A Trial in Progress: Gestational Diabetes

Treatment with metformin compared with insulin (the Metformin in Gestational Diabetes [MiG] trial)

JANET A. ROWAN, FRACP
ON BEHALF OF THE MiG INVESTIGATORS*

The Metformin in Gestational Diabetes (MiG) trial is a prospective randomized multicenter trial in women with gestational diabetes mellitus (GDM) that is testing the hypothesis that metformin treatment, compared with insulin, is associated with similar perinatal outcomes, improved markers of insulin sensitivity in the mother and baby, and improved treatment acceptability. Women with GDM who are at 20–33 weeks' gestation in a singleton pregnancy and meet entry criteria are randomized to insulin or metformin treatment. The primary outcome is a composite of neonatal morbidity, with 750 recruits required.

The trial finished recruiting in October 2006. Interim data on 200 women (and subsequently 550 women) have been reviewed by the data safety monitoring committee, which has reported that the trial should answer the hypotheses and no protocol changes are required. Data from 457 women show recruits are a mean age of 33.3 ± 5.3 years; BMI of 32.1 ± 7.8 kg/m^2; and ethnicity 47.2% European/Caucasian, 25.7% Polynesian, and 24.3% Indian/Asian. The mean fasting glucose at recruitment is 5.3 ± 1.1 mmol/l and A1C is 5.7 ± 0.8%. Long-term follow-up of children started at age 2 years, with assessments of body composition, neurodevelopment, diet, and activity levels. The MiG trial will address the efficacy and detailed safety of metformin compared with insulin in women with GDM. Long-term follow-up of offspring will examine whether treatment influences later health (Australasian Clinical Trials Registry number 12605000311651).

BACKGROUND — GDM is diagnosed in over 4% of pregnant women (1,2). The prevalence is increasing as the pregnancy population becomes older and fatter. Women with GDM have increased rates of pregnancy complications and risks of later type 2 diabetes (1,2). The offspring of women with GDM also have increased risks of perinatal complications and long-term risks of obesity and type 2 diabetes (1–7). There has been debate about the value of treating women with GDM, but prospective randomized data have recently demonstrated that treating women with GDM reduces adverse perinatal outcomes (8). Additional support for treatment comes from a large retrospective study comparing women with treated GDM to women who were diagnosed late in pregnancy and were therefore "untreated GDMs." Outcomes were significantly better in the treated group than the untreated group (9). There are no data showing how treatment affects later risks of type 2 diabetes in the mother and offspring.

The main aims of treatment are to prevent fetal hyperinsulinemia and improve maternal endothelial function by reducing elevated maternal glucose levels (3). This is achieved by giving advice about diet and exercise initially, but women often require additional treatment, which has conventionally been insulin (1). The disadvantages of insulin for the mother include the need to give injections, risks of hypoglycemia, and increase in appetite and weight (10). Women may be anxious about being on insulin, and treatment compliance is an issue. It would be useful if there were alternative treatment options to insulin, preferably oral agents. Glyburide has been shown to be as effective as insulin in achieving maternal glycemic control in an open prospective randomized trial of 400 women with GDM (11). However, glyburide works by stimulating insulin secretion and is also associated with risks of maternal hypoglycemia and weight gain. Metformin, an oral biguanide, may be a more logical alternative to insulin for women with GDM who are unable to cope with the increasing insulin resistance of pregnancy. Metformin works primarily by decreasing hepatic glucose output, improving peripheral glucose uptake, and decreasing free fatty acid levels, thus reducing insulin resistance (12,13). Outside pregnancy, metformin is as efficacious as insulin or a sulfonylurea in achieving glycemic control in people with newly diagnosed type 2 diabetes and it is not associated with weight gain (10). Metformin crosses the placenta (14–16); however, there is no evidence of adverse fetal effect, and it is a class B drug in pregnancy (17).

