Pregnancy outcomes after metformin treatment for gestational diabetes: a case-control study

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Summary

Background: There is increasing evidence that metformin is safe and effective in the treatment of gestational diabetes (GDM), although it has not yet been widely accepted for routine practice. We compared pregnancy outcomes in women with gestational GDM treated with metformin or dietary measures alone.

Methods: Women with GDM (324) not adequately controlled by diet received metformin according to protocol based on their home glucose results. Pregnancy outcomes in these women were compared with 175 GDM women treated with diet alone and matched for age and ethnicity.

Results: The percentage of macrosomic babies (birth weight [BW] centile >90th centile) and small for gestational age (SGA) (BW <10th centile) in the metformin group was significantly reduced compared with the diet group (12.7% versus 20%; $P < 0.05$ [macrosomia]; 7.7% versus 14.3% [SGA] $P < 0.05$).

Conclusions: Metformin treatment had a favourable impact on the rates of macrosomia and SGA despite more severe glucose intolerance at baseline.

Keywords: macrosomia, gestational diabetes, metformin, pregnancy

INTRODUCTION

In recent years, it has become clear that even mild degrees of glucose intolerance in pregnancy are associated with adverse outcomes.¹ The benefits of treatment for gestational diabetes (GDM) are now well established.^{2,3} Not only are complications for the neonate reduced by treatment, but also long-term obesity and diabetes in the offspring may be decreased.⁴

Traditionally, treatment has been based on dietary measures with strict glucose targets before and after meals. When these targets are exceeded, insulin is widely recommended. While effective, insulin has the disadvantages of needing to be injected, the risk of hypoglycaemia, excessive weight gain and high costs associated with health professional time as well as the cost of the drug.

Metformin is emerging as a safe alternative to insulin in GDM and has been included by National Institute for Health and Clinical Excellence (2008) as a treatment option in GDM, albeit unlicensed.^{5,6} We have previously reported favourable pregnancy outcomes in GDM women treated with metformin compared with an age, weight and ethnicity-matched group of insulin-treated women managed according to the same care pathway.⁷ We now extend this study by comparing

maternal and neonatal outcomes in a large cohort of metformin-treated GDM women with a group of exclusively diet-managed GDM women with milder carbohydrate intolerance at baseline and managed according to our GDM protocol.

METHODS

Women diagnosed with GDM were recruited into the study. GDM was defined as one or more values following a 75 g glucose load; plasma glucose >6 mmol/L, two hours glucose >7.8 mmol/L in line with WHO criteria and including impaired fasting glycaemia.⁸ Women with a history of GDM in previous pregnancies were also eligible to participate.

At the outset, all patients received individualized dietary advice from a specialist dietician taking into account the patient's weight, activity level and desired weight gain. They were taught home blood glucose monitoring by the diabetes specialist nurse and advised to self-monitor four times daily. Patients with three or more tests higher than target values (fasting >5.6 mmol/L, 1 hour postprandial >8 mmol/L, 2 hours postprandial >7 mmol/L) within a two-week period were considered to have inadequate glycaemic control. The treatment options of metformin and insulin were discussed with the patients. Metformin is contraindicated in renal (estimated glomerular filtration rate (eGFR) < 30 mL/minutes) or liver impairment, in hyperemesis gravidarum and where fetal growth is <10th centile. An information sheet on metformin

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was given to all patients. Patients who consented to take metformin were started on 500 mg twice daily with meals and the dose gradually titrated up to a maximum of 3 g daily according to the results of home glucose monitoring.

All women were managed according to a well-established care pathway in the joint antenatal diabetic clinic aiming for a vaginal delivery at term.⁹ According to this protocol, metformin is withdrawn in the presence of fetal growth restriction defined as fetal weight <10th centile, oligohydramnios amniotic fluid index <2 cm or reduced end diastolic flow in the umbilical artery.

Maternal (pre-eclampsia, gestational hypertension) and neonatal outcomes (congenital anomalies, shoulder dystocia, prematurity [<37 weeks gestation], birth weight, birth weight centile for gestational age,¹⁰ neonatal jaundice requiring phototherapy, hypoglycaemia [glucose <2.6 mmol/L] and respiratory distress needing respiratory support) were recorded for all patients.

