

Glycemia and its relationship to outcomes in the MiG trial

Running title: Glycemia and MiG trial outcomes

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Objective: To determine how glucose control in women with GDM treated with metformin and/or insulin influenced pregnancy outcomes.

Research, Design and Methods: Women randomized to metformin or insulin treatment in the Metformin in Gestational diabetes (MiG) trial had baseline glucose tolerance test (OGTT) results and HbA1c documented, together with all capillary glucose measurements during treatment. In the 724 women who had glucose data for analysis, tertiles of baseline glucose values and HbA1c, and of mean capillary glucose values during treatment, were calculated. The relationships between maternal factors, glucose values and outcomes (including a composite of neonatal complications, preeclampsia and large and small for gestational age (LGA, SGA) infants) were examined with bivariable and multivariate models.

Results: Baseline OGTT did not predict outcomes, but HbA1c predicted LGA ($p=0.003$). During treatment, fasting capillary glucose predicted neonatal complications ($p<0.001$) and postprandial glucose predicted preeclampsia ($p=0.016$) and LGA ($p=0.001$). Obesity did not influence outcomes and there was no interaction between glycemic control, randomized treatment or maternal BMI in predicting outcomes. The lowest risk of complications was seen in the lowest tertile when fasting capillary glucose was $<4.9\text{mmol/l}$ (mean(SD)= $4.6(0.3)\text{mmol/l}$) compared with $4.9\text{-}5.3\text{mmol/l}$ or higher and when postprandial glucose was $<6.5\text{mmol/l}$ (mean(SD)= $6.2(0.2)\text{mmol/l}$)

Conclusions. Glucose control in women with GDM treated with metformin and/or insulin is strongly related to outcomes. Obesity is not related to outcomes in this group. Targets for fasting and postprandial capillary glucose may need to be lower than currently recommended.

Although treatment of gestational diabetes (GDM) has been shown to improve perinatal outcomes,(1, 2) there is lack of consensus about ideal glucose targets and how other factors, such as fetal abdominal circumference, should influence these targets.(3, 4)

The Fifth International Workshop-Conference on Gestational Diabetes endorsed targets of capillary fasting glucose <5.3mmol/l, one hour postprandial <7.8mmol/l and/or 2 hour postprandial <6.7mmol/l until further data addressing optimal goals become available.(5) Improved pregnancy outcomes have been reported in women achieving these targets compared with women who did not;(6) the latter group had a higher baseline mean Body-Mass Index (BMI) and HbA1c, which may have influenced outcomes. Obesity has been reported as an independent factor influencing outcome in women with GDM treated with diet, but not when treated with insulin.(7, 8)

Published studies have compared women who aim for or achieve predetermined glucose targets with those who do not: it is not clear whether such aims are optimal and whether glycemia influences different outcomes equally. Several studies suggest that treatment intensity can be usefully stratified according to fetal abdominal circumference measured by ultrasound:(3) intensive treatment of women carrying fetuses with an abdominal circumference above the 70-75th percentile lowered the frequency of large-for-gestational age (LGA) infants without increasing rates of small-for-gestational age (SGA) infants. However, lowering of mean maternal glucose to <4.8mmol/l is associated with increased frequency of SGA infants.(9)

Data showing relationships between different fasting and postprandial glucose values and a range of outcomes would assist clinicians in setting target ranges for “optimal

glucose control” more objectively. In the Metformin in Gestational diabetes (MiG) trial, women with GDM, who had one or more home capillary blood glucose measures ≥ 5.5 mmol/l fasting or ≥ 6.7 mmol/l at 2-hour postprandial after lifestyle intervention, were randomized to either insulin or metformin treatment.(10) The primary objective of the trial was to compare metformin with insulin treatment, but a pre-specified secondary objective was to determine the impact of glycemia on outcomes and whether treatment with metformin or insulin was more effective at different levels of glycemia. Baseline glycemia measures and capillary glucose measures throughout treatment were recorded in the trial database.

The specific aims of the present analysis are:

1. To determine how glucose control influenced trial outcomes, including the primary outcome (a composite of neonatal complications), maternal preeclampsia and rates of LGA and SGA infants.
2. To identify additional baseline factors influencing outcomes, including baseline glycemia and obesity.
3. To examine any differences between treatment arms at different levels of glycemia.

