

Predictors of Preeclampsia in Women in the Metformin in Gestational Diabetes (Mig) Study

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Abstract

Background: Gestational Diabetes Mellitus (GDM), maternal obesity and pregnancy weight gain are associated with an increased risk of developing Preeclampsia (PE). The aim of this study was to examine the predictors of PE in women commencing pharmacotherapy for GDM in the Metformin in Gestational diabetes trial.

Methods: Descriptive and logistic regression analyses examined the relationship between maternal enrolment characteristics and later development of PE.

Results: 46 (6.3%) of 703 women developed PE. At enrolment ((30 (SD3.2) weeks gestation), women who later developed PE had higher HbA1c (6.14% (95%CI 5.84, 6.45) vs. 5.73% (95%CI 5.67, 5.78), $P=0.003$), fasting triglycerides (2.93 mmol/L (95%CI 2.57, 3.29) vs. 2.55mmol/L (95%CI 2.47, 2.62), $P=0.03$) and blood pressure. Their infants were born 9 days earlier ($P<0.001$) but were otherwise not different. In univariate analysis, the strongest positive predictors for PE were Polynesian ethnicity (OR 2.75 (95%CI 1.48, 5.09), $P=0.001$), personal or family history of PE (OR 2.65 (95%CI 1.36, 5.16), $P=0.004$), maternal HbA1c (OR 1.96 (95%CI 1.35, 2.89), $P<0.001$), triglycerides (OR 1.45 (95%CI 1.07, 1.97), $P=0.002$), and weight gain from early pregnancy (OR 1.09 (95%CI 1.03, 1.17), $P=0.01$). HDL-C was a negative predictor of PE (OR 0.29 (95%CI 0.09, 0.94), $P=0.04$). Following adjustment for Polynesian ethnicity and personal or family history of PE, and when further adjusted for HbA1c or early pregnancy BMI, these variables remained significant.

Conclusion: Treatment allocation and BMI were not associated with risk of PE. Personal or family history of PE, Polynesian ethnicity, degree of hyperglycemia, maternal triglycerides and weight gain prior to treatment signal increased risk of subsequent PE in women needing pharmacotherapy for GDM.

Keywords: Gestational diabetes mellitus; Preeclampsia; Glucose; Lipids; Metformin; Pregnancy; Ethnicity

Background

Preeclampsia (PE) is associated with increased maternal and infant morbidity and mortality [1] and is often defined for research purposes by the presence of maternal hypertension and proteinuria with onset after 20 weeks gestation. It is associated with the development of short term morbidity, such as eclampsia, placental abruption and intrauterine growth restriction, and long term issues, including a higher rate of maternal hypertension, cardiac and renal disease later in life and long term hypertension for the infant [2-4].

Increased risk of PE has previously been related to maternal hyperglycemia, maternal obesity, and gestational weight gain amongst other factors. Recent studies suggest a relationship of PE frequency with ethnicity and in particular that Maori women may be at higher risk of PE [5-11].

The Metformin in Gestational diabetes (MiG) Trial was a randomized controlled trial of metformin compared with insulin for the treatment of women requiring pharmacotherapy for Gestational Diabetes (GDM) [12]. The rate of PE did not differ between treatment arms (Metformin 5.5%, Insulin 7.0%, $P=0.40$) and the participants were extremely well characterized clinically and biochemically. This offers the opportunity to examine the associations of PE in a multiethnic group of women, including a large proportion of women from Maori and Pacific Islander background.

The aim of this study was to assess what may predict the later development of PE in women commencing pharmacotherapy with insulin or metformin for the treatment of GDM.

Methods

The trial was approved by institutional review boards at each participating site, and all subjects gave written informed consent.

Ethnicity was self-defined. In this analysis, Polynesian ethnicity combines women of Maori and Pacific Islander background.

PE and Gestational Hypertension (GH) were defined by the Society of Obstetric Medicine of Australia and New Zealand guidelines [13]. Of 733 women in who completed the original MiG trial, thirty (4.1%) women had GH alone and were excluded from the analysis, giving 703 women in the current analyses. Data were collected of a personal history of Chronic Hypertension (CH), aspirin use and a personal or family history (in first or second degree relatives) of PE at their initial visit [12].