We compared pregnancy outcomes in women managed exclusively by dietary and lifestyle measures with women requiring metformin in addition to diet and lifestyle advice. In addition, we compared outcomes in the metformin-treated women in our series with those reported in the seminal MiG study.⁵

ANALYSIS

Comparisons between groups were made using unpaired Student's *t*-test for normally distributed data and Fisher's exact or chi-squared tests for categorical data. Two-tailed tests were used for all analyses and statistical significance taken as $P < 0.05$. Continuous results were expressed as mean and standard deviation or median and range according to data distribution. Categorical data are presented as proportions.

RESULTS

Of 352 women identified as suitable for metformin, 10 declined the treatment after further discussion, and in 14 women metformin was withdrawn due to intolerance. In three patients, metformin was started at 29 weeks and then withdrawn one week later as the growth scan at 30 weeks showed babies at 10–15th centile. In one patient, metformin was initiated but stopped a few days later because the patient developed obstetric cholestasis. The latter four patients were excluded because their exposure to metformin was very limited (1 week or less) and too brief to have influenced outcome. The results presented are for the 324 women who took metformin to term either alone (286) or with supplemental insulin (38).

Baseline characteristics of women in the diet and metformin groups are shown in Table 1. The groups were similar in mean age, ethnic mix and history of previous GDM. Patients in the metformin group had greater body mass index (BMI), were more likely to have a family history of diabetes, and had significantly greater fasting and two-hour values during glucose tolerance testing at 28 weeks screening.

Maternal outcomes are shown in Table 2. Compared with women managed with diet alone, women receiving metformin were more likely to have an induced labour or planned caesarean section. Postpartum, glucose tolerance was more likely to be abnormal in the metformin-treated women.

Perinatal outcomes in the two groups are shown in Table 3. Mean birth weight and mean birth centile were lower in metformin-treated patients although this failed to reach

Table 1 Baseline maternal characteristics

	Metformin group (<i>n</i> = 324)	Diet group (<i>n</i> = 175)	Significance
Mean age (years)	33.4 $\pm$ 5.4	32.4 $\pm$ 5.3	NS
Ethnicity, <i>n</i> (%)			
Caucasians	181 (55.9)	100 (57.1)	NS
Asians	115 (35.5)	62 (35.4)	NS
Africans	28 (8.6)	13 (7.5)	NS
HbA1c on entry	5.6 $\pm$ 0.6	5.4 $\pm$ 0.5	$P < 0.01$
Early pregnancy BMI (kg/m ²)	30.2 $\pm$ 7.1	27.2 $\pm$ 5.8	$P < 0.01$
Family history of diabetes (%)	131 (40.4)	42 (24)	$P < 0.01$
Previous gestational diabetes (%)	72 (22.2)	34 (19.4)	NS

BMI, body mass index; HbA1c, glycosylated haemoglobin; NS, non-significant

statistical significance. The proportion of large for gestational age (LGA) babies (birth centile >90 th centile) or small for gestational age (SGA) babies (birth centile <10 th centile) was significantly lower in the metformin group. No significant difference was noted in the proportion of babies with congenital abnormalities, hypoglycaemia, shoulder dystocia, respiratory distress or requiring admission to the neonatal unit among the two groups. More babies of metformin-treated mothers required ultraviolet therapy for neonatal jaundice.

We further compared neonatal outcomes in obese and non-obese women within the metformin group (Table 4). Mean birth weight and numbers of babies >4000 g were significantly higher in the obese women.

Compared with metformin-treated participants in the MiG study, the metformin cohort in this study were of different ethnic mix, had lower mean BMI and lower glucose values during the 28 week screening glucose tolerance test (Table 5). The development of gestational hypertension during pregnancy was similar although pre-eclampsia was less frequent in our study cohort in comparison with the MiG cohort (Table 6). In all, 13.3% of metformin GDM mothers required additional insulin compared with 46.3% in the MiG trial.