RESEARCH, DESIGN AND METHODS

The MiG trial was a prospective, randomized, multicentre trial comparing metformin with insulin treatment in women with GDM. The methodology and outcomes have been published.(10) The mean gestation at recruitment was 30 \pm 3 weeks. All women gave written informed consent. The trial was approved by ethics committees at each participating site.

Assessment of glycemia. Baseline glycemia measures included the diagnostic 75g oral glucose tolerance test (OGTT)

results and HbA1c at randomization to treatment with insulin or metformin.

Treatment glycemia measures included capillary glucose measurements that were documented four times daily, fasting and 2 hours from the start of each meal. Medisense (now Optium) meters (Abbott Diabetes Care Inc Alameda, Ca, USA), and occasional Accu-Chek Advantage meters (Roche Diagnostics Mannheim, Germany), were used and the stored results downloaded. Relevant results were transcribed into the trial database from the day after medication was started until delivery. Of 733 women who had data collected, seven women did not have fasting glucose, eight did not have postprandial glucose, and nine did not have any glucose recordings documented, leaving 724 women for assessment. The median number (interquartile range) of capillary glucose values documented for each woman included 46 (34-60) fasting and 115 (83-161) postprandial measures. The means of fasting and postprandial glucose measures were calculated separately for each patient.

Outcomes and definitions. Several pre-specified outcomes from the trial were selected to examine the impact of glycemia measures: the primary outcome composite (neonatal complications), preeclampsia and rates of LGA (customised birth weight >90th percentile) and SGA (customised birth weight <10th percentile) infants.

The primary outcome composite included one or more of the following neonatal complications: recurrent hypoglycemia (two or more blood glucose measurements <2.6mmol/l), respiratory distress (need for four or more hours of respiratory support with supplemental oxygen, continuous positive airway pressure or intermittent positive-pressure ventilation during first 24 hours), need for phototherapy, birth trauma, 5 minute Apgar score less than 7, and preterm birth (less than 37⁰ weeks of gestation). The birth weight percentile was

calculated using customized calculators (www.gestation.net), which adjust for sex and gestational age of the infant as well as maternal height, weight in early pregnancy, ethnic group and parity.(11) In this calculator, birth weight is adjusted if a woman's BMI is between 20 kg/m² and 30 kg/m², but not further adjusted for BMI above this range; European, Maori, Chinese, Indian and other specific Asian and Pacific Island ethnicities can be selected. In the MiG database, the specific Pacific Island ethnicity was not documented, so Samoan ethnicity was used to represent this group in the calculations. Of note, customised charts applied to a general non-diabetic obstetric population with similar ethnicities to the MiG population report rates of SGA between 12.1% and 12.8% and LGA between 8.4% and 8.8% (www.adhb.govt.nz/nwhealthinfo).

Statistical Analysis. Mean capillary glucose values were calculated from the daily records. They are shown as mean fasting, mean postprandial and/or overall mean glucose (mean fasting plus mean postprandial divided by two).

Fasting, postprandial and overall mean glucose measures and their relationship to outcomes were explored using continuous measures and categorized quartile and tertile groupings; all methods yielded similar relationships. Tertile groups were chosen for this report as, with larger numbers in each group, they provided a simple demonstration of relationships between glucose levels and outcomes. A bivariable analysis of baseline characteristics was performed to explore associations with outcomes. Interactions with glycemic control, both of randomized treatment (metformin or insulin) and of obesity, were explored using the Breslow-Day test through stratified analysis and logistic regression analysis. Multivariable binary logistic regression was performed to identify independent risk factors associated with both the primary composite outcome measure and

preeclampsia. For the customized birth weight percentiles, multinomial logistic regression was used, given that the outcome measure was categorized into three groups: appropriate-for-gestational-age (AGA), SGA, and LGA. In these analyses, the backwards elimination method was used. Specifically, any potential risk factors identified through bivariable analysis and stratified analysis ($p < 0.25$), as well as others considered potentially relevant for clinical reasons or from the literature, were included in the initial models; variables were then eliminated stepwise from the models if their contributions were not significant, until all variables retained were significantly associated with the outcome measure. Two multivariable analysis models were examined. In the first, the glycemic measures included the baseline OGTT results, HbA1c values, and mean fasting, postprandial and overall capillary glucose concentrations in addition to other potential baseline risk factors (total available $n=582$ for this model for the primary composite outcome). In the second model, the baseline glycemia measures were excluded, giving a total $n=724$ for the analysis of primary composite measures.

