Original Article

Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide – A randomised controlled trial

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Background: Two oral hypoglycaemic agents, metformin and glibenclamide, have been compared with insulin in separate large randomised controlled trials and have been found to be as effective as insulin in gestational diabetes. However, very few trials have compared metformin with glibenclamide.

Materials and Methods: Of 159 South Indian women with fasting glucose ≥5.5 mmol/l and ≤7.2 mmol/l and/or 2-h post-prandial value ≥6.7 mmol/l and ≤13.9 mmol/l after medical nutritional therapy consented to be randomised to receive either glibenclamide or metformin. 80 women received glibenclamide and 79 received metformin. Neonatal outcomes were assessed by neonatologists who were unaware that the mother was part of a study and were recorded by assessors blinded to the medication the mother was given. The primary outcome was a composite of neonatal outcomes namely macrosomia, hypoglycaemia, need for phototherapy, respiratory distress, stillbirth or neonatal death and birth trauma. Secondary outcomes were birthweight, maternal glycaemic control, pregnancy induced hypertension, preterm birth, need for induction of labour, mode of delivery and complications of delivery.

Results: Baseline characteristics were similar but for the higher fasting triglyceride levels in women on metformin. The primary outcome was seen in 35% of the glibenclamide group and 18.9% of the metformin group [95% CI 16.1 (2.5, 29.7); $P = 0.02$]. The difference in outcome related to a higher rate of neonatal hypoglycaemia in the glibenclamide group (12.5%) versus none in the metformin group [95% CI 12.5(5.3, 19.7); $P = 0.001$]. Secondary outcomes in both groups were similar.

Conclusion: In a south Indian population with gestational diabetes, metformin was associated with better neonatal outcomes than glibenclamide.

Key words: gestational diabetes, glibenclamide, metformin, neonatal hyperbilirubinemia, neonatal hypoglycaemia.

Background

Over the last decade, a number of large studies[1–5] have made a major impact on the management of gestational diabetes mellitus (GDM).

Two large randomised controlled studies[2,3] have now established that the treatment of mild gestational diabetes can prevent adverse perinatal outcomes. There has been a steep increase in the prevalence of gestational diabetes worldwide[6,7] in the last decade. Until recently, the only mode of treatment for gestational diabetes mellitus not controlled with medical nutritional therapy (MNT) was insulin. Besides having to be administered parenterally, insulin administration has the disadvantage of being expensive, dependent on glucose monitoring, requiring refrigeration and significant training for acquiring the technique for administration.[8,9]

Two oral hypoglycaemic agents, metformin and glibenclamide, have been compared with insulin in separate randomised controlled trials[4,5] and have been found to be as effective as insulin. Glibenclamide is a sulfonylurea that achieves glycaemic control by stimulating insulin secretion. It is known to cause hypoglycaemia and weight gain in the mother. According to earlier studies,[10] glibenclamide did not cross the placental barrier. Recent studies have revealed that umbilical cord plasma glibenclamide levels averaged 70% of maternal concentrations.[11] This should be considered especially if glibenclamide doses are increased to achieve stricter glycaemic control. Metformin, a biguanide derivative, works primarily by reducing hepatic glucose output, improving peripheral glucose uptake, reducing endogenous insulin levels and reducing insulin resistance probably by

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activating AMP kinase.[12,13] AMP kinase independent mechanisms of the drug that include mitochondrial actions have been known for many years and are still believed to be the primary site of drug action. AMP kinase independent effects on the counter-regulatory hormone glucagon have also been recognised.[14]

Therefore, the aim of our study was to compare the neonatal and maternal outcomes in women with gestational diabetes not controlled with MNT with moderate levels of hyperglycaemia treated with glibenclamide or metformin.