Laboratory analyses

Blood samples were collected from each woman after an overnight fast at enrolment (20-33 weeks gestation), and at 36 weeks gestation. Maternal spot urine Albumin: Creatine Ratio (ACR) was measured at enrolment. Cord blood was collected after ligation of the umbilical cord postpartum. All blood was collected in EDTA and plain tubes and processed within 10 minutes of collection or stored on ice for processing within 90 minutes. Aliquots were stored at -80°C for subsequent analysis. Plasma variables were measured as previously described [12].

Statistical analysis

Descriptive statistics include mean and 95% confidence interval (95%CI) for continuous variables and numbers and percentages for

categorical variables. Statistical analysis was performed using Kruskal-Wallis Test for continuous variables, and Pearson's Chi-Squared test for categorical variables. Correlation analyses were performed using Spearman's Correlation coefficient. Logistic regression analyses were performed for the outcome of PE diagnosis using only predictor variables measured at enrolment to the study. For each predictor, univariable relations were analysed, then Model I - the univariable relation adjusted for Polynesian ethnicity, and personal or family history of PE (1=yes). Model II included the variables in Model I as well as HbA1c at enrolment. Model III included the variables in Model I as well as Body Mass Index (BMI - kg/m²) in early pregnancy. Due to the lower numbers of women having data on HDL, LDL and total cholesterol, Model I was adjusted for Polynesian ethnicity (1=yes). Model II was adjusted for HbA1c at enrolment. Model III was adjusted for BMI in early pregnancy.

Backward regression modelling was undertaken, using the likelihood ratio, with the probability of the score statistic for entry of 0.05, and removal of 0.1. In this model, enrolment HbA1c, triglycerides, early pregnancy BMI, Polynesian ethnicity, nulliparity, personal or family history of PE, and maternal age were included in the initial model. HDL-C, despite being significantly associated with PE in the other models, was not included in the stepwise regression analysis, given that fewer women had this variable available (Table 1).

	Normotensive	PE	P
Maternal characteristics at enrolment			
Maternal Age (years)	32.9 (32.5-33.3)	31.44 (29.58-33.29)	0.12
Nulliparous n (%)	204 (31.3) [652]	20 (43.5)	0.09
Metformin treatment	330 (50.2)	20 (43.5)	0.78
Caucasian n (%)	319 (48.6)	18 (39.1)	0.02
Indian n (%)	89 (13.5)	4 (8.7)	
Polynesian n (%)	134 (20.4)	19 (41.3)	
Asian n (%)	86 (13.1)	4 (8.7)	
Other n (%)	29 (4.4)	1 (2.2)	
Tertiary education n (%)	292 (44.9)	17 (37.0)	0.30
Aspirin use in pregnancy	40 (6.1)	3 (6.5)	0.91
Personal history of chronic hypertension	48 (7.3)	9 (19.6)	0.003
Previous preeclampsia *	43 (9.2) [448]	8(30.8) [26]	<0.001
Family history of preeclampsia	58 (8.8)	8 (17.4)	0.05
Personal or family history of preeclampsia	93 (14.2)	14 (30.4)	0.003
Smoking in pregnancy n (%)	106 (16.1)	9 (19.6)	0.54
Gestational age at enrolment (weeks)	30.1 (29.8-30.3)	30.40 (29.62-31.18)	0.96
BMI in early pregnancy (kg/m ²)	31.89 (31.22-32.56) [535]	33.49 (30.74-36.23) [29]	0.22

Change in maternal weight from early pregnancy to randomization (kg)	6.50 (6.05-6.95) [533]	9.44 (6.53-12.37) [29]	0.10
Systolic BP at enrolment (mmHg)	112.0 (111.0-113.0) [641]	124.9 (121.0-128.7)	<0.001
Diastolic BP at enrolment (mmHg)	67.6 (66.9-68.3)	77.0 (74.4-79.7)	<0.001
Fasting glucose (mmol/L)	5.20 (5.12-5.28) [558]	5.76 (5.21-6.31) [35]	0.09
HbA1c (%)	5.73 (5.67-5.78) [598]	6.14 (5.84-6.45) [39]	0.003
Fasting triglycerides (mmol/L)	2.55 (2.47-2.62) [550]	2.93 (2.57-3.29) [37]	0.03
Fasting cholesterol (mmol/L)	6.07 (5.91-6.24) [342]	5.82 (5.22-6.42) [22]	0.37
Fasting HDL-cholesterol (mmol/L)	1.72 (1.67-1.76) [350]	1.53 (1.38-1.68) [22]	0.08
Fasting LDL-cholesterol (mmol/L)	3.21 (3.06-3.36) [342]	2.87 (2.38-3.36) [22]	0.25
Infant Characteristics			
Gestational age at delivery (days)	269.3 (268.6-270.0)	261.6 (258.4-264.8)	<0.001
Born less than 37 weeks n (%)	55 (8.4)	15 (32.6)	<0.001
Female n (%)	322 (49.0)	20 (43.5)	0.47
Adjusted birth weight centile (%) ***	54.10 (51.76-56.44)	52.44 (42.14-62.74)	0.82
<10th centile n (%)	68 (10.4)	8 (17.4)	0.14
APGAR 1 min **	9	9	0.44
APGAR 5 min **	9	10	0.37
Cord glucose (mmol/L)	4.73 (4.59-4.88) [417]	4.23 (3.69-4.77) [15]	0.23
Cord triglycerides (mmol/L)	0.41 (0.39-0.43) [419]	0.52 (0.36-0.68) [15]	0.11