There are data from over 20 years ago reporting use of metformin in women with GDM or type 2 diabetes in pregnancy in South Africa. Published cohort studies showed similar perinatal mortality and morbidity for women treated with metformin compared with insulin (18–20). A total of 30% of metformin-treated women with GDM and 50% of women with type 2 diabetes required insulin for adequate glucose control. More recently in Australia, 30 women with GDM were randomized to metformin or insulin treatment, and offspring cord C-peptide levels were similar in both groups (21). At a single center in New Zealand, 214 pregnancies between 1998 and 2003 in women with type 2 diabetes were reviewed. Those who had taken metformin (93 pregnancies) had more risk factors for adverse perinatal outcomes, but outcomes were no different from those of women

From National Women's Health, Auckland, New Zealand.
Address correspondence and reprint requests to Janet A. Rowan, National Women's Health, Level 9 Support Building, Auckland City Hospital, Park Rd., Grafton, Auckland, New Zealand. E-mail: jrowan@internet.co.nz.
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Abbreviations: GDM, gestational diabetes mellitus; MiG, Metformin in Gestational Diabetes.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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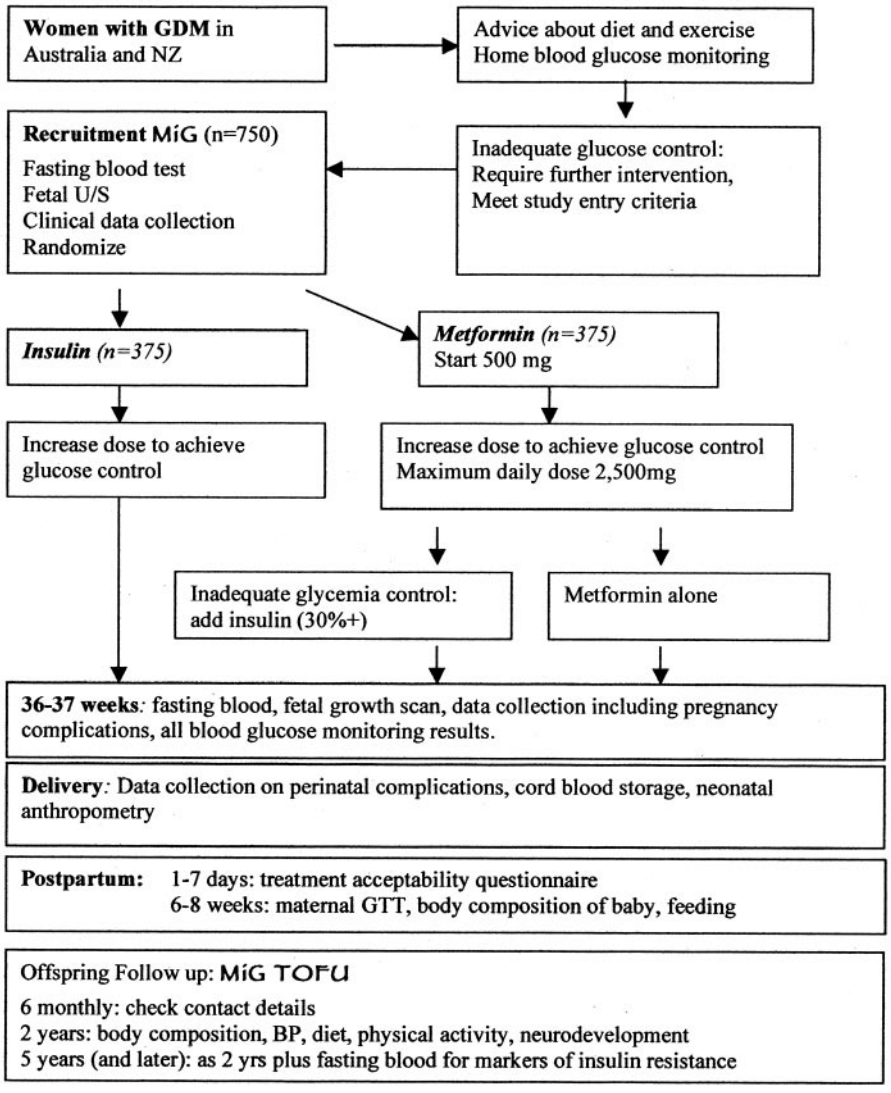