Materials and Methods

This study was conducted in a large tertiary centre in south India that has had 10 000 deliveries per annum between the years 2007 and 2010. The protocol was approved by the institutional review board IRB No 6012 19/09/2006 and Clinical Trials Registry of India (CTRI) CTRI/2014/02/004418. A history of high risk factors for gestational diabetes was used as a screening tool. All women who were at a high risk for gestational diabetes had a 100 gm glucose tolerance test performed between 24 to 28 weeks of gestation. The criteria recommended by the National Diabetes Data group[15] were used to diagnose gestational diabetes, (ie when any of two values of fasting glucose ≥5.3 mmol/l, 1 h – ≥10 mmol/l, 2 h – ≥8.6 mmol/l, and 3 h – ≥7.8 mmol/l were abnormal), a diagnosis of gestational diabetes was made. Fourteen per cent of women visiting our antenatal clinic were diagnosed to have gestational diabetes.

The majority of these women (80%) were managed with MNT. Twenty per cent of women with GDM not controlled with MNT who had a fasting blood sugar value ≥5.5 mmol/l, and ≤7.2 mmol/l, or a 2-h postprandial sugar value ≥6.7 mmol/l, and ≤13.9 mmol/l, and who fulfilled the other inclusion and exclusion criteria (Refer Table 1) were invited to participate in the study. Out of the 470 eligible women (Refer Fig. 1), 159 women consented to be randomised to receive either glibenclamide (Daonil – Sanofi-aventis, 54/A, Sir Mathuradas Vasanji Road, Andheri East, Mumbai 400 093 India) or metformin (Glyciphage – Franco Indian Pharmaceuticals Pvt. Ltd. 20, Dr. E. Moses Road Mahalaxmi Mumbai - 400 011) after informed consent was obtained in the local language.

Thus, 80 women were randomised to receive glibenclamide and 79 to receive metformin.

Randomisation to either the metformin or glibenclamide group was done using sequentially labelled opaque sealed envelopes that were arranged by a computer generated random list in a central research office by research officers not involved in patient care. Baseline characteristics (Refer Table 2) were recorded for all randomised women.

Blood for serum HbA1c, serum creatinine, liver enzymes and serum triglycerides were drawn from all patients. Women recruited in the study were taught home capillary blood glucose monitoring using a glucometer. They were taught machine calibration, finger prick technique and strategies to tackle error readings. They were asked to check a minimum of four readings in a week, that is a fasting value, and three 2-h postprandial readings in a week from the beginning of breakfast, lunch and dinner at rotating times. They were advised to record hypoglycaemic symptoms. At each antenatal visit, the research officer recorded the home blood glucose levels documented in her log book after counter checking the values on the recall mode of the glucometer.

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria
1. Pregnant women from 20–33 weeks gestation
2. Fasting glucose ≥5.5 mmol/l and ≤7.2 mmol/l- and/or 2-h post prandial value ≥ 6.7 mmol/l and ≤13.9 mmol/l after MNT.
Exclusion criteria
1. Pre-existing type 1 or 2 diabetes
2. Currently taking metformin for some other indication
3. Multiple pregnancy
4. Recognised fetal congenital anomaly
5. Known abnormal renal or liver function
6. Hypoxic cardio-respiratory disease
7. Malabsorption or some other significant gastrointestinal disease
8. Sepsis
9. Ruptured membranes
10. Gestational hypertension or pre-eclampsia

Women in the glibenclamide group were started on 2.5 mg of glibenclamide, which was given 30 min before a meal. It was started before dinner if the fasting sugars were uncontrolled or before breakfast if the post breakfast or lunch blood glucose levels were not controlled. Blood glucose levels were checked after a week of initiating medication or increasing the dose. The doses were increased once a week in a stepwise fashion if any one fasting value was ≥6.1 mmol/l, or any one postprandial value ≥8.3 mmol/l, or if more than two values were above target values. A maximum total dose of 15 mg of glibenclamide per day was allowed, and a target value of fasting ≤5.3 mmol/l and 2-h postprandial level 6.7 mmol/l had to be achieved in 2–3 weeks.

Similarly, women who were recruited to receive metformin were started on 500 mg, once a day, and this was also increased in a weekly stepwise manner to a maximum of 2500 mg a day allowing a total of 2–3 weeks to achieve target blood glucose values. When women did not achieve target values in 2–3 weeks, insulin was added or women were switched over completely to insulin. Once the target values were achieved, women had antenatal care once every 2–3 weeks.

