and mealtime insulin doses and the use of oral diabetes medications at week 36 of pregnancy (on the first day of the 36th week or the closest recorded day ± 1 week). Daily insulin dose per kilogram was calculated using pre-pregnancy weight. Mean fasting glucose was the average of all recorded 36-week values or 35-week values if 36-week values were not recorded. The treatment group (intervention or control) was determined by basal insulin at any point during pregnancy. If delivery occurred prior to 35 weeks gestation, then women were not eligible for inclusion in the diabetes outcomes analysis as no 35–36 week data were available.

Additionally, we assessed the number of women with a mean fasting glucose below the NICE recommended target (<5.3 mmol/L; 95 mg/dl), recorded hypoglycaemic episodes requiring assistance (severe hypoglycaemia) at any point after GDM diagnosis, and the proportion of fasting glucose values <4.0 mmol/L (72 mg/dl) and <3.5 mmol/L (63 mg/dl) during weeks 35 and 36 gestations for each woman. Recent consensus guidelines consider a glucose value <3.5 mmol/L (63 mg/dl) to be below target for pregnancy, in contrast to <4.0 mmol/L (72 mg/dl) outside pregnancy.[18] For completeness, however, we report the proportion of glucose values below <4.0 mmol/L (72 mg/dl) and <3.5 mmol/L (63 mg/dl).

2.3.2 | Pregnancy outcomes

Our primary pregnancy outcome was the birthweight Z-score (adjusted for gestation). Secondary pregnancy

outcomes comprised; neonatal macrosomia (birthweight ≥4000 g), gestation at delivery, preterm delivery (prior to 37 weeks gestation), deliveries requiring obstetric intervention (caesarean section or assisted vaginal delivery), need for admission to the neonatal unit, maternal and perinatal mortality. We also report infant sex, unadjusted birthweight, mean adjusted birthweight centile and the proportion of who were large for gestational age (LGA) (>90th adjusted birthweight centile) and small for gestational age (SGA) (<10th adjusted birthweight centile). Women were included for all pregnancy outcomes analyses regardless of gestation at delivery.

2.4 | Statistical analysis

We report continuous variables as means and standard deviations (SD) and are compared across groups using the Student's t-test. Categorical variables are expressed as absolute numbers and frequencies and compared across groups with the chi-square test. All *p*-values reported are two-sided. For the primary diabetes outcomes (total daily insulin dose per kilogram at 36 weeks gestation and mean fasting glucose at 36 weeks gestation) and primary pregnancy outcome (birthweight Z-score adjusted for gestation). Adjusted birthweight centiles were calculated from maternal height, weight, ethnicity, parity, birthweight, infant sex and pregnancy gestation, using a validated method implemented using GROW software (www.gestation.net).[20] We conducted post hoc linear regression analysis to explore whether our intervention was associated with changes in the outcomes after adjustment for baseline characteristics (maternal age, pre-pregnancy BMI, smoking status and ethnicity) and metformin use during pregnancy. We used stepwise backward elimination of variables to select final model variables through minimisation of AIC (Akaike information criterion) using the stepAIC function within the R package 'MASS' and R version 4.0.3.

2.5 | Ethics requirements

This study was conducted as part of routine quality improvement within the National Health Service (NHS) and falls under the definition of a service evaluation as defined by the NHS Health Research Authority, therefore, did not require a research ethics committee review. The audit was registered with the Clinical Audit Programme at our centre (reference: 19–4413). All patient identifiable data were stored in compliance with local requirements and data was fully anonymised prior to analysis.

3 | RESULTS

3.1 | The before and after intervention groups had similar baseline characteristics

A total of 198 of the 213 potentially eligible cases of GDM diagnosed in 2016 or 2018 had sufficient data recorded to be included in the final analysis (Figure S1); 105 women before (2016) and 93 women after (2018) the implementation of the insulin titration algorithm. There were no differences in the baseline characteristics of the women in the before versus after groups (Table 1). Overall, 73 (36.9%) women were initiated on insulin basal during pregnancy and 125 (63.1%) were on no treatment, metformin or mealtime insulin. There were also no differences in baseline characteristics between those who were initiated on basal insulin before versus after and between those not initiated on basal insulin before versus after (Table 1).

