Benefit of metformin in reducing weight gain and insulin requirements in pregnancies complicated by gestational diabetes

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Citation: Iftakhar R (2012) Benefit of metformin in reducing weight gain and insulin requirements in pregnancies complicated by gestational diabetes. *Diabesity in Practice* **3:** 108–13

Article points

1. Insulin has historically been the treatment of choice for women diagnosed with gestational diabetes mellitus (GDM).
2. However, the risk of hypoglycaemia, cost of GDM treatment and necessitated injections have resulted in a quest to find a suitable alternative or adjunct; metformin is now widely used as an alternative during pregnancy.
3. This study investigated the effects of metformin over insulin on weight gain and insulin unit requirements in women with GDM.
4. Women on metformin, with or without supplemental insulin, gained significantly less weight during pregnancy than those on insulin alone; metformin was well tolerated and reduced the overall insulin unit requirements.

Key words

- Gestational diabetes mellitus
- Metformin
- Pregnancy
- Weight gain

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A retrospective study was conducted to compare weight gain and insulin requirements in women with gestational diabetes mellitus (GDM) treated either with metformin with or without supplemental insulin, or with insulin alone; 55 women with GDM were managed on metformin (metformin cohort) and 37 women with GDM were treated with insulin alone (insulin cohort). Metformin with or without supplemental insulin versus insulin alone was associated with less weight gain from initial booking visit to last appointment (8.1±6.9 kg versus 13.3±14.4 kg, *P*=0.02) and during the third trimester (1.41±3.1 kg versus 2.7±3.5 kg, *P*=0.03). Comparing a subgroup (*n*=13) in the metformin cohort diagnosed by 2006–07 GDM criteria with women in the insulin cohort confirmed that women on metformin gained less weight (8.3±5.1 kg versus 13.3±14.4 kg, *P*=0.04). Fifty-three women (96.4%) tolerated metformin (eight required metformin slow-release) and 23 (41.8%) required adjunctive insulin; insulin requirements were lower in the metformin cohort (42.9±32.7 units versus 60.8±39.9 units, *P*=0.03). Thus women on metformin had significantly less weight gain during pregnancy compared with those on insulin; metformin was well tolerated and reduced insulin requirements.

Gestational diabetes mellitus (GDM) is a growing health problem worldwide (Wild et al, 2004); it is 10-fold more prevalent in Asian than in Caucasian women (Chawla et al, 2006). The prevalence is set to rise further as pregnancies in women who are older and obese increase (Dabelea et al, 2005; Hunt and Schuller, 2007). Studies have shown that significant weight gain in pregnancy may worsen insulin resistance and therefore contribute to adverse outcomes such as macrosomia (Nolan, 2011).

Obesity is independently associated with adverse outcomes, and obese mothers are at a three-fold risk of developing GDM, having a baby with congenital malformation and developing hypertensive disorders in pregnancy (Bianco et al, 1998; Reece et al, 2009). Thus studies have demonstrated that a fall in BMI correlates with better pregnancy outcomes (shoulder dystocia, Caesarean section rate and normosomia; Paglia and Coustan, 2011).

Background to the study

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (Metzger et al, 2008) has shown that maternal BMI independent of blood glucose levels was associated with adverse outcomes, such as macrosomia and an increased incidence of pre-eclampsia. The HAPO study

has shown the advantages of treating GDM early with lifestyle, dietary or pharmacotherapy interventions, which can all improve outcome.

Until recently, insulin has been the only pharmacological therapy used for GDM, but it is expensive, necessitates injections, may cause hypoglycaemia and is associated with weight gain (Rowan et al, 2008). The safety and efficacy of metformin in GDM has been shown, and metformin is now widely adopted as first-line therapy; evidence from Balani et al (2009) and the Metformin in Gestational Diabetes (MiG) trial (Rowan et al, 2008; Ijäs et al, 2011) compared metformin use with insulin and found no associated increase in adverse perinatal outcomes.

Study objective

The study objective was to identify the effects of metformin on weight gain and insulin requirements in pregnancies complicated by GDM, compared with management with insulin alone. In addition, the authors investigated the tolerability of metformin during pregnancy.