Interpretation of the results relating to risk factors for SGA and LGA took into account that the “customized” classification of SGA and LGA had already been adjusted for infant sex, gestation, maternal ethnicity, parity and BMI between 20 kg/m² and 30 kg/m².

Maternal weight at earliest booking was missing in 147 women, so these data were imputed using a regression method. Specifically, the weight was first imputed using a formula based on the post pregnancy weight. If this variable was missing, then a formula based on the randomization weight was used instead. The imputed mean of weight at earliest booking was 85.98 kg, very close to the mean of 85.25 kg before

imputation, suggesting that the imputation is robust.

All analyses were performed using SAS (version 9.1, SAS Institute Inc., Cary, NC USA), using $\alpha=0.05$ to determine significance.

RESULTS

Table 1 shows tertiles of baseline glycemia measures and capillary glucose levels during treatment. Table 1A (see online supplement at <http://care.diabetesjournals.org>) shows baseline characteristics of the women according to tertiles of capillary glucose during treatment.

The relationships between tertiles of mean fasting, postprandial and overall capillary glucose during treatment and outcomes are shown in table 2. Examining the components of the primary outcome composite, the frequencies of recurrent neonatal hypoglycemia and preterm birth increased across tertiles of control, and there was a trend to higher rates of respiratory distress and need for phototherapy. Maternal preeclampsia and LGA also increased across tertiles of achieved glycemia. The frequency of SGA fell across the tertiles of fasting and mean glycemia, but not across the postprandial tertiles. The frequency of SGA in the lowest fasting tertile was not increased compared with the background population.

The bivariable relationships between maternal baseline characteristics, glycemia measures and outcomes are shown in table 3. Baseline factors that were related to the primary outcome composite included maternal ethnicity, nulliparity, previous preeclampsia and previous delivery of a baby weighing >4000g. Baseline glycemia measures were not related to the primary outcome composite, but mean capillary glucose measures on treatment were strongly related. Preeclampsia was associated with Polynesian ethnicity, chronic hypertension, previous hypertensive complications during

pregnancy and maternal weight gain from early pregnancy to recruitment. It was also associated with baseline HbA1c and all measures of glucose control on treatment. Additional factors (not all shown) that were not related to either the primary outcome composite or preeclampsia included gestation at recruitment (20-27 weeks vs 28-33 weeks), tertiary education level, smoking in pregnancy, past history of GDM, previous recurrent miscarriage/termination (3 or more), and maternal first degree family history of diabetes, hypertension or preeclampsia.

In table 3, SGA was associated with Asian ethnicity and with the woman having a first degree relative with diabetes. It was inversely related to maternal weight gain from early pregnancy to recruitment. Baseline glycemia measures were not predictive of SGA. During treatment, risk of SGA was lower in women in the highest tertile of capillary fasting glucose but there was no relationship with postprandial glucose. Large for gestational age was associated with Polynesian ethnicity, previous delivery of a baby weighing >4000g, maternal weight gain from early pregnancy to recruitment and HbA1c at recruitment. The LGA rate was increased in women whose capillary glucose during treatment was in the highest tertile. Other factors (not shown) that did not relate to SGA or LGA included: chronic hypertension, gestation at recruitment, smoking in pregnancy, tertiary education, previous history of recurrent miscarriages/terminations, GDM or hypertensive complications, and a family history of preeclampsia.

The Breslow-Day Test and logistic regression analysis showed no interactions of glycemic control with randomized treatment or with maternal BMI in predicting the primary outcome composite, preeclampsia or LGA/SGA.