3.2 | The intervention was associated with increased insulin doses, lower fasting glucose and lower birthweight

Despite a high rate (67%) of glucose target attainment in those treated with basal insulin prior to the intervention, we demonstrated those initiated on insulin after the algorithm implementation had improvements in all our primary outcomes; a substantially higher total daily insulin dose at 36 weeks (36.4 vs. 53.1 units; $p = 0.027$ and 0.37 vs. 0.56 units/kg; $p = 0.029$), a lower fasting glucose at 36 weeks (5.12 vs. 4.57 mmol/L; $p = 0.031$) and lower birthweight Z-scores (0.92 vs. 0.34; $p = 0.005$) (Figure 2). Additionally, the proportion of LGA babies was significantly lower (36.7 vs. 9.3%; $p = 0.011$) but there was no significant increase in the proportion of SGA babies (3.3 vs. 4.7%; $p = 1.000$).

There was no significant difference in the proportion of recorded fasting glucose readings at 35–36 weeks below <4.0 mmol/L [72 mg/dl] before versus after algorithm implementation (27.2% vs. 17.4%; $p = 0.913$) (Table 2) and only one woman had a fasting glucose value less than 3.5 mmol/L (95 mg/dl) on a single occasion. Furthermore, there were no hypoglycaemic episodes requiring assistance before or after implementation at any time during pregnancy in any of the study groups. Secondary pregnancy outcomes were not significantly altered by the intervention (Table 2) including no significant changes in macrosomia (before; 17% vs. after; 2%; $p = 0.078$), admissions to the neonatal unit (before; 30% vs. after; 16%; $p = 0.268$), or normal vaginal deliveries (before; 43% vs. after; 65%; $p = 0.116$).

TABLE 1 The baseline characteristics of women with gestational diabetes ($n = 198$) included in the study before and after the implementation of a patient-led insulin dose titration algorithm.

	Not treated with basal insulin ($n = 125$)			Treated with basal insulin ($n = 73$)			All participants ($n = 198$)		
	Before implementation	After implementation		Before implementation	After implementation		Before implementation	After implementation	
	$n = 75$	$n = 50$	p value	$n = 30$	$n = 43$	p value	$n = 105$	$n = 93$	p value
Maternal age (years): mean (SD)	31.6 (5.6)	32.4 (6.0)	0.412	32.0 (5.4)	31.0 (5.3)	0.462	31.7 (5.5)	31.8 (5.7)	0.901
Maternal Ethnicity: *n* (%)			0.993			0.727			0.855
White	60 (80.0)	40 (80.0)		26 (86.7)	38 (88.4)		86 (81.9)	78 (83.9)	
Asian	11 (14.7)	7 (14.0)		1 (3.3)	1 (2.3)		12 (11.4)	8 (8.6)	
Other	3 (4.0)	2 (4.0)		1 (3.3)	3 (7.0)		4 (3.8)	5 (5.4)	
Missing	1 (1.3)	1 (2.0)		2 (6.7)	1 (2.3)		3 (2.9)	2 (2.2)	
Pre-pregnancy weight (kg): mean (SD)	82.6 (19.6)	80.6 (17.3)	0.596	97.9 (24.3)	98.6 (17.7)	0.888	86.6 (21.9)	89.5 (19.6)	0.367
Pre-pregnancy BMI (kg/m^2): mean (SD)[a]	31.2 (6.9)	30.6 (6.1)	0.637	34.9 (7.6)	36.7 (5.7)	0.233	32.2 (7.3)	33.4 (6.6)	0.237
Current smoker: *n* (%)	9 (12.0)	10 (20.0)	0.334	4 (13.3)	7 (16.3)	0.989	13 (12.4)	17 (18.3)	0.339
Oral glucose tolerance test: mean (SD)									
Fasting glucose (mmol/L)	5.2 (1.0)	5.1 (0.8)	0.531	6.4 (1.6)	6.1 (1.3)	0.397	5.5 (1.3)	5.6 (1.2)	0.842
120-min glucose (mmol/L)	8.1 (1.5)	8.3 (1.4)	0.489	7.9 (2.7)	8.0 (1.7)	0.862	8.1 (1.9)	8.2 (1.6)	0.712

[a]Data was missing for one (0.5%) patient.