Table 2 Maternal pregnancy outcomes

	Metformin group (<i>n</i> = 324)	Diet group (<i>n</i> = 175)	Significance
Pre-eclampsia (%)	5 (1.5)	3 (1.7)	NS
Induction of labour (%)	84 (25.9)	31 (17.7)	$P < 0.01$
Caesarean delivery (%)			
Total	134 (41.4)	56 (32)	$P < 0.05$
Elective	65 (20.1)	21 (12)	$P < 0.05$
Emergency	69 (21.3)	35 (19.4)	NS
Postnatal OGTT glucose (mmol/L)	<i>N</i> = 226	<i>N</i> = 119	
Fasting	4.9 $\pm$ 1.7	4.7 $\pm$ 1.3	NS
2 hour	5.8 $\pm$ 2.7	5 $\pm$ 1.9	$P < 0.01$
Abnormal postnatal GTT	39 (17.3)	8 (6.7)	$P < 0.01$
Diabetes <i>n</i> (%)	7 (3.1)	0	$P < 0.01$
Impaired fasting glucose no./total no.	11 (4.9)	3 (2.5)	NS
Impaired glucose tolerance no./total no.	21 (9.3)	5 (4.2)	NS

NS, non-significant; OGTT, oral glucose tolerance test; GTT, glucose tolerance test

Table 3 Perinatal outcomes

	Metformin group (n = 324)	Diet group (n = 175)	Significance
Congenital abnormalities			
Major, n (%)	1 (0.3)	1 (0.6)	NS
Minor, n (%)	22 (6.8)	13 (7.4)	NS
Birth weight (BW) (g), mean $\pm$ SD	3387.3 $\pm$ 519	3429.9 $\pm$ 535	NS
BW centile, mean $\pm$ SD	49.4 $\pm$ 31.1	52.1 $\pm$ 32.6	NS
BW centile >90, n (%)	41 (12.7)	35 (20)	$P < 0.01$
BW centile < 10, n (%)	25 (7.7)	25 (14.3%)	$P < 0.01$
Preterm < 37 weeks, n (%)	11 (3.4)	2 (1.1)	NS
Jaundice requiring phototherapy	23 (7.1)	2 (1.1)	$P < 0.05$
Hypoglycaemia	21 (6.5)	6 (3.3)	NS
Neonatal unit admissions	33 (10.2)	12 (6.6)	NS
Shoulder dystocia	3 (0.9)	2 (1.1)	NS

NS, non-significant; BW, birth weight

Table 4 Perinatal outcomes of obese and non-obese women within the metformin-treated group

	GDM on metformin BMI < 30 (n = 156)	GDM on metformin BMI > 30 (n = 130)	Significance
Birth weight (g) mean $\pm$ SD	3288 $\pm$ 420	3457 $\pm$ 593	$P < 0.01$
BW centile mean $\pm$ SD	47.9 $\pm$ 29.6	48.6 $\pm$ 32.2	NS
BW centile >90, n (%)	13 (8.3)	18 (13.9)	NS
Birth weight (g) > 4000 g, n (%)	9 (5.8)	18 (13.9)	$P < 0.01$
Caesarean delivery			
Total	50 (32.1)	69 (53.1)	$P = 0.0005$
Emergency	25 (16)	38 (29.2)	$P = 0.009$
Neonatal hypoglycaemia	4 (2.6)	13 (10)	$P = 0.01$

NS, non-significant; BMI, body mass index; GDM, gestational diabetes; BW, birth weight

Labour was induced less often in our patients and preterm births occurred less frequently compared with the MiG group although emergency caesarean section was performed more often in our cohort. A much smaller proportion of women in our group required additional insulin to achieve glycaemic targets.

Perinatal outcomes in comparison to the MiG study group are shown in Table 7. Mean birth weight centile was lower in our cohort. The proportion of LGA babies was significantly reduced in our metformin study population (12.7%) compared with the MiG cohort (19.3%) while the proportion of SGA babies was similar.

Preterm delivery (3.4%) was much reduced in our patients compared with MiG patients (12.1%). Admission to neonatal unit and numbers of neonates with significant hypoglycaemia was also reduced.

Table 5 Maternal baseline characteristics compared with MiG study participants

	St Helier Hospital Metformin group (n = 324)	MiG Trial Metformin group (n = 363)	Significance
Mean age (years)	33.4 $\pm$ 5.4	33.5 $\pm$ 5.4	$P = NS$
Ethnicity, n (%)			
Caucasians	181 (55.9)	175 (48.2)	$P < 0.05$
Asians	115 (35.5)	87 (24)	$P < 0.01$
Africans	28 (8.6)		
Polynesian/ mixed/others		73 (20.1)	
HbA1c on entry	5.6 $\pm$ 0.6	5.7 $\pm$ 0.6	$P < 0.05$
Early pregnancy BMI (kg/m ²)	30.2 $\pm$ 7.1	32.2 $\pm$ 8.2	$P < 0.01$
Family history of diabetes (%)	131 (40.4)	162 (44.6)	NS
Previous gestational diabetes (%)	72 (22.2)	94 (25.9)	NS
OGTT glucose (mmol/L)			
Fasting	5.2 $\pm$ 0.9	5.7 $\pm$ 1.2	$P < 0.01$
2 hour	8.5 $\pm$ 1.8	9.7 $\pm$ 2.1	$P < 0.01$