Figure 1—*Diagram of study design. BP, blood pressure; GTT, glucose tolerance test.*

who did not take metformin (22). There is one retrospective study from Denmark that reported increased rates of preeclampsia and perinatal loss in a cohort of women with GDM or type 2 diabetes treated with metformin between 1966 and 1991 ($n = 50$), compared with a reference group treated with insulin (23). The metformin group was obese, and outcomes could not be attributed to treatment. Additional data regarding use of metformin in pregnancy comes from studies of women with polycystic ovarian syndrome, also associated with insulin resistance. Metformin has been shown to increase ovulation rates and fertility (24–26), and continuing it through pregnancy may reduce risks of miscarriage (27,28) and GDM (27). Rates of preeclampsia and perinatal loss were not increased in women taking metformin compared with the community delivery population (29). Larger prospective studies are underway reporting outcomes in women who continue metformin through pregnancy and following the offspring's growth and development (27,30).

The lack of prospective randomized data, however, creates uncertainty about the use of metformin in women with diabetes in pregnancy. In Australasia, we are running a prospective randomized multicenter open-label trial comparing metformin with insulin treatment in women with GDM (the MiG trial). The aim of the trial is to test the hypothesis that in women with GDM, metformin treatment, compared with insulin, will result in similar perinatal outcomes, improve markers of insulin sensitivity in the mother and baby, and be associated with improved treatment acceptability.

MiG STUDY DESIGN AND METHODS

— The MiG study has had ethics committee approval at all participating sites and informed written consent was obtained from all recruits.

The study design is summarized in Fig. 1. Women 18–45 years old with GDM who are at 20–33 weeks' gestation in a singleton pregnancy are eligible for study entry if home blood glucose monitoring includes a fasting glucose >5.4 mmol/l or 2-h postprandial glucose >6.7 mmol/l after diet and exercise advice has been given. More specific criteria are avoided, as clinicians base their decision about treatment on additional factors, such as gestation and fetal size. Women who have glucose elevations consistent with undiagnosed diabetes are eligible. Exclusion criteria include women who have a contraindication to taking metformin, a prepregnancy diagnosis of diabetes, a recognized fetal anomaly, or, at the time of study entry, ruptured membranes, gestational hypertension, preeclampsia, or fetal abdominal circumference <10th percentile. Women who consent are randomized to metformin or insulin treatment with stratification by site (as it is recognized there are variations in thresholds for treatment and glycemic aims between centers) and gestation (20–27 and 28–33 weeks). Treatment is initiated the following day, after checking results of a fasting blood sample that includes measurement of renal and liver function to ensure unexpected contraindications to metformin treatment are not missed. Metformin is started at a dose of 500 mg daily and increased up to 2,500 mg daily as tolerated and depending on maternal glucose levels. All sites have agreed to aim for fasting capillary glucose levels <5.5 mmol/l and 2-h postprandial levels <7.0 mmol/l, although a number of sites aim for lower levels. If inadequate diabetes control is achieved with metformin, insulin is started, but metformin is continued. Metformin is stopped if significant maternal conditions arise, such as severe preeclampsia, sepsis, or pregnancy cholestasis and also if fetal growth restriction develops. Insulin is prescribed as usual clinic practice, typically a short-acting insulin analog before meals and intermediate insulin once or twice daily.

At study entry, background maternal demographic data, medical history, family history, obstetric history, medication

intake through pregnancy, early pregnancy data, and any pregnancy complications are recorded. Paternal demographic data and height and weight are also recorded. Fetal ultrasound growth within 2 weeks before or 1 week after study entry is documented. During the study, women are asked to continue measuring capillary glucose levels fasting and 2 h after the start of each meal. These are performed on a Precision (now Optium) Medisense meter, which is downloaded each clinic visit and relevant readings are recorded in the database. At 36/37 weeks' gestation, fasting maternal blood samples are taken for repeat measurement of A1C, glucose, and lipids; a urine albumin-to-creatinine ratio is measured, and a fetal growth scan is repeated. At delivery, pregnancy complications, indication for induction (if performed), mode of delivery, and complications are recorded from the hospital notes. Detailed neonatal morbidity is also recorded. Trained personnel perform anthropometric and blood pressure measurements on the baby within 48 h of birth. If consented, cord blood is stored for assessment of insulin and other markers of the adipoinsular axis.