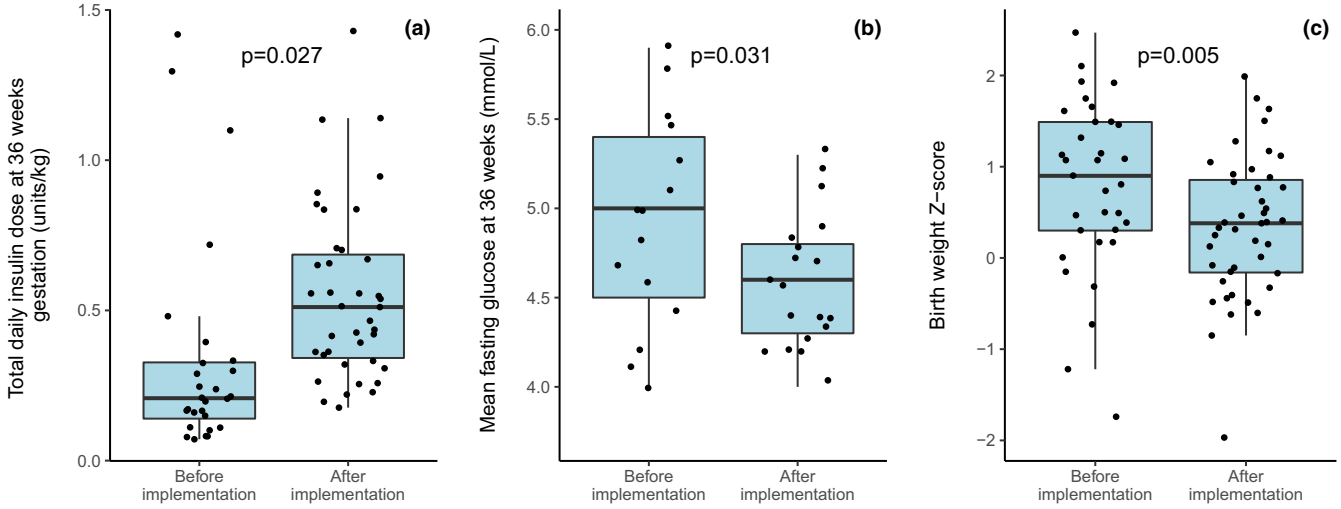

FIGURE 2 Outcomes of gestational diabetes pregnancies treated with basal insulin before ($n = 30$) and after ($n = 43$) the implementation of a patient-led daily insulin titration algorithm: (a) Total daily insulin dose at 36 weeks gestation (units per kg of pre-pregnancy weight), (b) Mean fasting glucose at 36 weeks gestation, and (c) Birthweight Z-score. The blue boxes display the interquartile range and median value.

By comparison, in the non-basal insulin-treated (control) groups, there were no differences before vs. after implementation in fasting glucose at 36 weeks, birthweight Z-scores (Figure S2) or any other pregnancy or neonatal outcome (Table 2). There were no maternal or perinatal deaths in any group during the study.

In adjusted linear regression models the implementation of the intervention was also significantly associated with a significant increase in insulin dose, a reduction in fasting glucose, and a reduction in birthweight (Table 3). The implementation of the intervention was not associated with any changes in outcomes in the non-insulin-treated comparator group (Table 3).

4 | DISCUSSION

Implementation of a simple patient-led basal insulin titration algorithm in GDM is associated with higher insulin dose use, improved fasting glucose and lower birthweight without evidence of increased hypoglycaemia frequency. Additional benefits of the intervention were that it had no associated financial cost (other than the cost of higher insulin doses) and that it involved patient enablement. Prior to implementation most women with GDM (67%) already achieved national fasting glucose targets in our clinic with support from intense (weekly) follow-up. Even in this context, the addition of the patient-led insulin titration algorithm was associated with substantially improved outcomes.

4.1 | Strengths and weaknesses

The simplicity and minimal cost of our intervention are major strengths. This strategy could be applied in both high and low-resource settings and does not require a high level of specialist knowledge to implement. We also found that our intervention was received positively by women, who reported satisfaction owing to the autonomy they experienced and with the results they achieved. This simple pragmatic approach to insulin treatment in pregnancy has excellent results in a real-world setting with no women excluded from the intervention.

The primary weaknesses of our study were, by necessity, the quasi-experimental, the single centre design, and relatively small sample size. As an observational study, opposed to a randomised trial, we cannot robustly demonstrate a causal effect of our intervention. We have attempted to mitigate this limitation by including a natural control patient group of women with GDM not treated with basal insulin and therefore not subject to our intervention. Whilst the lack of change over the study period in this control (non-basal insulin-treated) group, supports our assertion that the changes we observed were unlikely to be caused by alternative factors. However, this group has, by definition, a less severe form of GDM. To our knowledge there were no other significant changes in obstetric or diabetes management over the study period which would have altered our study outcomes, however, we cannot exclude informal changes in practice which may have occurred over time. Mirroring our local ethnicity distribution, we only included a small number of people

TABLE 2 The maternal and neonatal outcomes of gestational diabetes pregnancies treated with insulin before and after the implementation of a patient-led insulin dose titration algorithm.

