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Use of metformin earlier in pregnancy predicts supplemental insulin therapy in women with gestational diabetes

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ABSTRACT

The use of metformin in gestational diabetes is safe and effective, yet some women require additional insulin therapy to achieve glycaemic targets. We found a significant association between earlier gestational age at initiation of metformin therapy and the necessity for supplemental insulin in women treated with metformin during pregnancy.

1. Introduction

The standard treatment for gestational diabetes mellitus (GDM) is lifestyle modification through dietary manipulation and exercise counselling, followed by pharmacologic therapy if target blood glucose levels are not met [1]. Several studies have found that metformin, the first line oral anti-hyperglycaemic agent for type 2 diabetes (T2D), is equivalent to insulin at achieving satisfactory glycaemic control in GDM and reducing the risk of adverse perinatal outcomes [2,3]. However, in a proportion of women, despite metformin therapy, supplementary insulin is required to achieve desirable blood glucose levels [4]. The factors that predict the requirement of subsequent insulin therapy are unclear. Thus, the aim of this study was to examine the predictors of supplemental insulin therapy in a cohort of women with GDM treated with metformin for glycaemic control.

2. Methods

A retrospective, cohort study was carried out by reviewing the medical records of women with GDM who attended Royal

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North Shore Hospital, Sydney, between the years of 2012–2015. The metformin group comprised women with GDM whose blood glucose levels were adequately controlled with metformin alone, whereas the metformin–insulin group included women requiring additional insulin therapy to achieve glycaemic targets. Approval for this study was obtained from the NSLHD Human Research Ethics Committee. The primary outcome was to identify the differences between women with GDM that were managed with metformin alone versus those requiring insulin in addition to metformin. We further assessed perinatal outcomes. Differences between groups were compared using student's independent *t*-test or chi-square test and logistic regression was used to determine the association between individual maternal factors and insulin use. Statistical analyses were carried out using GraphPad Prism V6 and IBM SPSS V22. A p value of <0.05 was considered statistically significant.

3. Results

Between the years of 2012–2015, 98 women were identified as taking metformin during pregnancy. Several women were excluded from the study due to a pre-existing diagnosis of T2D (n = 16), one patient had steroid-induced hyperglycaemia and six women were taking metformin pre-pregnancy for polycystic ovarian syndrome or insulin resistance. There was insufficient data on the treatment of GDM in the records of ten women. In addition, two women received insulin in pregnancy prior to metformin, leaving a total of 63 women fulfilling the criteria for inclusion in the present study. The proportion of women taking metformin that required supplemental insulin therapy was 53.9%, which is similar to that observed by Rowan et al. [4]. Thus, the study population comprised 29 women (46%) in the metformin group and 34 (54%) in the metformin–insulin group.

The predominant reason for women requiring additional insulin therapy was elevated fasting blood glucose levels (n = 22; 64.7%; Supplementary Table 1) and there was a trend towards fasting hyperglycaemia being predictive of women that would fail metformin monotherapy (p = 0.097; Table 1). For women that required treatment with supplemental insulin, the average time between commencement of metformin and introduction of insulin was 29 ± 22 days. In addition, 35% of women ceased metformin therapy when insulin was initiated, due to a lack of benefit (66%) or gastrointestinal side effects (33%). The total daily dose of insulin was similar for women that ceased or continued metformin (26.5 ± 22.6 vs. 19.7 ± 14.2 units; p = 0.349).

There was no significant difference in maternal age, BMI (recorded at the first antenatal visit), history of GDM or family history of diabetes between groups (Table 1). However, with the exclusion of one woman with a BMI > 60 kg/m^2 (greater than 4 standard deviations above the mean) in the metformin group, the difference in maternal BMI was highly significant (p = 0.003). Fasting and 2-h plasma glucose at OGTT, gestational age and HbA1c at diagnosis of GDM were similar for women managed with metformin alone or metformin and insulin. Conversely, women requiring additional therapy with insulin started taking metformin earlier in pregnancy (25.3 ± 5.8 vs. 28.9 ± 4.9 weeks; p = 0.009; Table 1). When the data were adjusted for maternal age, BMI, previous GDM, family history of diabetes and gestation at diagnosis of GDM, gestational age at initiation of metformin therapy remained significantly associated with supplemental insulin (p = 0.02). Of note, the gestational age at which insulin was initiated as first-line therapy (in women with GDM matched to the metformin and metformin–insulin groups for age, gestational age at diagnosis of GDM and previous history of GDM) was 28 ± 5.4 weeks, which was similar to when metformin was started in the metformin group and significantly later than metformin commencement in the metformin–insulin group (p = 0.019). This further suggests that women requiring earlier pharmacologic intervention in pregnancy will require escalation of therapy.

Birth weight and gestational age at delivery were similar between the metformin and metformin–insulin groups (Table 2). The incidence of large for gestational age neonates was higher in the metformin–insulin group (26.5% vs. 6.9%; p = 0.042), however this effect lost significance when the data were adjusted for maternal BMI. There was no significant difference in other adverse perinatal outcomes between groups.

Table 1 – Characteristics and demographics of women with GDM treated with metformin alone or metformin and supplemental insulin. Blood glucose levels (BGL) were assessed by review of 4-point self-monitoring of blood glucose profiles.

	Metformin alone (n = 29)	Metformin–insulin (n = 34)	p
Maternal age (years)	32.9 ± 4.6	32.8 ± 5.3	0.976
History of GDM	17.2% (n = 5)	11.8% (n = 4)	0.568
Family history of DM	48.3% (n = 14)	44.1% (n = 15)	0.824
Early pregnancy BMI (kg/m^2)	25.9 ± 8.3	30.0 ± 7.8	0.061
Gestation at diagnosis of GDM (weeks)	24 ± 6	23 ± 6	0.219
Gestation at metformin initiation (weeks)	28.9 ± 4.9	25.3 ± 5.8	0.009
Time between metformin and insulin therapy (days)	–	29 ± 22	–
HbA1c at diagnosis of GDM (%)	5.0 ± 0.3	5.2 ± 0.4	0.078
Fasting plasma glucose at OGTT (mmol/L)	4.8 ± 0.6	4.9 ± 0.6	0.492
2-h plasma glucose at OGTT (mmol/L)	8.5 ± 1.4	8.3 ± 1.4	0.551
Elevated fasting BGL at metformin initiation	21.4% (n = 7)	44.1% (n = 15)	0.097
Elevated post-prandial BGL at metformin initiation	13.8% (n = 4)	11.8% (n = 4)	0.810
Elevated fasting & post-prandial BGL at metformin initiation	62.1% (n = 18)	44.1% (n = 15)	0.155