Method

This was a retrospective cohort study comparing weight gain and insulin requirements in 55 women with GDM treated with metformin (metformin cohort) with that of 37 women with GDM treated with insulin alone (insulin cohort); prior to this study, the authors' unit routinely uses metformin. Participants for both cohorts were identified via referrals to the specialist joint diabetes antenatal service.

Women with GDM who were managed on metformin with or without adjunctive insulin were identified over a 6-month period, from January to June 2010. Of the 103 GDM referrals, 55 women were treated with metformin with or without adjunctive insulin, 35 women were managed with lifestyle and dietary changes, and four women were managed on insulin alone; the remaining nine referrals had incomplete data and were excluded. Therefore, comparisons were performed on the 55 women who were treated with metformin with or without adjunctive insulin (metformin cohort).

If the participant's pregnancy was at less than 34 weeks' gestation, metformin was commenced after informed consent and was titrated depending on home blood glucose self-monitoring (HBGSM) results, up to 2000 mg daily. If glycaemia was not controlled on metformin or the woman's pregnancy was at more than 34 weeks' gestation, insulin was initiated. Women continued metformin until the time of delivery.

The comparison cohort was managed solely on insulin; they were identified over 18 months, from April 2006 to December 2007. During this time there were 87 referrals; 37 referrals were identified to be managed on insulin alone, and the remaining 50 referrals were managed with lifestyle and dietary modifications. Thus comparisons were

Table 1. Maternal baseline characteristics

	Insulin cohort (2006–07; *n*=37)	Metformin cohort (2010; *n*=55)	Significance; unpaired *t*-test/ chi-squared test
Age (years)	33.1 (±4.2)	33.1 (±5.4)	*P*=0.49
Booking weight (kg)	82.6 (±22.6)	77.9 (±21.3)	*P*=0.16
Booking BMI (kg/m^2)	31.0 (±8.1)	29.7 (±7.2)	*P*=0.21
Ethnicity			
– Caucasian	75.7%	60.0%	*P*=0.18
– Non-Caucasian	24.3%	40.0%	
Previous GDM	59.5%	18.2%	*P* <0.01
New GDM	40.5%	81.8%	*P* <0.01

GDM=gestational diabetes mellitus.

Page points

1. Until recently, insulin has been the only pharmacological therapy used for gestational diabetes mellitus (GDM), but it is expensive, necessitates injections, may cause hypoglycaemia and is associated with weight gain.
2. The safety and efficacy of metformin in GDM has been shown, and metformin is now widely adopted as firstline therapy.
3. The study objective was to identify the effects of metformin on weight gain and insulin requirements in pregnancies complicated by GDM, compared with management with insulin alone.
4. This was a retrospective cohort study comparing weight gain and insulin requirements in 55 women with GDM treated with metformin (metformin cohort) with 37 women with GDM treated with insulin alone (insulin cohort).

performed on the 37 women managed on insulin alone (insulin cohort). This cohort had similarities in ethnicities, age and BMI to the metformin cohort (*Table 1*). Insulin treatment involved intermediately acting isophane insulin at bedtime or pre-prandial short-acting insulin, or both, depending on HBGSM results.

Both cohorts were diagnosed with a 75 g oral glucose tolerance test (OGTT). The 2-hour glucose tolerance test cut-off differed between the cohorts because local guideline changes were made in 2008. Nevertheless, the thresholds for initiating pharmacotherapy were identical (home blood glucose fasting <5.5 mmol/L and 2-hour <7.0 mmol/L), and both groups were on pharmacotherapy by 34 weeks' gestation; thus comparisons were deemed acceptable (*Figure 1*). Both cohorts had attended the same joint specialist clinic (diabetes and obstetric team-led) and had been managed within the local GDM framework.

All participants were reviewed by a specialist diabetes midwife and a dietitian and were taught HBGSM, which was performed before breakfast and 2 hours postprandially. The set target capillary glucose values were <5.5 mmol/L for fasting (before breakfast) and <7.0 mmol/L 2 hours postprandially.