Table 1: Comparison of demographic and pregnancy variables at enrolment between normotensive women and those with preeclampsia. Data is mean and 95% CI [n], and n= 657 for normotensive, and 46 for PE except where indicated, *in non-nulliparous women, **median, *** Adjusted birth weight centile [35].

We also undertook additional analyses comparing the clinical characteristics of three groups: normotensive, GH, PE. A logistic regression was performed for the outcome of PE or GH. As there were a greater number of outcomes, the models were able to accommodate a higher number of variables. For each association, univariable relations were analyzed, then Model I with each variable adjusted for nulliparity (yes=1), Polynesian ethnicity (1= yes), and personal or family history of PE (1=yes). Model II was each variable adjusted for the variables in Model I as well as for HbA1c at enrolment. Model III was each variable adjusted for the variables in Model I as well as BMI in early pregnancy.

Results

In the 703 women, who were enrolled at an average of 30 weeks gestation, 46 (6.5%) were diagnosed subsequently with PE; 6 (13.0%) delivered prior to 36 weeks gestation and 67.4% delivered after 37 weeks gestation. Maternal and infant characteristics of women who did not develop hypertensive complications compared with those who developed PE are seen in Table 1. At enrolment, women who went on to develop PE had higher systolic and diastolic blood pressure, higher HbA1c, and higher triglycerides. Ethnicity was different between the groups but maternal BMI, weight gain prior to randomization and smoking were not. The babies of women who developed PE were born

on average 8 days earlier (P<0.001) but were otherwise not different. There were no differences in cord blood metabolic parameters.

The strongest univariate positive predictors of the development of PE at commencement of pharmacotherapy were Polynesian ethnicity (OR 2.75 (95%CI 1.48,5.09), P=0.001), personal or family history of PE (OR 2.65 (95%CI 1.36, 5.16), P=0.004), HbA1c (OR 1.96 (95%CI 1.35, 2.89), P<0.001), fasting glucose (OR 1.48 (95%CI 1.15, 1.91), P=0.002), triglycerides (OR 1.45 (95%CI 1.07, 1.97), P=0.02), and weight gain from early pregnancy (OR 1.09 (95%CI 1.03, 1.17), P=0.01) (Table 2). Increasing maternal HDL-C was associated with lower odds of developing PE (OR 0.29 (95%CI 0.09, 0.94), P=0.04). No other ethnic group (Caucasian, Indian, Asian) was related to a diagnosis of PE (not shown).

Polynesian women had a higher early pregnancy BMI (37.2 kg/m², 95%CI 35.8, 38.6) than women of other ethnic groups ((Caucasian 33.3 kg/m² (95%CI 32.4, 34.3), Indian 26.8 kg/m² (95%CI 25.7, 27.8), Asian (25.9 kg/m² (95%CI 25.0, 26.8), other 32.6 kg/m² (29.9, 35.4), P<0.001). They also had higher enrolment fasting glucose (P<0.001) and HbA1c ((Polynesian 6.17% (95%CI 6.04, 6.30), Caucasian 5.52% (95%CI 5.46, 5.58), Indian 5.89% (95%CI 5.75, 6.03), Asian 5.80% (95%CI 5.66, 5.94), other 6.02% (95%CI 5.69, 6.34), P<0.001)). Triglycerides did not differ between ethnic groups at enrolment

(P=0.29). There was a trend to higher enrolment urinary albumin: creatinine ratio (ACR) in Polynesian women (mean ACR 4.00 mg/mmol (95%CI 1.90, 6.20), compared with the other ethnic groups (P=0.20) (Caucasian mean ACR 1.72 mg/mmol (95%CI 1.03, 2.40), Indian 1.40 mg/mmol (0.72, 2.08), Asian 2.05 mg/mmol (0.39, 3.71),

Other 0.95 mg/mmol (0.62, 1.23)). Polynesian women had a lower rate of CH than Caucasian women (Polynesian 11 (7.2%), Caucasian 39 (11.6%), Indian 6 (6.5%), Asian 0, and Other 1 (3.3%) P=0.01). There were no ethnic differences in rates of aspirin use (p=0.07), or personal or family history of PE (P=0.17).