	Not treated with basal insulin ($n = 125$)			Treated with basal insulin ($n = 73$)		
	Before implementation	After implementation		Before implementation	After implementation	
	$n = 75$	$n = 50$	p value	$n = 30$	$n = 43$	p value
Diabetes treatment usage						
Metformin treatment: n (%)	24 (32.0)	18 (36.0)	0.787	8 (26.7)	16 (37.2)	0.490
Meal-time insulin: n (%)	4 (5.3)	1 (2.0)	0.641	12 (40.0)	15 (34.9)	0.842
Basal insulin: n (%)	0 (0.0)	0 (0.0)	NA	30 (100.0)	43 (100.0)	NA
Diabetes outcomes at 36 weeks gestation						
Total daily insulin dose[a] (units): mean (SD)	0.55 (2.32)[a]	0.25 (1.73)[a]	0.448	36.4 (35.0)[a]	53.1 (27.4)[a]	0.027
Total daily insulin dose[a] (units/kg): mean (SD)	0.01 (0.03)[a]	0.00 (0.03)[a]	0.639	0.37 (0.38)[a]	0.56 (0.29)[a]	0.029
Total daily insulin dose excluding meal-time insulin[a] (units): mean (SD)	0.0 (0.0)[a]	0.0 (0.0)[a]	NA	26.6 (21.7)[a]	40.6 (18.8)[a]	0.005
Mean fasting glucose[b] (mmol/L): mean (SD)	4.85 (0.36)	4.76 (0.45)	0.555	5.12 (0.71)	4.57 (0.38)	0.031
Mean fasting glucose below recommended target[b] <5.3 mmol/L (95 mg/dl): n (%)	21 (75.0)[b]	21 (84.0)[b]	0.724	8 (66.7)[b]	18 (94.7)[b]	0.117
Per cent of fasting glucose values[b] <4.0 mmol/L [72 mg/dl]: mean (SD)	3.7 (11.2)[b]	2.8 (8.6)[b]	0.793	11.1 (27.2)[b]	12.2 (17.4)[b]	0.913
Per cent of fasting glucose values[b] <3.5 mmol/L [63 mg/dl]: mean (SD)	0.0 (0.0)[b]	0.0 (0.0)[b]	NA	0.0 (0.0)[b]	1.1 (4.3)[b]	0.541
Neonatal characteristics						
Gestation at delivery (weeks): mean (SD)	38.3 (1.0)	38.1 (1.3)	0.407	37.2 (1.7)	37.9 (1.1)	0.049
Male sex: n (%)	36 (48.0)	22 (44.0)	0.798	16 (53.3)	22 (51.2)	1.000
Birthweight (kg): mean (SD)	3.33 (0.49)	3.23 (0.50)	0.238	3.38 (0.61)	3.24 (0.42)	0.268
Birthweight Z-score: mean (SD)	0.36 (0.85)	0.23 (0.93)	0.420	0.92 (0.91)	0.34 (0.77)	0.005
Adjusted birthweight centile: mean (SD)	59.6 (29.9)	54.7 (29.4)	0.364	72.3 (31.3)	55.7 (27.8)	0.020

TABLE 2 (Continued)

	Not treated with basal insulin ($n = 125$)			Treated with basal insulin ($n = 73$)		
	Before implementation	After implementation		Before implementation	After implementation	
	$n = 75$	$n = 50$	p value	$n = 30$	$n = 43$	p value
LGA [>90th adjusted birthweight centile]: n (%)	15 (20.0)	8 (16.0)	0.742	11 (36.7)	4 (9.3)	0.011
SGA [<10th adjusted birthweight centile]: n (%)	4 (5.3)	4 (8.0)	0.823	1 (3.3)	2 (4.7)	1.000
Delivery outcomes						
Induction of labour: n (%)	46 (61.3)	30 (60.0)	0.694	15 (50.0)	28 (65.1)	0.294
Delivery mode: n (%)			0.839			0.116
Vaginal delivery	44 (58.7)	30 (60.0)		13 (43.3)	28 (65.1)	
Instrumental vaginal delivery	3 (4.0)	3 (6.0)		3 (10.0)	1 (2.3)	
Caesarean section	28 (37.3)	17 (34.0)		14 (46.7)	14 (32.6)	
Preterm delivery: n (%)	4 (5.3)	3 (6.0)	1.000	4 (13.3)	5 (11.6)	1.000
Macrosomia: n (%)	7 (9.3)	4 (8.0)	1.000	5 (16.7)	1 (2.3)	0.078
Neonatal unit admissions: n (%)	9 (12.0)	9 (18.0)	0.499	9 (30.0)	7 (16.3)	0.268

Abbreviations: LGA, large for gestational age; NA, not applicable; SD, standard deviation; SGA, small for gestational age.