Women with three tests or more outside HBGSM targets within 2 weeks, or 1 week of treatment modifications were classed as inadequately controlled; treatment was titrated and intensified according to the local GDM framework. Participants attended the specialist clinic after 1 week of any pharmacotherapy adjustments and remained under close supervision by the multidisciplinary team.

Weight gain was analysed during two time periods: from the initial booking visit (around 11 weeks' gestation) to the last diabetes appointment (around 37 weeks' gestation); and during the third trimester of pregnancy, from the time of the first specialist diabetes appointment (around 29 weeks' gestation) to the last diabetes appointment. Thus, the period assessing weight gain for the two cohorts was similar.

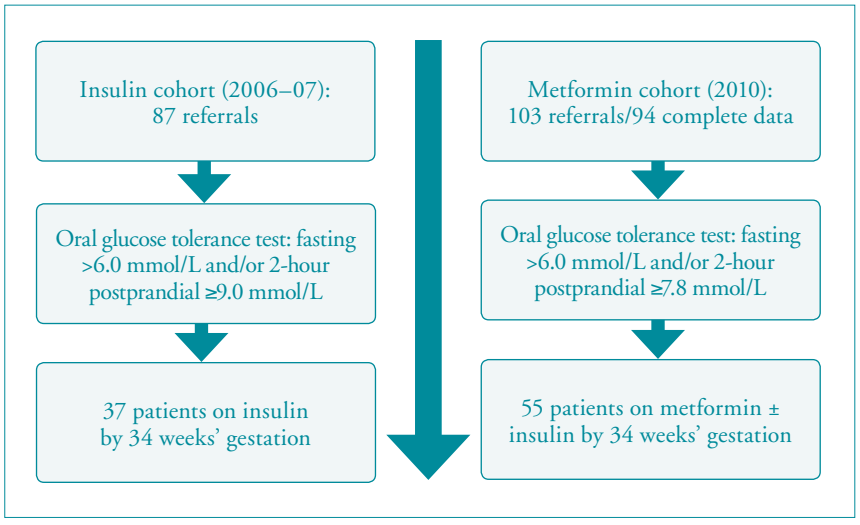

Figure 1. Study participants and diagnostic criteria for gestational diabetes mellitus (GDM).

Analysis

Data were analysed using StatsDirect version 2.7.8 (StatsDirect, Cheshire, UK). Unpaired *t*-tests were used for continuous variables and chi-squared tests for categorical data; a significance level of $P<0.05$ was used. Continuous data are presented as mean ± standard deviation or medians with ranges, depending on data distribution. Frequency data are presented as proportions (%).

Results

The maternal baseline characteristics in the two cohorts investigated were similar; however, the screening OGTT results and proportion of women with previous GDM did differ between cohorts.

The median duration of metformin treatment was 7 weeks (range 5–29 weeks) and the median duration of insulin treatment was 8 weeks (range 3–27 weeks). The median daily dosage of metformin to sustain glycaemic control was 2000 mg (range 500–2000 mg).

The mean weight gain during pregnancy was significantly lower in women treated with metformin with or without supplemental insulin compared with the cohort managed on insulin alone from the initial booking visit to the last appointment (8.1±6.9 kg versus 13.3±14.4 kg, $P=0.02$) as well as during the third trimester (1.41±3.1 kg versus 2.7±3.5 kg, $P=0.03$; *Figures 2a* and *2b*).

In order to provide further evidence that metformin reduced total weight gain and that the differences were not just because of the differences in diagnostic criteria, the authors directly compared a subgroup of women (*n*=13) in the metformin cohort who were diagnosed using 2006–07 GDM criteria (i.e. 2-hour OGTT glucose level ≥9.0 mmol/L) with women in the insulin cohort. Results showed that women on metformin still gained less weight from initial booking visit to the last appointment (8.3±5.1 kg versus 13.3±14.4 kg, *P*=0.04) as well as during the third trimester (0.5±2.0 kg versus 2.7±3.5 kg, *P*<0.01; *Figures 3a* and *3b*).

The metformin cohort had a higher proportion of women with new GDM, first seen around 29 weeks' gestation. In the insulin cohort, the greater proportion of women with previous GDM had the advantage of regular reviews and lifestyle advice from early in pregnancy. Despite this difference, women in the metformin cohort gained less weight.