	Univariate	P	Model I	P	Model II	P	Model III	P
	OR (95%CI)		OR (95%CI)		OR (95%CI)		OR (95%CI)	
Maternal Age (years)	0.95 (0.90-1.01)	0.07	0.96 (0.91-1.02)	0.15	0.97 (0.91-1.03)	0.29	0.97 (0.93-1.07)	0.92
Personal or family history PE	2.65 (1.36-5.16)	0.004	2.80 (1.43-5.51)	0.003	2.66 (1.28-5.57)	0.01	1.77 (0.73-4.33)	0.21
Polynesian Ethnicity	2.75 (1.48-5.09)	0.001	2.87 (1.54-5.35)	0.001	2.03 (0.98-4.22)	0.06	2.93 (1.26-6.85)	0.01
Nulliparity	1.69 (0.92-3.10)	0.09	2.66 (1.37-5.20)	0.004	2.61 (1.25-5.42)	0.01	2.35 (1.04-5.30)	0.04
Smoking	1.26 (0.59-2.70)	0.54	1.19 (0.55-2.58)	0.66	1.35 (0.58-3.11)	0.49	1.27 (0.49-3.26)	0.62
Metformin Therapy	0.76 (0.42-1.39)	0.38	0.78 (0.42-1.44)	0.42	0.93 (0.48-1.81)	0.83	0.87 (0.41-1.86)	0.72
Maternal BMI in early pregnancy (kg/m ²)	1.03 (0.98-1.07)	0.29	1.00 (0.95-1.06)	0.9	1.01 (0.96-1.07)	0.67	-	-
Weight gain from early pregnancy to enrolment (kg)	1.09 (1.03-1.17)	0.01	1.08 (1.02-1.15)	0.02	1.08 (1.00-1.15)	0.04	-	-
HbA1c (%)	1.96 (1.35-2.89)	<0.001	1.48 (1.08-2.04)	0.02	-	-	1.74 (1.05-2.87)	0.03
Fasting glucose (mmol/L)	1.48 (1.15-1.91)	0.002	1.71 (1.13-2.58)	0.01	-	-	1.60 (1.13-2.27)	0.01
Fasting triglycerides (mmol/L)	1.45 (1.07-1.97)	0.02	1.31 (1.00-1.72)	0.05	1.40 (1.01-1.95)	0.05	1.66 (1.14-2.42)	0.01
Fasting cholesterol (mmol/L)*	0.89 (0.66-1.20)	0.44	0.97 (0.70-1.33)	0.83	0.95 (0.69-1.30)	0.73	0.94 (0.68-1.31)	0.72
Fasting HDL-cholesterol (mmol/L) *	0.29 (0.09-0.94)	0.04	0.26 (0.08-0.86)	0.03	0.30 (0.09-0.94)	0.04	0.29 (0.08-1.09)	0.07
Fasting LDL-cholesterol (mmol/L) *	0.82 (0.57-1.17)	0.27	0.89 (0.62-1.28)	0.54	0.89 (0.61-1.30)	0.55	0.83 (0.55 - 1.24)	0.36

Table 2: Logistic regression for the outcome of preeclampsia diagnosis using variables at enrolment in study (i.e. the point women were started on pharmacotherapy for GDM), showing Univariate then adjusted models. These regressions include PE and normotensive women, but did not include those women with gestational hypertension in the cohort. For each association, univariable relations are presented in the first column. Model I is each variable adjusted for Polynesian ethnicity (1=yes) and personal or family history of preeclampsia (1=yes). Model II is each variable adjusted for the variables in Model I as well as HbA1c at enrolment. Model III is each variable adjusted for the variables in Model I as well as BMI in early pregnancy. *Due to the lower numbers in these variables, Model I is each variable adjusted for Polynesian ethnicity (1=yes). Model II is adjusted for HbA1c at enrolment. Model III is adjusted for BMI in early pregnancy.