The obstetric care was continued by the attending obstetrician. All women were induced not later than 39 weeks of gestation. If sugars were not controlled and if a woman had completed 37 weeks, all attending obstetricians chose to induce labour rather than start insulin.

After delivery, all neonates whose mothers received oral antidiabetic agents were transferred to a special care

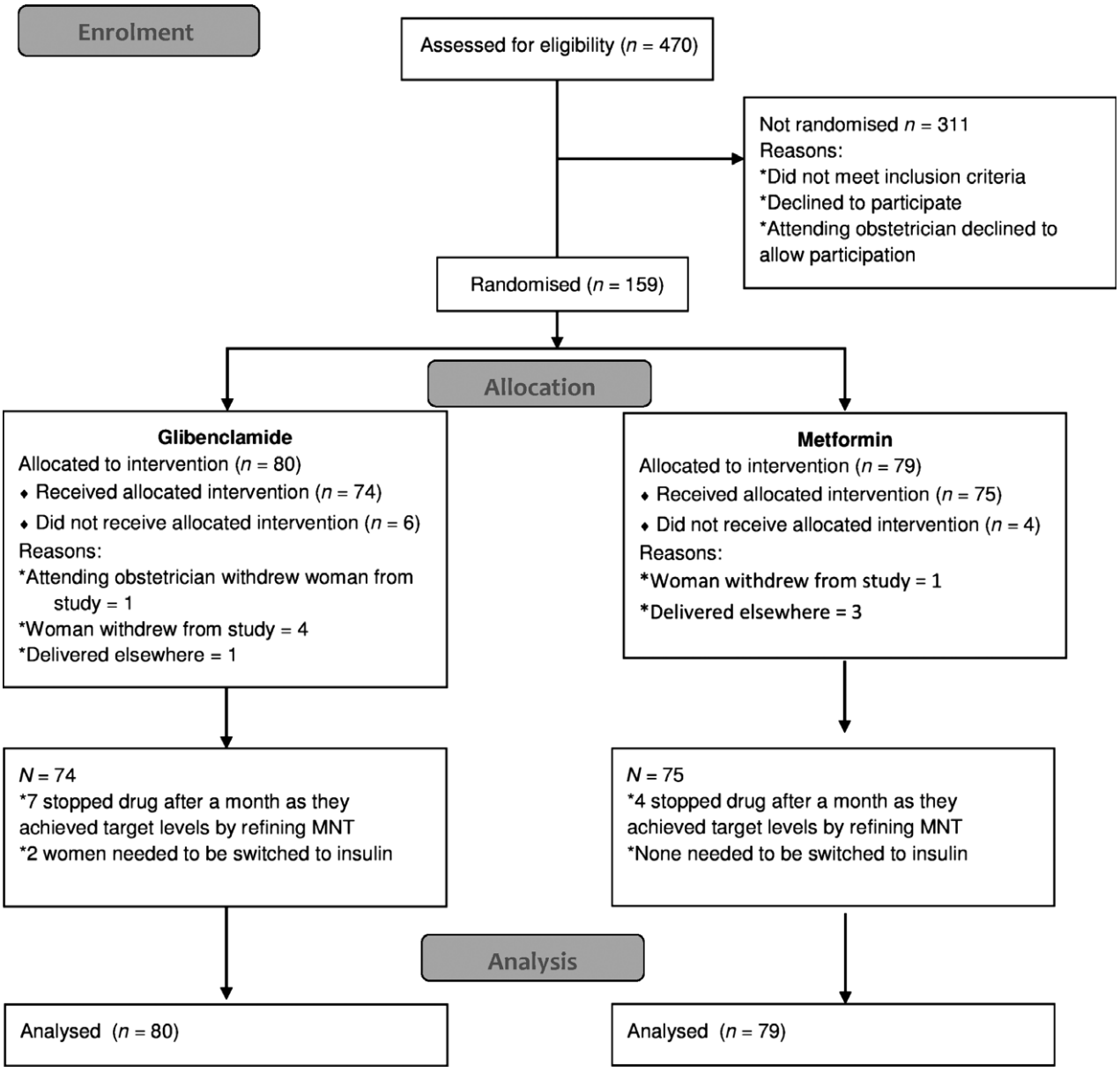

Figure 1 Randomisation flow chart.