The first multivariable analysis model included baseline glycemia measures to

examine whether they related to the chosen outcome measures (model 1). After backward elimination, none of the baseline glycemia measures predicted the primary outcome or preeclampsia, but treatment capillary glucose was strongly related. None of the glucose measures predicted SGA. For LGA, HbA1c at recruitment was the only predictive glycemia measure ($p=0.003$). Compared with the lowest HbA1c tertile, the second tertile had an OR for LGA of 2.64 (95% confidence interval [CI] 1.33-5.24) and the third tertile had an OR for LGA of 4.0 (95% CI 2.03-7.87).

The results of the second multivariable analysis model (excluding baseline glycemia measures, thus including larger numbers) are summarized in table 4. Variables that were eliminated for all outcomes are not shown. In this analysis, fasting capillary glucose on treatment was associated with the primary outcome composite, and postprandial capillary glucose was related to LGA and preeclampsia. Overweight women were more likely to develop preeclampsia than normal weight women, but the rate of preeclampsia in obese women was not increased. Numbers of women taking aspirin ($n=45$) were too small to determine whether this was a confounding factor. Polynesian ethnicity, chronic hypertension and previous gestational hypertension remained factors for preeclampsia. Having a previous baby weighing >4000g reduced the risk of neonatal complications but increased the risk of LGA. Weight gain from early pregnancy to recruitment increased the risk of preeclampsia and LGA.

CONCLUSIONS

The key finding from this study is that capillary glucose values during treatment for GDM with metformin and/or insulin related strongly and independently to the primary outcome composite of neonatal outcomes, to maternal preeclampsia and to frequency of LGA. These data are novel in that the

outcomes examined appear to be sensitive to different levels of glycemia: rates of neonatal hypoglycemia increased between the lowest and middle tertiles of glycemia control, whereas risk of LGA and maternal preeclampsia increased between the middle and highest tertiles. These differential effects may be important to consider when determining treatment goals and which outcomes to report when assessing treatment of GDM.

The diagnostic OGTT values were not predictive of outcomes but HbA1c at recruitment was predictive of LGA. It may be that intervention in the trial was too late to modify this outcome. The fetal ultrasound measurements at recruitment and at 37 weeks' have not yet been analyzed to see whether growth velocity was modified differentially according to glycemic control, as others have shown. (3)

During treatment, fasting capillary glucose predicted neonatal complications while postprandial capillary glucose was related to risks of preeclampsia and LGA. It is therefore important to focus on both fasting and postprandial glucose control in order to optimize outcomes. The relationship between postprandial glucose levels and complications may be relevant for obese women without GDM, who have higher postprandial glucose levels and increased rates of preeclampsia and LGA infants compared with lean women.(12) Also, the HAPO study demonstrated that maternal glycemia, as measured by a 75g OGTT at 28 weeks', is an important risk factor for preeclampsia and LGA at values below those used currently to diagnose GDM.(13) A further study has shown that fluctuating glucose levels have a stronger effect on endothelial function (important in the pathogenesis of preeclampsia (14)) than sustained hyperglycemia.(15) From these observations, it can be speculated that reducing postprandial glucose fluctuations in

obese women could reduce rates of preeclampsia and/or LGA.

There was no independent effect of obesity on the primary outcome composite, preeclampsia or LGA, consistent with previous findings in women treated with insulin.(7) It may be that pharmacotherapy more strongly modifies fetal nutrient supply than dietary intervention alone, overriding the effects of obesity *per se*.

There was no increase in SGA in the lowest glucose tertile, but mean glucose values were above the threshold previously shown to increase risk of SGA.(9) Customised centiles were used as, particularly in heterogeneous populations, they perform better than a population centile for identifying SGA infants, both in the general obstetric population and in women with type 2 diabetes.(11,16) It is recognized that these calculators require further development in relation to the adjustment for ethnicity and maternal BMI.(16)

The rate of SGA was increased in women with a first degree relative with diabetes. The reason for this may relate to genetic associations between low birth weight and type 2 diabetes.(17)

There were no differences seen between metformin and insulin treatment groups at different levels of glucose control. This suggests that, if metformin is used, supplemental insulin should be used readily if glucose targets are not achieved.