[a]Data was available in the non-insulin-treated group for all insulin-treated women in the before and after groups and in the insulin treated group for 29 (97%) women before implementation and 42 (98%) after.

[b]Data was available in the non-insulin treated group for 25 (36%) women before implementation and 24 (51%) after and the insulin-treated group for 15 (46%) before and 19 (44%) after.

TABLE 3 The associations between the initiation of patient-led basal insulin titration and pregnancy outcomes in linear regression models.

	Adjusted change associated with the intervention	
	Non-insulin treated (comparator) group estimate (95% CI; p value)	Insulin treated group estimate (95% CI; p-value)
Increase in total daily insulin dose at 36 weeks gestation[a] (units per kg of pre-pregnancy weight)	NA	0.21 (0.03 to 0.38; $p = 0.020$)
Change in mean fasting glucose at 36 weeks gestation[b] (mmol/L)	−0.12 (−0.42 to 0.18; $p = 0.408$)	−0.54 (−1.07 to −0.02; $p = 0.042$)
Change in birthweight Z-score[c]	−0.18 (−0.50 to 0.14; $p = 0.270$)	−0.61 (−1.01 to −0.22; $p = 0.003$)

Abbreviation: NA, not applicable.

[a]Complete data was available in the insulin-treated group for 29 (97%) women before implementation and 41 (95%) after. Retained model adjustment variables: maternal age and maternal BMI.

[b]Complete data was available in the non-insulin-treated group for 25 (36%) women before implementation and 24 (51%) after and the insulin-treated group for 15 (46%) before and 18 (42%) after. Retained model adjustment variables: maternal ethnicity, and metformin use.

[c]Complete data was available in the non-insulin-treated group for 75 (100%) women before implementation and 50 (100%) after and the insulin-treated group for 30 (100%) before and 42 (98%) after. Retained adjustment variables: maternal age, maternal ethnicity, and metformin use.

from non-white backgrounds. The acceptability and effectiveness of our approach may be different in other settings and other cultures. Additionally, in some populations, for example, some Asian ethnic groups, our starting dose of 14 units of intermediate-acting insulin might be too high; whilst in others, such as those with high levels of insulin

resistance like Pacific Islanders, the starting dose could be increased. Therefore, the algorithm we used may require adjustment for dissimilar populations. Data were not available on weight gain during pregnancy for our study. We therefore cannot assess for this as a potential adverse effect of increased insulin dose usage on maternal pregnancy weight gain, nor could we assess whether the insulin dose increments were associated with maternal weight gain.

We have demonstrated our intervention is associated with substantially higher insulin doses, and lower fasting glucose readings toward the end of pregnancy. Whilst improved birthweight is a biologically plausible causal result, to establish causality these findings merit robust testing in a randomised controlled trial.

4.2 | Comparison with the literature

There is a paucity of data reporting the current achievement of glycaemic targets in women with GDM in routine clinical practice and therefore it is difficult to contextualise the level of target attainment in our clinic prior to the intervention. However, our before-intervention glycaemic outcomes are comparable to those from other observational analyses.[13–15] In our before-intervention insulin-treated group, mean fasting glucose at 36 weeks was the same as those treated with insulin in the metformin in gestational (*MiG*) diabetes *trial*, where insulin was titrated according to 'usual practice' (mean fasting glucose 4.93 mmol/L [88.7 mg/dl] vs. 4.90 mmol/L [88.2 mg/dl] in MiG).[21] These data suggest that our pre-intervention glycemic outcomes are similar to those elsewhere and therefore our results are likely to have external validity.