nursery and monitored by neonatologists who were masked to the fact that the mother was part of an ongoing clinical trial. The details of the pregnancy, delivery and neonatal outcomes were then recorded by trained research officers who again were masked to the allocation group. Neonates were given hourly feeds. The first feed was usually given within 30 min of birth, and blood glucose levels were checked at 1, 3, 5, 9 and 12 h after birth with a glucometer (Accucheck sensor, Roche, Germany).

The primary outcome of the study was a composite of neonatal outcomes that included:

- Macrosomia – defined as birthweight >3.7 kg based on the 90th percentile by local birthweight data[16]
- Hypoglycaemia defined as blood glucose level ≤2.2 mmol/l[4]
- Need for phototherapy
- Respiratory distress – if the neonate required more than 4 h of respiratory support
- Stillbirth or neonatal death
- Birth trauma – if there was shoulder dystocia, fracture or brachial plexus injury

Thus, a composite outcome was defined as the presence of one or more of the above outcomes.

Secondary outcomes included birthweight, maternal glycaemic control, pregnancy induced hypertension, preterm birth before 34 weeks, need for induction of

Table 2 Baseline characteristics

	Glibenclamide; (n = 80)		Metformin (n = 79)	
Characteristics	Mean	SD	Mean	SD
Age (years)	33.6	4.6	33.4	4.4
Maternal education ≤ 10th standard, *n* (%)	25	31.3	33	42.3
Family history of diabetes mellitus, *n* (%)	47	58.8	39	49.4
Glucose Tolerance Test (GTT) mmol/l				
(a) Fasting	5.6	0.8	5.7	0.8
(b) At 1 HR	11.6	2.0	12.1	1.9
(c) At 2 HR	10.1	2.5	10.8	2.6
(d) At 3 HR	7.8	2.4	8.1	2.7
Fasting Glucose level at randomisation mmol/l	6.1	1.0	6	0.6
Postprandial level at randomisation mmol/l	8.7	1.8	8.6	1.7
BMI (kg/m^2)	28.8	4.0	28.7	4.4
HbA1c %	5.9	0.5	5.8	0.6
Creatinine μmol/l	56.2	6.2	54.5	6.1
SGOT U/L	15.3	4.5	17.7	10.3
SGPT U/L	13.8	8.9	16.1	14.4
Fasting triglycerides mmol/l	2.4	0.6	2.7	0.8
Gestational age at recruitment (wks)	29.7	3.7	29.3	3.3
Gestational age at delivery (wks)	37.8	1.6	38.1	1.6

labour, mode of delivery and complications of delivery such as third and fourth degree perineal tears.

86 women per group were required to detect a difference of at least 20% in the neonatal composite outcome with 80 per cent power using a two-sample proportion test with two-sided 5% level of significance. At the inception of the study, a retrospective analysis of women with gestational diabetes on glibenclamide over 6 months in our institution showed a composite neonatal outcome of 40%. Findings from a small cohort of women on metformin published by Coetzee et al[17] showed low neonatal morbidity. Hence, we assumed a composite neonatal outcome of 40% in glibenclamide group and 20% in metformin group. An interim analysis requested by the local data monitoring committee showed significant difference in outcomes in the two groups, and hence, this study was stopped before we achieved the total sample size.