Rates of smoking during pregnancy also differed between ethnicities: 22.6% Caucasian, 17.6% Polynesian, 3.2% Indian, 5.6% Asian and 13.3% women of Other ethnicity were smoking during pregnancy (P<0.001). Smoking during pregnancy was not a predictor in univariate analysis (OR 1.26 (95%CI 0.59, 2.70), P=0.54) and remained non-significant under all models.

The adjusted models are also shown in table 2. Both HbA1c and fasting glucose at enrolment were significant predictors. However, they were moderately correlated (Spearman's rho=0.47, P=0.001) and so only HbA1c has been adjusted for in the regression models and included in the backward regression. The associations of maternal HbA1c, fasting glucose, weight gain from early pregnancy and triglycerides at enrolment were unchanged under the adjusted models. The relationship between lower maternal HDL-C and PE remained

robust, even after adjustment for Polynesian ethnicity, HbA1c or early pregnancy BMI.

While the mean gestation of enrolment in the MiG trial was 30 weeks, randomization was stratified by gestation 20-27 weeks and 28-33 weeks, in case duration of treatment influenced outcomes differently between treatment arms. There were 135 women randomized between 20-27 weeks, of which 128 are included in this analysis (after excluding 7 women with GH). In this group, 7/128 (5.4%) developed PE vs. 39/575 (6.8%) of those randomized after 27 weeks (P=0.59). Treatment duration (as measured by gestation at enrolment in the study) was not a predictor for PE, either as a continuous variable which showed no relation to the outcome of PE (OR 1.03 (95%CI 0.94, 1.14), P=0.52) or as a categorical variable assessing those enrolled prior to 28 weeks gestation (OR 0.78 (95%CI

0.35, 1.82), P=0.59). An examination of treatment allocation showed that 20/330 (6.1%) of women allocated metformin and 26/327 (7.8%) of women allocated insulin developed PE (P=0.38). Of those who were randomized early, 1/65 (1.5%) of women allocated metformin and 6/63 (9.5%) of women allocated insulin developed PE (P=0.05). However, there was no association of PE with treatment allocation under any of the regression models.

The backward logistic regression analysis for the outcome of PE found a combination of HbA1c (OR 1.80 (95%CI 1.06, 3.04), P=0.03), triglycerides (OR 1.58 (95%CI 1.08, 2.32), P=0.02) and Polynesian ethnicity (OR 3.17 (95%CI 1.20, 8.36), P=0.02) was the most predictive of the development of PE.

We also examined differences between normotensive women, those with GH, and those with PE (Supplementary Table 1). A logistic regression was performed for the outcome of PE or GH. As there were a greater number of outcomes, the models were able to accommodate a higher number of variables. There were minor differences in the results of these logistic regressions, compared with those performed with PE alone as an outcome. Weight gain and triglycerides became non-significant in model II, but there was little other variation in the significance of odds ratios (Supplementary Table 2).