At 6–8 weeks' postpartum, women and their infants are seen again. The woman's medications, weight, blood pressure, fasting triglyceride levels, and oral glucose tolerance test results are recorded. Details of the infant's feeding and health are documented and anthropometric measurements are repeated. Contact details are confirmed for women who consent to the follow-up of their offspring.

The primary outcome is a composite of neonatal morbidity, including hypoglycemia (14% expected to have two results <2.6 mmol/l, 7% requiring intravenous dextrose), respiratory distress (estimate 5%), phototherapy (5%), birth trauma (1.5%), low 5-min Apgar (<7, <1%), and prematurity (15%). The protocol for monitoring for hypoglycemia is based on the Auckland Newborn Services Guidelines (31). Neonatal hypoglycemia is defined as a capillary glucose level <2.6 mmol/l. In addition, recurrent glucose levels <2.6 mmol/l and any levels <1.6 mmol/l are recorded. Treatment of hypoglycemia and duration of treatment is detailed. Respiratory distress is recorded if an infant requires ≥4 h of respiratory support in the first 24 h after delivery. Again, duration of support and diagnosis are recorded. Birth trauma is classified as minor, moderate, or severe according to subsequent recovery, with detailed definitions in the study manual. In brief, it is mild if resolved by 6 weeks postpartum, moderate if expected to recover within 3 months, and severe if long-term impact on function is anticipated. Admission to level 2 or 3 neonatal nursery and duration of stay is recorded as another way of capturing neonatal morbidity.

Secondary outcome measures include the following: maternal glycemia control, neonatal body composition and other markers of neonatal insulin sensitivity including cord blood assays, maternal hypertensive complications as defined by the Australasian Society for Study of Hypertension in Pregnancy (32), maternal postpartum glucose tolerance, and acceptability of treatments by questionnaire. With respect to maternal glycemia, there are data entry points for every fasting and 2-h postprandial glucose level so that details of control and testing compliance can be assessed. Neonatal body composition is assessed from anthropometric measurements, which include crown heel and crown rump lengths using a Harpenden neonatometer. Circumference measurements of head, mid–upper arm, chest, and waist are performed to the nearest 0.1 cm according to guidelines outlined in the study manual. Subscapular and triceps skinfold thickness is measured to the nearest 0.2 mm using a Holtain or Harpenden caliper. Study personnel are trained and have regular review of technique at each site. Cord blood samples are collected in a 30-ml syringe after clamping of the cord and are placed into EDTA and plain tubes. Samples are sent directly to the laboratory for processing within 10 min of collection or stored on ice to be processed within 90 min. Samples are centrifuged and plasma and serum aliquots are stored in 1-mm nunc tubes in a −80° freezer for later use.

Acceptability of treatments is assessed by a short questionnaire that is administered to the woman after her baby has been measured and within a week of delivery. There are five questions that ask about which medication she had, how often she forgot medication, medication preferences in a subsequent pregnancy, and how adherence to medication compared with adherence to diet and glucose monitoring.

Adverse events are reported routinely through the study datasheets or immediately if they are severe. A data safety monitoring committee reviews all serious adverse events at the time they are reported and provides recommendations to the principal investigators. The data safety monitoring committee has reviewed an interim analysis of 200 women and will be reviewing an analysis of ~500 women by the end of 2005.

The Green Lane Coordinating Centre, Auckland, is involved with several aspects of the study, including data management, site monitoring, and statistical support. Randomization is performed and data are entered on an Oracle version 8.0.1 web-based database, which uses Secured Socket Layer 128 bit for data transmission security. Monitors initially check 25% of data entries at each site and subsequently 10% if data entries are accurate and the site satisfies good clinical practice guidelines.