These data do not provide definitive answers regarding optimal glucose targets. However, women with mean post-treatment fasting capillary glucose <4.9mmol/l had significantly better outcomes than women with post-treatment fasting capillary glucose between 4.9 and 5.3mmol/l or higher. At 2-hours postprandial, mean capillary glucose <6.5mmol/l was associated with improved outcomes and a further, but small, improvement was seen with mean postprandial capillary glucose <5.9mmol/l. In

an earlier study, women in a “well-controlled” group had a mean fasting capillary glucose of 4.7mmol/l and either a mean 1-hour capillary glucose of 6.5mmol/l or a mean 2-hour capillary glucose of 5.7mmol/l, whereas a “less well-controlled” group had a mean fasting capillary glucose of 5.3mmol/l and either a mean 1-hour capillary glucose of 7.2mmol/l or a mean 2-hour capillary glucose of 6.8mmol/l.(6) The glucose means in the “well-controlled” group were very similar to the means seen in women in the lowest tertile in the current study. These data suggest that clinicians should aim for lower targets than currently recommended.

In conclusion, these data demonstrate that glucose control in women with GDM is

strongly related to pregnancy outcomes. Targets for fasting and postprandial capillary glucose may need to be lower than current guidelines recommend.

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Table 1 Baseline and treatment glycemia tertiles

Measure of glycemia (Glucose mmol/L, HbA1c %)	Tertile 1 Upper Limit	Tertile 1 Mean (SD)	Tertile 2 Limits	Tertile 2 Mean (SD)	Tertile 3 Lower Limit	Tertile 3 Mean (SD)
<i>Baseline measures</i>						
OGTT fasting glucose	5.2	4.7 (0.3)	5.2-5.8	5.5 (0.2)	5.8	6.8 (1.1)
OGTT 2 hr glucose	8.8	7.5 (1.0)	8.8-9.9	9.4 (0.3)	9.9	11.6 (1.8)
HbA1c	5.4	5.1 (0.3)	5.4-5.8	5.7 (0.1)	5.8	6.5 (0.6)
<i>Treatment measures</i>						
Fasting capillary glucose	4.9	4.6 (0.3)	4.9-5.3	5.1 (0.1)	5.3	5.9 (0.6)
Postprandial capillary glucose	5.9	5.6 (0.2)	5.9-6.4	6.2 (0.2)	6.4	7.2 (0.7)
Mean capillary glucose	5.4	5.2 (0.2)	5.4-5.8	5.7 (0.1)	5.8	6.5 (0.6)

Tertile boundaries and Mean (SD) glycemia measures within each tertile. Glucose (mmol/L) and HbA1c (%) recorded to one decimal place.

Table 2: Outcomes by fasting, postprandial and overall mean glucose tertiles

Frequency of outcome (%)	Fasting tertiles				Postprandial tertiles				Mean glucose tertiles			
	1	2	3	P value*	1	2	3	P value*	1	2	3	P value*
Primary outcome components	22.9	32.5	39.6	<0.001	25.6	29.4	40.3	<0.001	23.0	31.1	41.4	<0.001
Recurrent glucose <2.6 mmol/l	10.4	18.3	21.3	0.002	13.0	17.7	19.3	0.07	11.7	15.3	23.2	<0.001
Respiratory distress	2.9	2.9	5.4	0.15	2.5	1.6	7.1	0.01	2.5	3.2	5.5	0.09
Phototherapy	5.4	8.1	10.8	0.03	7.1	6.9	10.5	0.18	5.4	9.7	9.3	0.13
Birth trauma	4.2	4.1	5.0	0.66	3.8	3.2	6.3	0.18	5.0	2.4	5.9	0.64
Apgar <7 at 5 minutes	0.4	0	0.8	0.48	0	0	1.3	0.03	0	0	1.3	0.03
Prematurity <37 weeks'	5.8	10.2	13.3	0.006	5.5	9.3	14.7	<0.001	5.9	10.5	13.1	0.008
Maternal preeclampsia	4.2	4.9	9.6	0.01	3.4	4.4	10.9	<0.001	3.4	5.2	10.1	0.002
Birth weight‡				<0.001†				<0.001†				<0.001†
<10 th (customised)	13.8	11.4	6.7	0.01	11.8	10.5	9.7	0.46	13.8	9.7	8.4	0.06
>90 th (customised)	12.1	11.4	24.6	<0.001	10.1	12.9	24.8	<0.001	10.5	13.3	24.1	<0.001
<2500g	5.0	6.5	5.0	1.0	2.9	6.5	7.1	0.045	4.6	6.5	5.5	0.672
>4000g	8.3	10.2	19.6	<0.001	6.7	13.3	17.7	<0.001	6.7	12.9	18.1	<0.001

* Cochrane-Armitage trend test

† Chi-square test of three levels of customized birth weight.