	Normotensive (n=657)	GH (n=30)	PE (n=46)	P
Maternal characteristics				
Maternal Age (years)	32.9 (32.5-33.3)	31.9 (29.5-34.2)	31.44 (29.58-33.29)	0.24
Nulliparous n (%)	204 (31.3) [652]	13 (43.3)	20 (43.5)	0.10
Metformin Treatment n (%)	330 (50.2)	20 (43.5)	13 (43.3)	0.53
Caucasian n (%)	319 (48.6)	20 (66.7)	18 (39.1)	0.03
Indian n (%)	89 (13.5)	3 (10.0)	4 (8.7)	
Polynesian n (%)	134 (20.4)	6 (20.0)	19 (41.3)	
Asian n (%)	86 (13.1)	1 (3.3)	4 (8.7)	
Other n (%)	29 (4.4)	0	1 (2.2)	
Tertiary education n (%)	292 (44.9)	14 (46.7)	17 (37.0)	0.56
Smoking in pregnancy n (%)	106 (16.1)	6 (20.0)	9 (19.6)	0.73
Gestational age at enrolment (weeks)	30.1 (29.8-30.3)	30.5 (29.5-31.5)	30.40 (29.62-31.18)	0.93
BMI at enrolment (kg/m ²)	34.60 (34.02-35.18) [656]	36.83 (33.89-39.77)	36.24 (34.02-38.46)	0.14
Maternal weight change from early pregnancy to enrolment	6.50 (6.05-6.95) [533]	9.45 (6.53-12.37) [29]	9.44 (6.53-12.37) [29]	0.15
Systolic BP (mmHg)	112.0 (111.0-113.0) [641]	122.3 (117.9-126.8)	124.9 (121.0-128.7)	<0.001
Diastolic BP (mmHg)	67.6 (66.9-68.3)	73.9 (70.3-77.4)	77.0 (74.4-79.7)	<0.001
Fasting glucose (mmol/L)	5.20 (5.12-5.28) [558]	5.40 (4.85-5.96) [25]	5.76 (1.61) [35]	0.20
HbA1c (%)	5.73 (5.67-5.78) [598]	5.86 (5.54-6.18) [27]	6.14 (0.94) [39]	0.01
Fasting triglycerides (mmol/L)	2.55 (2.47-2.62) [550]	2.92 (2.26-3.58) [21]	2.93 (2.57-3.29) [37]	0.05
Fasting cholesterol (mmol/L)	6.07 (5.91-6.24) [342]	5.80 (4.94-6.66) [16]	5.82 (5.22-6.42) [22]	0.34
Fasting HDL-cholesterol (mmol/L)	1.72 (1.67-1.76) [350]	1.66 (1.49-1.83) [16]	1.53 (1.38-1.68) [22]	0.18
Fasting LDL-cholesterol (mmol/L)	3.21 (3.06-3.36) [342]	2.77 (1.93-3.61) [14]	2.87 (2.38-3.36) [22]	0.16
Infant characteristics				
Gestational age at delivery (days)	269.3 (268.6-270.0)	270.0 (267.0-273.1)	261.6 (258.4-264.8)	<0.001
Female gender n (%)	322 (49.0)	13 (43.3)	20 (43.5)	0.65
Birth weight centile (%)	54.10 (51.76-56.44)	49.25 (39.15-59.35)	52.44 (42.14-62.74)	0.66
<10th centile n (%)	68 (10.4)	2 (6.7)	8 (17.4)	0.25

APGAR 1 min **	9	9	9	0.28
APGAR 5 min **	9	10	10	0.23
Cord glucose (mmol/L)	4.73 (4.59-4.88) [417]	4.33 (3.83-4.83) [19]	4.23 (3.69-4.77) [15]	0.24
Cord triglycerides (mmol/L)	0.41 (0.39-0.43) [419]	0.45 (0.35-0.56) [19]	0.52 (0.36-0.68) [15]	0.16

Supplementary Table 1: Comparison of demographic and pregnancy variables at enrolment between women with normotension, gestational hypertension or preeclampsia diagnosis. [n], Data is mean and 95% CI and n= 657 for normotensive, 30 for GH and 46 for PE except where indicated ** median

	Univariate	P	Model I	P	Model II	P	Model III	P
	OR (95%CI)		OR (95%CI)		OR (95%CI)		OR (95%CI)	
Maternal Age (years)	0.96 (0.91-1.00)	0.05	0.97 (0.92-1.03)	0.3	0.98 (0.92-1.05)	0.54	1.01 (0.94-1.06)	0.88
Nulliparity	1.69 (1.04-2.73)	0.03	2.66 (1.37-5.20)	0.004	2.61 (1.25-5.42)	0.01	2.35 (1.04-5.30)	0.04
Personal or family history of PE	2.65 (1.36-5.16)	0.004	3.11 (1.56-6.19)	0.001	2.83 (1.34-5.97)	0.006	1.90 (0.77-4.67)	0.16
Polynesian Ethnicity	2.75 (1.48-5.09)	0.001	3.87 (1.97-7.60)	<0.001	2.78 (1.27-6.10)	0.01	3.73 (1.53-9.10)	0.004
Smoking	1.28 (0.70-2.33)	0.42	1.12 (0.51-2.43)	0.78	1.29 (0.56-3.00)	0.55	1.19 (0.46-3.08)	0.72
Metformin Therapy	0.76 (0.47-1.23)	0.26	0.78 (0.42-1.44)	0.42	0.94 (0.48-1.84)	0.85	0.87 (0.40-1.86)	0.71
Maternal BMI in early pregnancy (kg/m ²)	1.03 (0.99-1.07)	0.1	1.01 (0.95-1.06)	0.86	1.01 (0.96-1.07)	0.05	-	-
Weight gain from early pregnancy to enrolment (kg)	1.07 (1.01-1.12)	0.01	1.08 (1.01-1.15)	0.03	1.07 (0.99-1.15)	0.07	-	-
HbA1c (%)	1.69 (1.23-2.32)	0.01	1.72 (1.14-2.61)	0.01	-	-	1.72 (1.04-2.84)	0.04
Fasting glucose (mmol/L)	1.36 (1.10-1.69)	0.04	1.30 (0.98-1.71)	0.07	-	-	1.56 (1.10-2.20)	0.01
Fasting triglycerides (mmol/L)	1.43 (1.12-1.83)	0.04	1.43 (1.04-1.98)	0.03	1.36 (0.98-1.89)	0.07	1.60 (1.09-2.33)	0.02
Fasting cholesterol (mmol/L)	0.89 (0.70-1.12)	0.31	0.97 (0.71-1.34)	0.86	1.00 (0.72-1.38)	0.98	1.02 (0.72-1.45)	0.89
Fasting HDL-cholesterol (mmol/L)	0.42 (0.17-1.02)	0.06	0.26 (0.08-0.89)	0.03	0.28 (0.08-0.92)	0.04	0.24 (0.06-0.96)	0.04
Fasting LDL-cholesterol (mmol/L)	0.80 (0.60-1.07)	0.13	0.91 (0.64-1.29)	0.58	0.94 (0.65-1.35)	0.73	0.89 (0.60-1.33)	0.58