BMI, body mass index; HbA1c, glycosylated haemoglobin; OGTT, oral glucose tolerance test

Table 6 Maternal pregnancy outcomes compared with MiG study participants

	St Helier Hospital Metformin group (n = 324)	MiG Trial Metformin group (n = 363)	Significance
Gestational hypertension	15 (4.6)	14 (3.9)	NS
Pre-eclampsia	5 (1.5)	20 (5.5)	$P < 0.05$
Mothers requiring additional insulin	28 (10.5)	168 (46.3)	$P < 0.01$
Induction of labour	84 (25.9)	196 (54)	$P < 0.01$
Caesarean delivery			
Total	134 (41.4)	186 (51.2)	$P < 0.01$
Elective	65 (20.1)	131 (36.1)	$P < 0.01$
Emergency	69 (21.3)	55 (15.2)	$P < 0.05$
Post-natal OGTT glucose (mmol/L)	226	270	
Fasting	4.9 $\pm$ 1.7	5.1 $\pm$ 0.8	NS
2 hour	5.8 $\pm$ 2.7	6.4 $\pm$ 2.4	$P < 0.05$
Abnormal postnatal GTT			
Diabetes no./total no. (%)	7 (3.1)	23/270 (8.5)	$P < 0.05$
Impaired Fasting glucose no./total no. (%)	11 (4.9)	13/270 (4.8)	NS
Impaired glucose tolerance no./total no. (%)	21 (9.3)	30/270 (11.1)	NS

NS, non-significant; OGTT, oral glucose tolerance test

DISCUSSION

Despite greater glucose intolerance and hence increased risk at the start of our study, we found better pregnancy outcomes in

Table 7 Perinatal outcomes compared with MiG study participants

	St Helier Hospital Metformin group (n = 324)	MiG Trial Metformin group (n = 363)	Significance
Birth weight (g), mean $\pm$ SD	3387.3 $\pm$ 519.5	3372 $\pm$ 572	NS
BW centile, mean $\pm$ SD	49.4 $\pm$ 31.1	54.6 $\pm$ 30.1	$P < 0.01$
BW centile > 90 , n (%)	41 (12.7%)	70 (19.3%)	$P < 0.01$
BW centile < 10 , n (%)	25 (7.7)	26 (7.2%)	NS
Preterm < 37 weeks, n (%)	11 (3.4)	44 (12.1%)	$P < 0.01$
Jaundice requiring phototherapy	23 (7.1)	29 (8)	NS
Hypoglycaemia	21 (6.5)	55 (15.2)	$P < 0.01$
Neonatal unit admissions	33 (10.2)	68 (18.7)	$P < 0.01$
Shoulder dystocia	3 (0.9)	6 (1.7)	NS

NS, non-significant; BW, birth weight

our metformin cohort compared with the diet-alone group. Metformin treatment was associated with less macrosomia and fewer SGA babies. These results support the use of metformin in GDM.

Labour was induced more frequently in the metformin group reflecting our care pathway whereby women not yet in spontaneous labour by their due dates are induced in contrast to those on dietary measures alone who are allowed to wait up to a further two weeks. Nevertheless, the prevalence of preterm delivery and prematurity was very low in both groups.

Because metformin crosses the placenta, there have been concerns raised about possible adverse effects in the developing fetus or in later life.¹¹ In accordance with other studies^{5,7,12} we found no evidence of teratogenicity or increase in anomaly rates which are to be expected as the metformin was not started until the third trimester. In this regard, results of studies of women with polycystic ovary syndrome treated with metformin throughout pregnancy are reassuring and include data on growth and motor-social development up to the first 18 months of life.¹³ Long-term childhood development is being recorded in the MiG Offspring Follow-up (TOFU) trial. Preliminary two-year data show no adverse effects compared with controls.¹⁴ Final results are expected in 2015 and will provide much needed safety information.