‡ Customised charts in general obstetric population with similar ethnicities to MiG population reported rate of SGA 12.1%-12.8% and LGA 8.4%-8.8% (www.adhb.govt.nz/nwhealthinfo)

Table 3: Bivariable analysis: Baseline characteristics, glucose measures at baseline and on treatment and their relationships to outcomes, including the primary outcome (a composite of neonatal outcomes – see text), preeclampsia, and customized small for gestational age (SGA) and large for gestational age (LGA)

		Primary outcome			Preeclampsia			Customised SGA and LGA				
		%	OR (95% CI)	P	%	OR (95% CI)	P	SGA (%)	OR (95% CI) *	LG A (%)	OR (95% CI) *	P
Baseline Characteristics												
Ethnicity												
European Caucasian/ mixed	373	34.6	1.00	0.03	5.1	1.00	0.004	8.0	1.00	15.6	1.00	0.001
Polynesian	156	35.9	1.06 (0.72-1.57)		12.2	2.59 (1.3-5.03)		9.0	1.26 (0.64-2.46)	23.1	1.67 (1.04-2.68)	
Asian/other	204	24.5	0.61 (0.42-0.90)		3.9	0.76 (0.3-1.77)		16.7	2.20 (1.29-3.73)	11.3	0.77 (0.46-1.30)	
BMI range (kg/m ²)												
<25	131	24.4	1.00	0.08	3.8	1.00	0.39	13.0	1.00	11.5	1.00	0.07
25-29	183	31.2	1.40 (0.84-2.32)		7.7	2.09 (0.7-5.95)		10.9	0.82 (0.41-1.65)	11.5	0.98 (0.48-1.99)	
≥30	419	34.8	1.65 (1.06-2.59)		6.4	1.74 (0.6-4.60)		9.8	0.80 (0.44-1.48)	19.3	1.80 (0.99-3.27)	
Adjusted BMI category *												
Normal	100	23.0	1.00	0.11	1.0	1.00	0.06	14.0	1.00	11.0	1.00	0.26
Overweight	210	32.9	1.64 (0.95-2.83)		9.1	9.85 (1.3-74.65)		11.4	0.82 (0.40-1.67)	13.8	1.26 (0.60-2.66)	
Obese	423	33.8	1.71 (1.03-2.84)		6.2	6.48 (0.87-48.36)		9.5	0.70 (0.36-1.35)	18.2	1.72 (0.87-3.39)	
Chronic hypertension												
No	675	31.3	1.00	0.12	5.5	1.00	0.004	10.2	1	16.4	1	0.28
Yes	58	41.4	1.55 (0.90-2.68)		15.5	3.17 (1.45-6.94)		15.5	1.5 (0.70-3.22)	10.3	0.62 (0.26-1.50)	
Nulliparity												
No	500	29.6	1.00	0.04	5.4	1.00	0.16	9.8	1.00	18.4	1.00	0.03
Yes	233	37.3	1.42 (1.02-1.97)		8.2	1.56 (0.85-2.86)		12.5	1.19 (0.73-1.94)	10.7	0.55 (0.34-0.88)	
Weight change (kg) from early pregnancy to recruitment	733		1.01 (0.98-1.04)	0.612		1.05 (1.01-1.10)	0.031		0.95 (0.90-0.99)		1.06 (1.02-1.09)	<0.001
<i>Past Obstetric History</i>												
Preeclampsia												
No	445	28.5	1.00	0.04	4.3	1.00	0.007	9.9	1	18.0	1	0.10
Yes	55	38.2	1.55 (0.87-2.77)		14.6	3.82 (1.58-9.19)		9.1	0.96 (0.36-2.57)	21.8	1.27 (0.63-2.54)	
Nulliparity	233	37.3	1.49 (1.07-2.09)		8.2	1.99 (1.03-3.84)		12.3	1.18 (0.72-1.96)	10.7	0.56 (0.35-0.91)	
Gestational hypertension												
No	440	28.9	1.00	0.07	3.9	1.00	<0.001	10.2	1	17.7	1	0.064
Yes	60	35.0	1.33 (0.75-2.35)		16.7	4.98 (2.16-11.46)		6.7	0.67 (0.23-1.96)	23.3	1.36 (0.71-2.60)	
Nulliparity	233	37.3	1.47 (1.05-2.06)		8.2	2.21 (1.13-4.34)		12.5	1.14 (0.69-1.88)	10.7	0.57 (0.35-0.92)	
Previous baby >4000g												
No	338	32.3	1.00	0.02	4.4	1.00	0.17	11.8	1.00	12.1	1.00	<0.001