Supplementary Table 2: Logistic regression for the outcome of preeclampsia OR gestational hypertension diagnosis using variables at enrolment in study (ie the point women were started on pharmacotherapy for GDM). Showing Univariate then adjusted models. For each association, univariable relations are presented in the first column. Model I is each variable adjusted for nulliparity (yes=1), Polynesian ethnicity (1= yes), and personal or family history of preeclampsia (1=yes). Model II is each variable adjusted for the variables in Model I as well as HbA1c at enrolment. Model III is each variable adjusted for the variables in Model I as well as BMI in early pregnancy.

Discussion

The current analyses demonstrate that, in women requiring pharmacotherapy in addition to lifestyle treatment for the treatment of GDM, a subsequent diagnosis of PE is most strongly predicted by Polynesian ethnicity, a family or personal history of PE, maternal glycaemia as reflected in HbA1c, maternal triglycerides and weight gain from early pregnancy. There was no association of PE with treatment allocation.

The strength of the current study is that the MiG trial participants were carefully phenotyped, both metabolically and clinically. There was no difference in rates of PE between the two treatment arms, allowing the data to be amalgamated here to analyse the predictors of PE. The rate of PE we report (6.5%) is similar to but slightly higher than that seen in a recent population-based study of PE in New Zealand (5.6%), which included normoglycaemic women as well as those with pre-gestational diabetes and GDM, but similar to other studies of GDM. If we include the 30 women with GH, the rate of PE

in the whole cohort is 6.28% [11]. The majority (67.4%) of the women with PE in our study delivered after 37 weeks gestation, consistent with late onset rather than early onset PE. The limitation of the current study is the low number of PE events, which meant that there was a limit to the number of variables that could be included in each model [14]. While it is a post-hoc analysis, the participants in MiG were extremely well characterised and the MiG trial has offered a unique opportunity to examine the predictors of PE at a point in time when women need pharmacotherapy, rather than examining parameters at diagnosis of GDM or at the end of pregnancy.

Maori ethnicity has previously been associated with higher rates of PE although a cautionary note about higher serum uric acid concentrations in this ethnic group has been raised that may make interpretation difficult [11,14,15]. In the current study, hyperuricemia was not included in the diagnostic criteria for PE, making it unlikely that there was a higher rate of PE diagnosis in Polynesian women due to this. Rates of PE do vary with ethnicity, with previous studies showing lower rates of PE in Chinese women (1.91%) and African-American women being at higher risk, while Hispanic women have similar rates but better clinical outcomes than Caucasian women. Healthy middle aged Polynesian people have previously been shown to have higher rates of microalbuminuria and increased urinary protein forms part of the diagnostic criteria for PE. In the current study, Polynesian women had marginally higher urine albumin: creatinine ratio on enrolment but this was not different from the other ethnic groups [8-10,16]. It could be postulated that higher early pregnancy BMI and higher fasting glucose at enrolment underlie the influence of Polynesian ethnicity. However, the strong relationship with Polynesian ethnicity remained once enrolment HbA1c and early pregnancy BMI were adjusted for in the modelling. Of course, it is possible that subsequent glucose control influenced baseline predictors. We have shown previously that there were no ethnic differences in change of maternal HbA1c from enrolment to 36 weeks, although HbA1c remained higher in Polynesian women overall [17]. We have also shown that glucose control on treatment is a predictor for PE, particularly post prandial glucose [18]. Whether Polynesian women have higher postprandial glucose fluctuations before and after treatment that might relate to their risk, or whether there are other ethnic specific factors, will require further study.