Of the 55 women on metformin, 53 women (96.4%) tolerated metformin until delivery (eight switched to metformin slow-release) and 23 (41.8%) required supplemental insulin to achieve glycaemic targets. Additionally, two

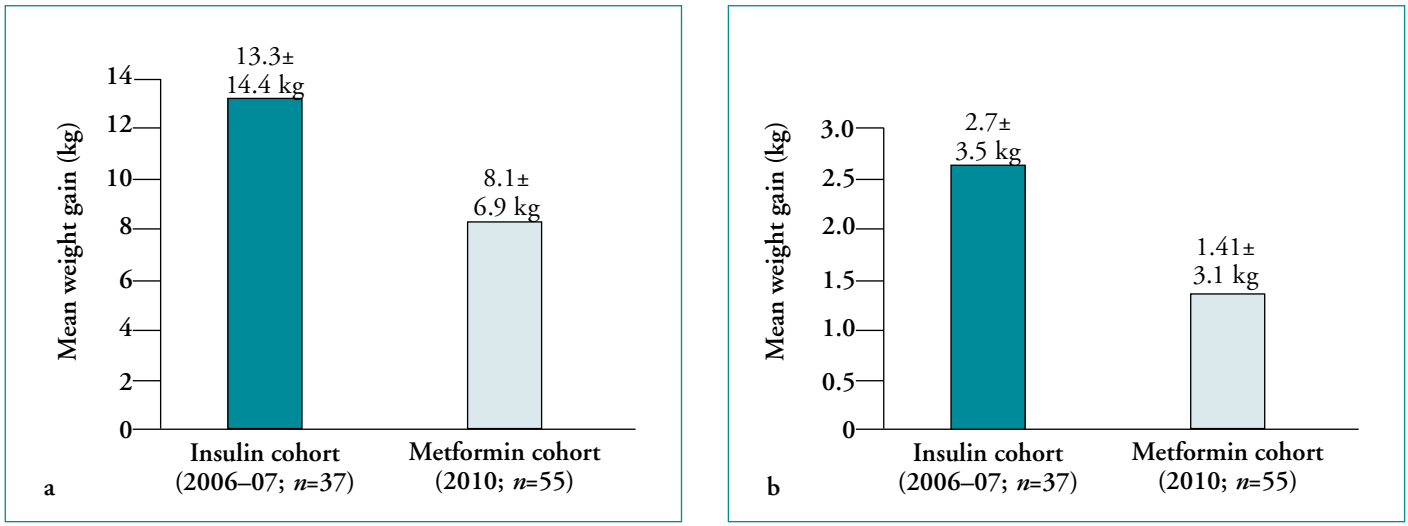

Figure 2. Mean weight gain (kg) (a) from initial booking to last specialist appointment (P=0.02) and (b) during third trimester (P=0.03) in the metformin cohort and insulin cohort of women with gestational diabetes.