Whilst current guidelines recommend clear glycaemic targets and treatment options, they do not provide guidance on the approach to insulin titration.[10–12] To our knowledge, there are no observational studies or randomised trials comparing approaches to insulin dose titration in GDM. We are aware of one other report where rapid insulin titration has been used in clinical practice for GDM. The authors report using an evening dose of 6 units of insulin detemir (Levemir) for women with GDM and high fasting glucose, with 4 unit up-titration increments every 2 days if fasting glucose remains above 5.0 mmol/L (90 mg/dl).[22] The authors do not report glycemic outcomes for this method and include women with T2D in their analysis, but they do compare outcomes in women experiencing low fasting or low postprandial glucose requiring insulin dose reduction in the third trimester to those who did not require dose reduction. They found no increased risk of adverse pregnancy outcomes in those who needed an insulin dose reduction.[22]

Several studies have compared patient-led and physician-led basal insulin titration in type 2 diabetes outside of pregnancy. A recent meta-analysis, including six studies ($n = 12{,}409$ non-pregnant patients with type 2 diabetes) found patient-led dose titration was associated with higher insulin dose (5.9 units/day; 95% confidence interval [CI] 0.2–11.8), lower HbA_{1c} −0.12% (95% CI -0.16 to −0.07) and lower fasting glucose (−0.29 mmol/L [−5.2 mg/dl]; 95% CI -0.52 to −0.07 mmol/L [−9.3 to −1.2 mg/dl]; $I^2 = 59\%$) than physician-led titration.[23] Patient-led dose titration was associated with a slightly increased risk of any hypoglycaemia (relative risk [RR] = 1.12; 95% CI 1.02–1.23) but no significant risk increase for severe hypoglycaemia (requiring assistance) (RR = 1.20; 95% CI 0.73–1.98).[23] These results are consistent with our findings in GDM. However, the patient-led dosage titration protocols in these studies outside pregnancy aimed to achieve glycaemic control over several months (with changes of 2–3 units being made every 3–4 days in most studies) which is unacceptably slow for use in GDM.[24–28] Only one study used daily titration, although this was with 1 unit increments.[29] A randomised trial comparison of low (3.9–5.0 mmol/L; 70-90 mg/dl) versus moderate (4.4–6.1 mmoL/L; 79–110 mg/dl) fasting glucose targets for patient-led basal insulin titration has also been conducted in non-pregnant people with type 2 diabetes.[30] This study found the low fasting target group used significantly higher insulin doses (0.57 vs. 0.51 units/kg) after 20 weeks and were more likely to achieve an HbA_{1c} <7% (odds ratio 1.86; 95% CI 1.03–3.37, $p = 0.04$). Hypoglycaemia rates were non-significantly higher in the tight-target group (2.74 vs. 2.02 events/subject/year; $p = 0.317$).[30] The tight target in this study was identical to that used in our algorithm although, again, we used more rapid insulin dose titration.

4.3 | Future research

Whilst our reported results are promising early data, additional analysis is needed. Ideally, our method would be compared to the usual practice in a randomised controlled trial setting across several centres in a population with a more diverse ethnicity mix. Any additional study should include an analysis of the impact on pregnancy weight gain, which we were unable to assess from our data. It should also focus on collecting data regarding hypoglycaemia frequency and severity throughout pregnancy. During the implementation of this approach in our clinic, anecdotally we found that during weekly contact sessions with women, nurses were able to spend more time on the management of post-prandial glucose and supporting with dietary and other lifestyle advice and needed to provide

minimal support for basal insulin titration. However, we were unable to collect accurate data on this outcome to provide a formal assessment. Any future study could look to explore this potential additional benefit with prospective data collection.

It also remains unclear whether a 'one-size fits all' insulin starting dose and four-unit daily titration rate is the most suitable approach. A weight-based starting dose may achieve more rapid glycaemic control in heavier women. Conversely, a lower starting dose and slower titration rate may be more appropriate in some groups e.g. lower-weight women or those of Asian ethnicity. Similarly, it remains unclear whether our fixed-dose increments are the optimal approach or whether a selected subgroup of women would benefit from greater or lesser increments. Additional observational data collection could be used to explore this further and identify groups for which our existing algorithm could be improved.

5 | CONCLUSIONS

Patient-led basal insulin titration has been shown to be effective and safe in type 2 diabetes outside of pregnancy, although in this setting there is time to perform titration slowly. We found a patient-led rapid basal insulin titration in GDM is associated with higher insulin dose use, lower fasting glucose, and reduced birthweight in a small single-centre observational analysis. There was no significant increase in measured hypoglycaemia or severe hypoglycaemic events. Our findings merit additional study and would be suitable for testing in a randomised controlled trial.

AUTHOR CONTRIBUTIONS

ATH conceived the intervention. APM conceived the study. KDH, AH, AKW, CJEH, IM and APM collected the data. APM performed the analysis. APM and KDH drafted the manuscript. All authors read, provided feedback, and approved the final manuscript. APM is the guarantor and takes responsibility for the content of the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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