Maternal obesity is an established predictor of PE in women with and without GDM [6]. The HAPO (Hyperglycaemia and Averse Pregnancy Outcome) study analysis reported that the diagnosis of GDM and maternal obesity were independent but additive risk factors for PE (GDM: OR 1.74, Obesity: OR 3.91, Both OR 5.98) [19]. An observational study of 2037 women with GDM found that pre-pregnancy maternal obesity was much more strongly associated with pregnancy-induced hypertensive disorders (OR 8.94 (95%CI 4.98, 16.04) than excess gestational weight gain (OR 1.91 (95%CI 1.08, 3.37) [20]. A relationship with obesity was not observed in the current study. This may be due to the mean BMI in the MiG cohort being in the obese range, giving a smaller range in maternal BMI than seen in other studies, or perhaps to the fact that all women in this cohort received treatment for GDM, which is known to reduce rates of PE [21,22].

In the current study, maternal weight gain up to the initiation of pharmacotherapy was a weak predictor of PE, and maternal early pregnancy BMI was not associated with PE. The ATLANTIC-DIP study recently reported that excessive weight gain was associated with greater odds of developing GH in 543 women with GDM (OR 1.72

(95%CI 1.04, 2.85)) [7]. The association of gestational weight gain and PE is not universally reported. A prospective cohort of 435 women with either type 2 diabetes mellitus or GDM showed no association of gestational weight gain with a composite outcome including PE, eclampsia, third and fourth degree perineal lacerations, read mission and wound infection [23]. The weak relationship of maternal weight gain with PE found in the current study may be due to subsequent treatment, which may alter later pregnancy weight gain, or to the influence that weight gain may have on glycaemia in late pregnancy.

Maternal lipid abnormalities are frequently described to precede and accompany PE. Abnormal lipids, in particular higher triglycerides and increased lipid peroxidation, are possibly involved in the pathogenesis of PE through endothelial dysfunction [24-26]. A meta-analysis of 19 case-control and 3 cohort studies showed a rising risk of PE with increasing triglycerides, at the time of PE, preceding PE diagnosis and postpartum [27]. A large retrospective database study of 9911 women found an association between an increase in triglycerides and a higher risk of PE, but did not find any association between HDL-C and PE [28]. An observational study of 470 normoglycemic women showed higher triglycerides, but similar HDL-C, LDL-C and total cholesterol at 28-32 weeks gestation in women who developed PE [29]. The positive association of maternal triglycerides and PE we found in our analyses is in keeping with these studies. This finding is not universal, with one study examining 184 women with GDM, and using metabolic measures taken at ~28 weeks gestation and prior to therapy for GDM, found no difference in maternal lipids (including triglycerides and HDL-C) and no association with the development of PE [30]. The negative association of HDL-C and PE we demonstrate has been reported previously [25,26], but the size of the effect does need to be interpreted with some caution since fewer women in our study had HDL-C measured. Metformin treatment has been shown to be associated with reduced rates of PE, when used from early gestation in women with polycystic ovarian syndrome [31]. However, this finding is not universal and other studies in PCOS, type 2 diabetes mellitus and GDM have not reported the same association [32-34]. The MiG trial, from which these data are taken, did not find any difference in rates of PE in women allocated to metformin compared with those allocated to insulin for treatment of GDM, and the two groups did not differ in glycemic control attained [12]. It is possible that the reduction in PE rates seen with the use of metformin in some studies is due to the metabolic control obtained, rather than to another, more direct, effect of the drug.

Conclusion

In a multiethnic cohort of Australasian women requiring pharmacotherapy in addition to lifestyle treatment for the treatment of GDM, development of PE is most strongly predicted by Polynesian ethnicity, a personal or family history of PE, longer duration of hyperglycemia and/or higher maternal fasting glucose at diagnosis, maternal triglycerides as well as weight gain from early pregnancy. The association of Polynesian ethnicity with PE requires further exploration.

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