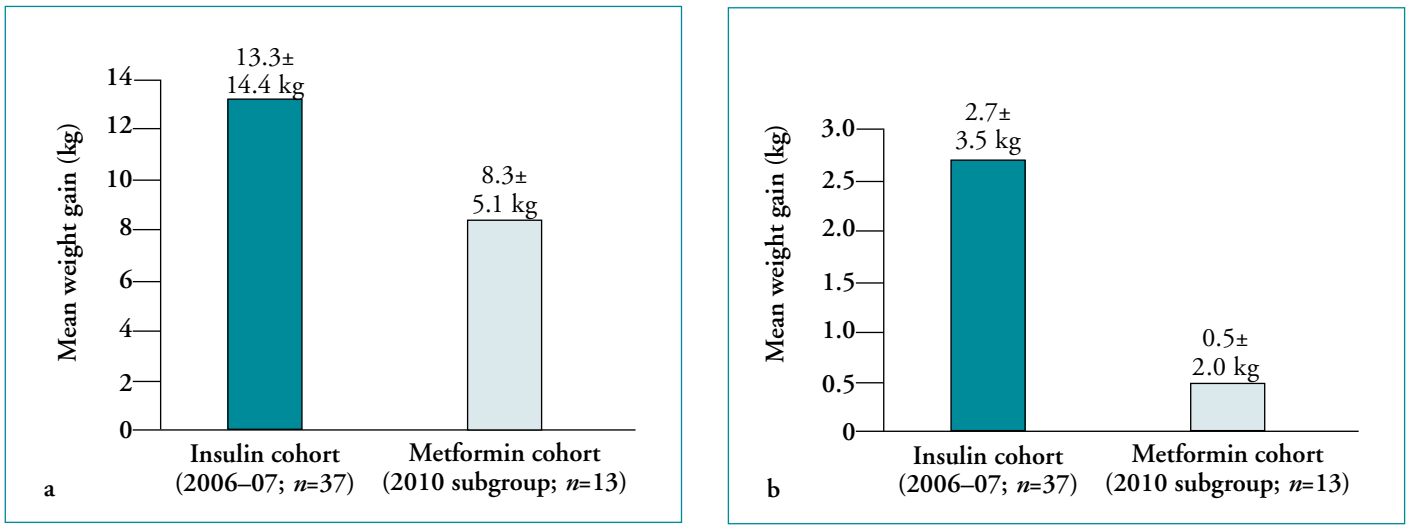

Figure 3. Mean weight gain (kg) comparing women with gestational diabetes mellitus (GDM) in the insulin cohort with a subgroup of 13 women in the metformin cohort classified according to 2006–07 GDM criteria (a) from initial booking to last appointment (P=0.04) and (b) during third trimester (P<0.01).

Page points

1. Metformin use during pregnancy still remains a contentious issue as metformin crosses the placenta, with a lack of data on its effect on future maternal and offspring outcomes.
2. Evidence from studies using metformin in women with polycystic ovary syndrome show reassuringly that there is no effect on social, motor or growth development.
3. This study has shown that the use of metformin with insulin in gestational diabetes mellitus was associated with less maternal weight gain than use of insulin alone.

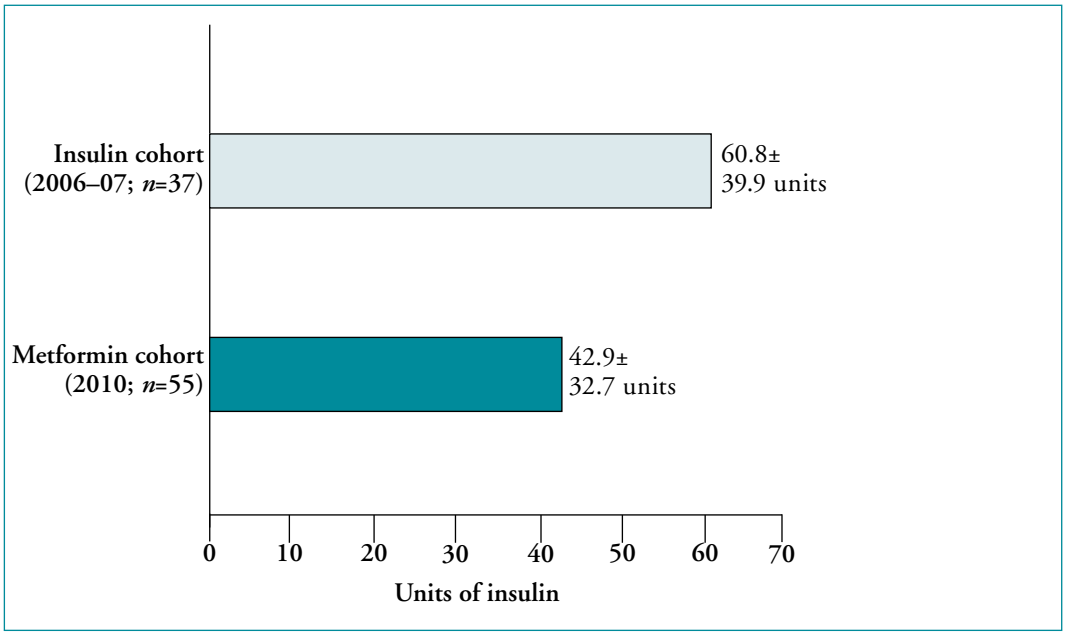

Figure 4. Mean insulin dose requirements (units) in the metformin cohort and insulin cohort of women with gestational diabetes (P=0.03).

women (3.6%) stopped taking metformin because of intolerable gastrointestinal side effects, mainly nausea, vomiting or diarrhoea, or a combination of these symptoms.