Statistical procedures

It was decided that an increase in neonatal morbidity from 30% (based on annual Auckland clinic data) to 40% would be required to reject the hypothesis that women treated with metformin will have similar neonatal morbidity to women treated with insulin. Using two-tailed calculations with a power of 80% and significance at <0.05, the study requires 375 women in each arm. The trial is also powered to address individual components of morbidity (e.g., neonatal hypoglycemia). Women will be analyzed on an intention-to-treat basis. Between-group comparison will be done using a *t* test or ANOVA where appropriate, or Mann-Whitney *U* test or Kruskal-Wallis where the data are not normally distributed. For categorical data, χ^2 test (with Yates' correction or Fisher's exact test where appropriate) will be used. The continuous results will be expressed as means and SDs or medians and interquartile ranges according to the data distribution, and categorical data will be presented as proportions with 95% CIs. Generalized linear models will be used to perform multivariate analysis to allow the comparison of groups while controlling for possible confounding variables. A logistic regression model for dichotomous outcomes will be used. As there are multiple associated outcomes, care will be exercised in the interpretation of the results. For the analyses reported, SAS 9.1 (SAS Institute, Cary, NC) has been used.

RESULTS — Recruitment commenced in October 2002 in Auckland, the largest site, and eight further sites have been

Table 1—*Maternal characteristics at recruitment*

	Treatment groups
	*n**
Age (years)	33.3 ± 5.3
BMI (kg/m²)	32.1 ± 7.8
Gestation (weeks)	30.2 ± 3.4
Ethnicity	
Caucasian/European	212 (47.2)
Polynesian (Pacific Islander, Maori)	115 (25.7)
Indian	57 (12.7)
Chinese/other Southeast Asian	52 (11.8)
Chronic hypertension	32 (7.1)
Smoking in pregnancy	72 (16.1)
Nulliparity	99 (22.5)
Fasting glucose at recruitment (mmol/l)	5.3 ± 1.1
A1C at recruitment (%)	5.7 ± 0.8

Data are means ± SD or *n* (%). **n* varies from 415 to 457, since all data are not completed on recruits.

added over the past 2 1/2 years. There are 512 women recruited (October 2005), and recruiting was completed in October 2006.

A detailed interim analysis of 200 recruits was reviewed by the data safety monitoring committee. They reported that the trial would address the hypotheses. There were no safety concerns or recommendations for protocol changes.

An analysis of just over 450 recruits has been reported to the data safety monitoring committee, and the background characteristics of these women are shown in Table 1. There have been four study withdrawals before delivery and one woman who declined postpartum follow-up. None of the serious adverse events reported have been related to study medication or the protocol. No other data have been or will be released to the investigators until the study is completed.

DISCUSSION — Metformin is being used increasingly in pregnancy and it is timely for the MiG trial to be undertaken so that benefits and risks of treatment are more clearly understood. The MiG trial is taking place in the clinic setting, so that outcomes will be relevant for clinicians caring for women with GDM. The background characteristics of women recruited so far reflect women that would meet criteria for additional treatment in many centers.

One difficulty with studies in women with GDM is that there is no single clinical outcome that reflects treatment effect. Birth weight or cesarean section rates, as markers of macrosomia, have often been used, but are fraught with problems. Birth weight does not accurately measure the type of fetal overgrowth associated with maternal diabetes (33,34). This is compounded by ethnic differences in body composition and birth weight (35–37) that are seen at birth, as illustrated in a study comparing the adiposity of Indian and European neonates (38). The Indian neonates were 800 g lighter than European neonates, but had similar adiposity. Cesarean section rate may also be a poor measure of fetal macrosomia, since it may be influenced by an obstetricians' response to a maternal diagnosis of GDM (39).