Yes	162	24.1	0.67 (0.44-1.02)		7.4	1.72 (0.79-3.77)		5.6	0.57 (0.27-1.21)	31.5	3.13 (1.96-5.02)	
Nulliparity	233	37.3	1.25 (0.88-1.78)		8.2	1.91 (0.95-3.85)		12.5	1.04 (0.62-1.74)	10.7	0.88 (0.51-1.49)	
<i>Maternal 1° family history</i>												
Diabetes												
No	390	32.3	1	0.88	6.4	1	0.87	7.7	1.00	17.2	1.00	0.02
Yes	343	31.8	0.98 (0.72-1.33)		6.1	0.95 (0.52-1.73)		14.0	1.91 (1.18- 3.11)	14.6	0.89 (0.60- 1.34)	
Hypertension												
No	447	30.9	1	0.39	6.0	1	0.74	10.1	1.00	18.3	1.00	0.09
Yes	286	33.9	1.15 (0.84-1.58)		6.6	1.11 (0.60-2.03)		11.5	1.08 (0.67- 1.74)	12.2	0.63 (0.41- 0.97)	
Glycemia measures												
<i>At baseline (venous plasma)</i>												
75 g OGTT result at diagnosis												
fasting tertile 1	208	29.8	1.00	0.39	3.4	1.00	0.06	12.5	1.00	9.6	1.00	<0.001
fasting tertile 2	218	32.6	1.14 (0.75-1.72)		6.4	1.97 (0.78-4.98)		11.5	0.94 (0.52-1.69)	12.4	1.32 (0.71-2.44)	
fasting tertile 3	228	36.0	1.32 (0.89-1.98)		9.2	2.91 (1.21-7.00)		9.7	0.91 (0.49-1.67)	24.1	2.95 (1.69-5.15)	
2-hr tertile 1	206	30.1	1.00	0.09	4.4	1.00	0.19	7.3	1.00	15.5	1.00	0.10
2-hr tertile 2	213	28.6	0.93 (0.61-1.42)		5.6	1.31 (0.54-3.17)		12.7	1.81 (0.93-3.53)	13.2	0.88 (0.51-1.53)	
2-hr tertile 2	222	37.8	1.41 (0.95-2.12)		8.6	2.05 (0.91-4.64)		13.5	2.12 (1.10-4.10)	18.9	1.39 (0.83-2.32)	
Recruitment HbA1c												
tertile 1	223	31.8	1.00	0.73	4.5	1.00	0.04	9.9	1.00	8.1	1.00	0.004
tertile 2	227	28.6	0.86 (0.57-1.29)		4.0	0.88 (0.35-2.21)		11.5	1.32 (0.72-2.42)	16.3	2.29 (1.26-4.19)	
tertile 3	214	31.3	0.98 (0.65-1.46)		9.4	2.20 (1.00-4.81)		9.8	1.19 (0.63-2.25)	21.5	3.18 (1.77-5.72)	
<i>During treatment (capillary glucose)</i>												
Fasting means												
tertile 1	240	22.9	1.00	0.001	4.2	1.00	0.03	13.8	1.00	12.1	1.00	<0.001
tertile 2	246	32.5	1.62 (1.08-2.42)		4.9	1.18 (0.50-2.78)		11.4	0.80 (0.46-1.37)	11.4	0.91 (0.52-1.58)	
tertile 3	240	39.6	2.20 (1.48-3.28)		9.6	2.44 (1.13-5.24)		6.7	0.52 (0.28-0.99)	24.6	2.20 (1.34-3.59)	
Postprandial mean glucose												
tertile 1	238	25.6	1.00	0.002	3.4	1.00	0.002	11.8	1.00	10.1	1.00	<0.001
tertile 2	248	29.4	1.21 (0.81-1.80)		4.4	1.33 (0.53-3.38)		10.5	0.91 (0.51-1.61)	12.9	1.31 (0.74-2.30)	
tertile 3	238	40.3	1.96 (1.33-2.90)		10.9	3.53 (1.56-7.96)		9.7	0.98 (0.54-1.77)	24.8	2.93 (1.74-4.93)	
Overall mean glucose (fasting + post prandial)/2												
tertile 1	239	23.0	1.00	<0.001	3.4	1.00	0.01	13.8	1.00	10.5	1.00	<0.001
tertile 2	248	31.1	1.51 (1.01-2.26)		5.2	1.60 (0.65-3.93)		9.7	0.69 (0.39-1.21)	13.3	1.25 (0.72-2.19)	
tertile 3	237	41.4	2.36 (1.59-3.51)		10.1	3.25 (1.43-7.40)		8.4	0.69 (0.38-1.24)	24.1	2.60 (1.54-4.32)	