Furthermore, in the metformin cohort, those that required supplemental insulin had reduced insulin unit requirements, when compared with the insulin cohort (42.9±32.7 units versus 60.8±39.9 units of insulin, P=0.03; *Figure 4*).

Discussion

Metformin use during pregnancy still remains a contentious issue as metformin crosses the placenta, with a lack of data on its effect on future maternal and offspring outcomes (Maymone et al, 2011). However, evidence from studies using metformin in women with polycystic ovary syndrome show reassuringly that there is no effect on social, motor or growth development (Glueck et al, 2004). There is now a widespread trend towards metformin use during pregnancy. The latest NICE (2008) guidance on diabetes in pregnancy states that metformin may be used in a "risk versus benefit" analysis when compared with insulin in achieving glycaemic targets.

This study has shown that the use of metformin with insulin in GDM was associated with less maternal weight gain than use of insulin alone. This is in line with similar findings from the MiG trial (Rowan et al, 2008), which found that metformin reduced total weight gain from enrolment to 36–37 weeks' gestation (0.4±2.9 kg versus 2.0±3.3 kg, P<0.001). Similarly, Balani et al (2009) found that metformin reduced weight gain from enrolment to delivery (0.94±0.3 kg versus 2.72±0.4 kg, P<0.001). Although neither study compared weights from initial booking visit to delivery, they did find significant differences between enrolment, varying from 20–33 weeks' gestation, to delivery (Rowan et al, 2008; Balani et al, 2009).

In the present study the authors found a reduction in insulin requirements in participants treated with metformin, in line with findings from the MiG trial (Rowan et al, 2008). Only 41.8% in the metformin cohort required supplemental insulin compared with 46.3% in the MiG trial (Rowan et al, 2008) and 10.2% in Balani et al's (2009) study. The large difference between the authors' study and Balani et al's (2009) study can be explained by differences in thresholds for intensifying treatments. Our HBGSM targets were tighter – a fasting threshold of <5.5 mmol/L versus

Balani et al's (2009) <6.0 mmol/L; the 2-hour postprandial targets were identical.

Only 3.6% of participants discontinued metformin, compared with 1.9% in the MiG trial (Rowan et al, 2008). The main reason given for the discontinuation was because of intolerable gastrointestinal side effects. This illustrates that metformin is well tolerated during pregnancy. A questionnaire analysis found women preferred metformin over insulin; 76.6% women stated they would be willing to receive metformin again in a subsequent pregnancy (Rowan et al, 2008). Nevertheless, a drawback of this study was that women were not randomised to treatment with either metformin or insulin use. Instead, the insulin cohort agreed to insulin use as per the protocol at the time. Thus, there are no available data on the probable number of women that may have declined insulin use.

The metformin cohort in this study had a lower BMI at the initial booking and lower 2-hour OGTT diagnostic thresholds than the insulin cohort, suggesting that women in the former group may be inherently less insulin resistant and therefore prone to less weight gain. However, it was appropriate to compare the two groups, as the HBGSM thresholds for commencing treatment were identical. Reassuringly, weight gain difference persisted in the subgroup analysis.

Conclusion

In conclusion, data from this study along with results from the MiG trial (Rowan et al, 2008) illustrate the benefits of metformin in treating GDM. Women on metformin with or without supplemental insulin had significantly less weight gain during pregnancy compared with those on insulin alone. Metformin was well tolerated and reduced the overall insulin unit requirements. ■

This article was derived from an oral and poster presentation at the Diabetes UK Annual Professional Conference, *March 2012, Glasgow, and from an oral presentation at the* 6th United Arab Emirates Medical Students' Conference, *May 2012, Dubai.*

Competing interests: none to declare.

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