The data were summarised as frequencies and percentages for categorical variables and mean and standard deviations for continuous variables. Differences in the primary and secondary outcome variables were compared by the chi-square test or Fisher's exact test for categorical variables and a two-sample *t*-test for continuous variables. Absolute differences in the outcomes between the two randomised groups were estimated with 95% CI. Statistical analyses were based on the intention-to-treat principle, and STATA statistical software version 13 was used. (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP)

Results

Of the 80 women (Fig. 1) in the glibenclamide group, the attending physician withdrew one woman from the study, four women withdrew from the study themselves and one woman delivered elsewhere. Seventy-four women completed the study, but seven stopped taking the drug after about a month as they achieved target levels without the drug by refining the MNT. Two of the women on glibenclamide needed to be switched to insulin, and two women had hypoglycaemic symptoms necessitating dose reduction by 2.5 mg. 65% (48/74) of women on glibenclamide needed only 2.5 mg to achieve target blood glucose values, and 22% (16/74) needed a total of 5 mg.

Of the 79 women randomised to the metformin group, one woman withdrew from the study and three women delivered elsewhere. Thus, 75 women completed the study. Four women stopped taking the drug as the target level was achieved without the drug, again by refining the MNT. None of the women in the metformin group were switched to insulin therapy. Maternal hypoglycaemia requiring a dose reduction of 250 gms was seen in three women. One woman complained of epigastric burning. 57% (44/75) needed 500 mg once a day, and 21% (16/75) needed 1 gm once a day to achieve target levels. The rest of the women needed higher doses.

Baseline characteristics were similar (Table 2) except that the group treated with metformin had significantly higher fasting triglyceride levels 2.7 mmol/l (±0.83) vs 2.4 mmol/l(±0.65) $P = 0.05$). The primary outcome that was the composite of any of the 6 neonatal outcomes (Table 3) was seen in 35% (28/80) of the glibenclamide group and 18.9% (15/79) of the metformin group [95% CI 16.1 (2.5, 29.7); $P = 0.02$]. Hypoglycaemia was seen in 12.5% of (10/80) neonates in the glibenclamide group, but none of the neonates in the metformin group [95% CI 12.5 (5.3, 19.7); $P = 0.001$] had hypoglycaemia. 22.5% (18/80) neonates born to women treated with glyburide needed phototherapy while 17.7% (14/79) neonates of women treated with metformin [95% CI 4.8 (−7.6, 17.2); $P = 0.45$] needed phototherapy. 7.2% of women had more than one outcome present. Among the neonates that had hypoglycaemia, six had two or more values that were ≤2.2 mmol/l and four had one value ≤2.2 mmol/l.

Among the secondary outcomes (Refer Table 4), the mean birthweight adjusted for gestational age at delivery, height of the mother, and gender of the newborn was similar in the glibenclamide group (3037 gms ± 204 gms) and metformin group (3064 gms ± 202 gms) [95% CI 27 (−90.6,36.6) $P = 0.40$]. Centiles of adjusted birthweights were also comparable between the groups. The glycaemic control as assessed by the average of home capillary blood

Table 3 Primary outcomes

	Glibenclamide (n = 80)		Metformin (n = 79)			
Characteristics	No.	%	No.	%	(95% CI)	P value
Composite outcome*	28	35.0	15	18.9	16.1 (2.5, 29.7)	0.02
Macrosomia (3.7 kg and above)	3	3.8	4	5.1	1.3 (−7.7, 5.1)	0.73
Hypoglycaemia	10	12.5	0	0.0	12.5 (5.3, 19.7)	0.001
Need for phototherapy	18	22.5	14	17.7	4.8 (−7.6, 17.2)	0.45
Respiratory distress	4	5.0	2	2.5	2.5 (−7.7, 5.1)	0.41
Stillbirth or neonatal death	0	–	0	–	–	–
Birth injury	0	–	0	–	–	–

*Composite outcome is defined as one or more of the neonatal complications (hypoglycaemia, hyperbilirubinemia, macrosomia, respiratory illness, birth injury, stillbirth or neonatal death).

glucose monitoring was similar in both groups. Other secondary outcomes were similar in both groups. More women in the glibenclamide group were induced when compared to the women allocated to the metformin group, 61.3% versus 49.4% [95% CI 11.9, (−3.4, 27.2); P = 0.13], but this was not significant.