Pregnancy outcomes in this study were more favourable than those reported in MiG.⁵ This may reflect the different populations studied; just over half of our patients were Caucasians and the remainder were either African or Asian whereas 55% of participants in the MiG trial were Polynesian, Indian and Chinese.⁵ Undiagnosed type 2 diabetes was much more frequent (8.5%) in the MiG subjects compared with our participants (3.7%). In addition, our cohort had lower mean BMI compared with the MiG patients and hence likely to have been less insulin resistant. In keeping with this suggestion, they were far less likely to require insulin to reach glucose targets. Thus they may have responded better to metformin.

Previous work on glucose-tolerant obese women suggests that obesity may have an independent effect on pregnancy outcomes.¹⁵ We noted that obese women in the metformin cohort had babies with higher mean birth weight and a higher frequency of LGA babies in comparison with non-obese subjects.

An unexpected finding was an increase in neonatal jaundice requiring phototherapy in the metformin group. This has been observed previously but not in all studies.^{16,5,7} Hyperbilirubinaemia could be a marker of hypoxia *in utero* or result from birth trauma but we found no evidence of this in this study and no difference in Apgar scores was observed. We suspect it related to a small increase in the number of preterm infants in the metformin group.

A strength of this study is the relatively large cohort of patients investigated and treated in one centre by the same team and to a standardized protocol. However, caution is needed in interpreting our results given that we did not perform a randomized or blinded trial and hence it is possible that metformin-treated patients were healthier and had better outcomes than would be expected.

The baseline maternal characteristics do not suggest this and indeed indicate they had higher risk and more severe glucose intolerance than the diet-treated group. Furthermore, after the pregnancy and after metformin had been stopped, their glucose tolerance results were again noted to be worse than the diet-only group.

CONCLUSION

Maternal and neonatal outcomes of women treated for GDM with metformin showed favourable outcomes compared with women with milder glucose intolerance managed by diet alone. Results for metformin in this study also compared well with those from the MiG study. These data add to increasing evidence supporting the use of metformin in GDM.

DECLARATIONS

Competing interests: The authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: The work was considered a retrospective audit by the ethics committee not requiring formal ethics committee approval. All patients treated with metformin were given a standard patient information sheet (available on request) and upon giving consent, received this treatment.

Contributorship: JB collected the data and performed the analysis; SH prepared the manuscript and helped the discussion; AJ interpreted the data and contributed to the discussion and HS conceived the study and contributed to interpretation and discussion. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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REFERENCES

- 1 The HAPO Study Cooperative research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;**358**:1991–2002
- 2 Crowther CA, Hiller JE, Moss JR, *et al.* Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;**352**:2477–86
- 3 Landon MB, Spong CY, Thom E, *et al.* A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;**361**:1339–48
- 4 Hillier TA, Pedula KL, Schmidt MM, *et al.* Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* 2007;**30**:2287–92
- 5 Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;**358**:2003–15
- 6 NICE (2008) Diabetes in Pregnancy Consultation Document (2007). See www.nice.org.uk. (last checked 24 November 2011)
- 7 Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. *Diabet Med* 2009;**26**:798–802
- 8 Alberti KGM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;**15**:539–53
- 9 Hyer SL, Shehata HA. Gestational diabetes mellitus. *Current Obstet Gynaecol* 2005;**15**:368–74
- 10 Gardosi J, Francis A. *Customised Centile Calculator – GROWCentile v 5.1*, 2006. *Gestation Network*. See <http://www.gestation.net> (last checked 24 November 2011)
- 11 Hague W, Davoren PM, McIntyre D, Norris R, Xiaonian X, Charles B. Metformin crosses the placenta: a modulator for fetal insulin resistance. *BMJ* 2003;**327**:880–1
- 12 Gutzin SJ, Kozer E, Magee LA, Feig DS, Koren G. The safety of oral hypoglycemic agents in the first trimester of pregnancy: a meta-analysis. *Can J Clin Pharmacol* 2003;**10**:179–83
- 13 Glueck CJ, Goldenberg N, Wang P, Loftspring M, Sherman A. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. *Hum Reprod* 2004;**19**:510–21
- 14 Rowan J. 2011 Oral communication, 6th International Symposium on Diabetes & Pregnancy (DIP) Salzburg, Austria, 24–26 March 2011
- 15 Owens L A, O'Sullivan E P, Kirwan B. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care* 2010;**33**:577–9
- 16 Coetzee EJ, Jackson WP. Metformin in management of pregnant insulin-independent diabetics. *Diabetologia* 1979;**16**:241–5

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