Maternal glucose control was the primary outcome in Langer's randomized study comparing glyburide (glibenclamide) and insulin in women with GDM (11). However, Langer reported that glyburide does not cross the placenta in significant amounts, so a direct influence of glyburide on the fetus was not felt to be a concern. The study was not powered to address neonatal morbidity and it is unclear whether the 4% placental passage of glyburide could have any adverse effects on the fetal pancreas, leading to increased rates of neonatal hypoglycemia or increased rates of future diabetes. Maternal glucose control is a secondary outcome in MiG, with the aim of achieving the same glucose levels in each arm. It is likely, based on Coetzee's data and because we have a GDM population with high rates of undiagnosed type 2 diabetes, that supplemental insulin will be required in >30% of women in the metformin group. However, as metformin is continued, its effects can still be examined in these pregnancies. It will be interesting to compare outcomes between the groups at the different levels of glucose control achieved, to see if metformin modulates any adverse effects of maternal hyperglycemia on the fetus. As the study protocol excludes growth-restricted fetuses at the time of study entry and metformin is stopped if significant preeclampsia or growth restriction develops, we may not be able to see if metformin is problematic if continued in situations of decreased nutrient transfer, when the fetus may adapt by altering insulin action in different tissues to maintain brain growth and survival.

The primary outcome of neonatal morbidity was chosen for the MiG trial, since prevention of fetal hyperinsulinemia and its consequences is an important aim of treating women with GDM, and neonatal morbidity is equally important when assessing potential direct effects of metformin in the fetus. Hypoglycemia and respiratory distress in term neonates are both markers of fetal hyperinsulinemia. Birth trauma is a potentially serious consequence of macrosomia. Hyperbilirubinemia requiring phototherapy, if increased, could be a marker of hypoxia and secondary polycythemia in utero or be a consequence of birth trauma. A low Apgar may reflect birth difficulties or another problem with fetal well-being, which is of interest particularly in the metformin group. Prematurity was included, as it is more prevalent in states of hyperglycemia (40,41) and is intimately tied up with management of diabetes if superimposed preeclampsia arises or there are antenatal concerns about fetal well-being. Additionally, premature infants are more likely to have other neonatal morbidity and possibly increased long-term risks of obesity and type 2 diabetes (42).

The secondary outcomes in the baby were chosen to give a detailed picture of whether metformin had any influence on the fetus with respect to body composition and the adipoinsular axis. It is important to compare anthropometric and cord blood measurements at birth and follow up on the offspring to examine how maternal glucose levels and treatment with insulin or metformin relates to later health. There are increased risks of obesity and type 2 diabetes in offspring of women with diabetes in pregnancy that relates to intrauterine programming (4–7), and treatment has the potential to influence this. In Auckland, the offspring follow-up (MiG TOFU) at 2 years of age

has begun with assessments of body composition, neurodevelopment, diet, and activity levels. We plan to reassess at 5 years and through to adult life, if possible.

The secondary outcomes in the mother relate to potential effects of metformin on rates of preeclampsia and postpartum glucose tolerance. Metformin may reduce endothelial activation and alter the excess maternal inflammatory response that is associated with preeclampsia and thus reduce the risk of it developing, though the timing of intervention may be too late in the MiG trial. Postpartum glucose tolerance may be influenced if women in the metformin arm put on less weight than insulin-treated women.

In summary, MiG is a key trial in assessing the potential role of metformin treatment during pregnancy. Outcomes will give us detailed information about effects of treatment on the fetus and the mother. Long-term follow-up will examine whether metformin has independent effects on later health of the offspring.

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APPENDIX — Bill Hague is the principal investigator in Adelaide and coordinator for the Australian arm of the trial and has had input into the design of the study and applied for Australian funds. The original steering committee members in New Zealand are Tim Cundy and Malcolm Battin (also coinvestigator for MiG TOFU); the recruiting sites principal investigators are John Griffiths, Dorothy Graham, Barry Walters, Karin Lust, Peter Moore, Jeremy Oats, Peter Wein, Carl Eagleton, Mark McLean, and David McIntyre; the site coordinators are Aida Siegers, Maggie Cropper, Jenny Rafferty, Suzette Coat, Claire Parker, Alison Barry, Gill Smith, Tessa Clarke, Michelle Cram, and Susan Hendon, Green Lane Clinical Trial Centre staff; the Data Safety Committee members are Jane Harding, Lesley McCowan, Rick Cutfield, and Wanzhen Gao. Elaine Rush is the coinvestigator for MiG TOFU.

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