Discussion

The main finding of this randomised controlled trial comparing metformin with glibenclamide in gestational diabetes with moderate levels of hyperglycaemia was that a composite of neonatal complications was significantly less common in neonates of women treated with metformin. Neonatal hypoglycaemia was the main complication that contributed to this difference in composite outcomes. The major strength of this trial was that, the neonatal outcomes were recorded by research officers who were masked to the treatment arm and the neonatologists looking after the babies were unaware that the mother was part of a study and this avoided bias.

The incidence of neonatal hypoglycaemia in the metformin and glibenclamide groups of our study was very similar to that seen in several studies[4,5,17–19] that looked at neonatal outcomes of women treated with metformin or glibenclamide. Most importantly, as in our study, the large MiG study[5] showed very low rates of neonatal hypoglycaemia in the metformin arm. The difference in hypoglycaemia could relate to placental passage of the two oral agents and their differing effects in the fetus. However, difference in glucose control and early delivery gestation could possibly be contributing factors.

Until now, there have been only two studies[19,20] with a relatively small sample size that compared these two oral antidiabetic agents. Both these studies were not adequately powered to look at neonatal outcomes. Unlike these studies, we included only women with moderate hyperglycaemia, and this may explain why very few of the women needed to be changed over to insulin. We included only women with moderate levels of hyperglycaemia because we wanted to study a group of women who were less likely to need insulin. A retrospective study[21] done in our centre showed

Table 4 Secondary outcomes

	Glibenclamide (n = 80)		Metformin (n = 79)			
Characteristics	No.	%	No.	%	95% (CI)	P value
Adjusted birthweight (g)*†	3037	204	3064	202	27 (−90.6, 36.6)	0.40
Maternal glycaemic control (mmol/l)						
Fasting*	4.8	0.8	4.9	0.6	0.1 (−0.3, 0.1)	0.37
Post breakfast*	6.8	1.0	7.0	1.1	0.2 (−0.5, 0.1)	0.23
Post lunch*	6.4	1.2	6.6	0.9	0.2 (−0.5, 0.1)	0.24
Post dinner*	6.7	1.3	7.0	0.3	5.0 (−0.7, 0.1)	0.13
Pregnancy induced hypertension	9	11.3	7	8.9	2.4 (−6.9, 11.7)	0.62
Preterm birth	1	1.25	3	3.79	2.54 (−7.4, 2.3)	0.31
Induction of labour	49	61.3	39	49.4	11.9 (−3.4, 27.2)	0.13
Mode of delivery						
caesarean delivery	28	35.0	31	39.2	4.2 (−19.2, 10.8)	0.58
Complications of delivery						
3rd and 4th degree perineal tear	1	1.3	1	1.3	0.0 (−3.5, 3.5)	0.99

*Summarised as mean and standard deviation.
†Birthweight adjusted for gestational age, maternal height and gender.

that among the women who needed additional treatment after MNT, 75% had moderate hyperglycaemia.

The drawbacks of our study were that we were unable to achieve intense home blood glucose monitoring as seen in previous large randomised controlled studies as our women refused to comply. As this study was performed with a relatively low budget, we could not record anthropometric measurements of the neonate or evaluate umbilical cord C peptide levels or fetal insulin assays. We did not check serum lactate levels in women randomised to receive metformin. A composite primary outcome was chosen but neonatal hypoglycaemia and need for phototherapy were the main contributors to the difference. However, multiplicity of data analyses made interpretation of statistical tests of individual primary outcomes difficult to interpret.

Despite the above drawbacks, use of these oral hypoglycaemics in our study was associated with good pregnancy outcomes and was comparable to optimally managed women with gestational diabetes. It would also be pragmatic to infer that decrease in neonatal hypoglycaemia was an indirect but important manifestation of decreased fetal hyperinsulinemia and that with the use of metformin there would be a decrease in neonatal hypoglycaemia and other complications associated with fetal hyperinsulinemia. Neonates of women on metformin would be likely to need less surveillance, admission to special care nursery and to have shorter hospital stays. This would result in financial benefits to the woman and to the hospital. Thus, the findings of our study show that in a south Indian population, metformin is the preferred oral hypoglycaemic agent in gestational diabetes with moderate hyperglycaemia.

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