*BMI (kg/m²) adjusted for ethnicity; Normal: Polynesian: 20-25, European: 20-24, Indo-Asian/other: 18-23 Overweight: Polynesian ≥26-32, European ≥25-30, Indo-Asian/other >23-27.5. Obese: Polynesian >32, European >30, Indo-Asian/other >27.5

Table 4 - Multiple logistic regression model 2 - significant factors relating to outcomes

<i>Significant Variable</i>	<i>Adjusted Odds Ratio (95% CI)</i>	<i>P value</i>
Primary outcome composite		
Fasting capillary glucose on treatment		
tertile 1	1.00	<0.001
tertile 2	1.75 (1.17-2.63)	
tertile 3	2.66 (1.76-4.01)	
Nulliparity		
no	1.00	<0.001
yes	1.85 (1.30-2.65)	
Previous baby >4000g		
no	1.00	0.001
yes	0.58 (0.37-0.90)	
Preeclampsia		
Postprandial capillary glucose on treatment		
tertile 1	1.00	0.016
tertile 2	1.38 (0.53-3.49)	
tertile 3	3.14 (1.31-7.32)	
BMI category		
normal	1.00	0.036
overweight	8.48 (1.09-66.22)	
obese	4.31 (0.55-33.50)	
Weight gain (kg) early pregnancy to recruitment	1.06 (1.00-1.11)	0.034
Ethnicity category		
European/Caucasian/mixed	1.00	0.041
Polynesian	2.40 (1.12-5.12)	
Asian/other	0.86 (0.35-2.11)	
Chronic hypertension		
no	1.00	0.034
yes	2.69 (1.08-6.73)	
Previous gestational hypertension		
no	1.00	0.008
yes	3.26 (1.26-8.40)	
nulliparity	2.74 (1.32-5.70)	
SGA or LGA		
	<i>SGA</i>	<i>LGA</i>
	<i>Adjusted Odds Ratio (95% CI)</i>	<i>Adjusted Odds Ratio (95% CI)</i>
Postprandial capillary glucose on treatment		
tertile 1	1.00	1.00
tertile 2	0.89 (0.50-1.58)	1.30 (0.73-2.33)
tertile 3	0.98 (0.54-1.78)	2.82 (1.65-4.84)
Previous baby >4000g		
no	1.00	1.00
yes	0.60 (0.28-1.28)	3.00 (1.84-4.89)
nulliparity	1.20 (0.71-2.04)	0.84 (0.48-1.45)
Weight gain (kg) from early pregnancy to recruitment	0.94 (0.90-0.99)	1.05 (1.02-1.09)
Maternal 1° relative: diabetes		
no	1.00	1.00
yes	2.04 (1.24-3.34)	0.84 (0.54-1.28)

BMI range was included in the model to determine if there was any effect of BMI ≥ 30 kg/m². (Customized birth weights already adjust for maternal BMI between 20 kg/m² and 30 kg/m²).