

## Comparison of Newborn Outcomes in Women with Gestational Diabetes Mellitus Treated with Metformin or Insulin: A Randomised Blinded Trial

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### ABSTRACT

**Background:** Few studies have been done on the use of metformin in pregnancy and their results were not similar, therefore this research is performed to compare neonatal outcomes of metformin and insulin in the treatment of gestational diabetes.

**Methods:** In this prospective randomized trial, 200 pregnant women within their 24<sup>th</sup> to 34<sup>th</sup> weeks of gestation with gestational diabetes, single fetus pregnancy, and in need of hyperglycemia treatment were entered and grouped as either metformin or insulin. Data related to maternal and neonatal outcomes were recorded and analyzed.

**Results:** Considering data recorded of HbA<sub>1c</sub> at the beginning of pregnancy, pregnancy induced hypertension, preeclampsia, birth weight, dystocia, first and 5<sup>th</sup> min APGAR, neonatal sepsis, rout of delivery, liver function tests of neonate, hypoglycemia, anomaly, and still birth, there were no significant statistical differences between groups. The end pregnancy HbA<sub>1c</sub>, maternal weight gain during pregnancy, preterm labor, neonatal jaundice, respiratory distress and hospitalization of infants were higher in insulin group.

**Conclusions:** Considering data from this study, metformin is efficient to control hyperglycemia in pregnancy. It is suggested performing more studies to evaluate long term side effects of metformin in pregnancy with higher sample size and longer follow-up of newborns.

**Keywords:** Hemoglobin A<sub>1c</sub>, glucose tolerance test, hyperglycemia, pregnancy

### INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any glucose intolerance that occurred or is diagnosed for the first time during pregnancy.<sup>[1]</sup> It is common<sup>[2]</sup> and complicates about 3-6% of all pregnancies.<sup>[1,3]</sup> These days GDM prevalence is thought to be increasing due to increased pregnancy age and higher maternal weight.<sup>[4,5]</sup>

Women with uncontrolled GDM are at higher risk for pregnancy related complications such as preterm labor, septic effects, hydramnios, and hypertensive disturbances<sup>[6,7]</sup>.

Some adverse effects of GDM affect fetus including fetal anomalies, macrosomia, fetal distress, metabolic disorders, growth imbalance, hyper bilirubinemia, and some long term complications.<sup>[3]</sup> Considering adverse effects mentioned, GDM treatment seems to have great benefits.<sup>[8,9]</sup>

Medical treatment is initiated if glucose control levels are not achieved by lifestyle modifications such as exercise and dietary changes.<sup>[10]</sup> Traditionally, insulin has been the golden key for treatment in GDM patients. No placental passage and fine glucose level control are established benefits of insulin administration in pregnancy.<sup>[11]</sup> On the other hand, insulin usage has some disadvantages and doubts remain about insulin consumption inconveniences in pregnancy. These include the need for multiple injections, maternal hypoglycemic risk, higher maternal weight gain during pregnancy (possibly due to increased appetite), and increased treatment costs.<sup>[2,12]</sup>

Various studies have shown that an oral anti glycemetic drug may not only have better maternal and fetal consequences but also could bring patients' acceptance.<sup>[12-14]</sup> Metformin has been introduced as an alternative drug for insulin in GDM treatment theoretically.<sup>[15]</sup> This agent induces less gluconeogenesis and higher peripheral glucose uptake. Reducing insulin resistance is of great concern as well.<sup>[12]</sup> Tertti *et al.*, in 2008 after studying 173 patients with GDM concluded that metformin did not induce maternal hypoglycemia, excessive maternal weight gain during pregnancy, and major fetal anomalies.<sup>[15]</sup> In some other studies, it has been shown that metformin administration in GDM has not been accompanying neonatal disorders.<sup>[16-18,21]</sup>

Reviews of some studies comparing metformin and insulin in GDM show discrepancies about few complications. Rowan *et al.*, in 2008 showed that pre-term labor in metformin takers was rather higher than those injecting,<sup>[18]</sup> but Hyer and colleagues demonstrated that this effect was higher in the insulin group compared with metformin group.<sup>[19]</sup> Clinical trial of Lavanya *et al.*, showed that small for gestational age neonates (SGA) were significantly more in the insulin group versus the metformin group<sup>[20]</sup> but two other studies mentioned that SGA incidence was not of significant statistical

concern.<sup>[12,15]</sup> Results of studies accomplished by Hyer *et al.*, and Balani *et al.*, show that birth weight percentile in the metformin group has been vividly lower when compared to the insulin group.<sup>[12,19]</sup> Tertti *et al.*, observed no significant statistical difference between insulin and metformin groups considering neonatal hyperbilirubinemia (in need of photo therapy), but neonatal hypoglycemia during first 2 h of birth (which necessitated intravenous glucose administration) has been more prevalent in insulin group.<sup>[15]</sup> In the study of Balani *et al.*, neonatal hyperbilirubinemia and NICU admission were more in the insulin group.<sup>[12]</sup> Rowan *et al.*, showed that neonatal hypoglycemia was less in the metformin group compared with the insulin group.<sup>[18]</sup> Two other studies have proposed that there has been no statistical significance considering birth weight and macrosomia between two groups of insulin and metformin.<sup>[12,14]</sup>

As mentioned above, considering globally, so far, the number of studies designed to compare the benefits and the adverse effects of insulin and metformin on pregnancy outcomes are not so much. On the other hand, results from these studies are not similar. Considering national concerns about GDM treatment in Iran, to date, it is not well accepted to subscribe any drug other than insulin for GDM treatment. So, for the first time in Iranian medical history this study was done in order to introduce an oral anti hyperglycemic agent to Iranian obstetricians.

The aim of this study was to investigate metformin outcomes in early neonatal period in neonates of women treated with this drug and comparing it with insulin taker outcomes.

## METHODS

In this prospective, blinded randomized clinical parallel-group trial performed in Shabih Khani hospital, Kashan University of Medical Sciences, Isfahan, Iran, 200 pregnant women, 18 to 45 years old with a single fetus pregnancy and without any history or documented diagnosis of diabetes prior to pregnancy and with gestational age of 24-34 weeks, were screened for GDM with glucose challenge test (GCT) (plasma glucose level test 1 h after oral intake of 50 grams glucose) [Figure 1]. Any patient with impaired GCT was evaluated with a complementary test (glucose tolerance test,

GTT: checking fasting blood sugar and BS of 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> h after oral intake of 100 grams glucose). GDM diagnosis was made if 2 out of following 4 results were obtained:

- FBS > 95 mg/dl – BS 1h > 180
- BS 2h > 155 – BS 3h > 140

Sample size was calculated based on data of previous studies; (12)

$$\alpha = 95\% \quad \beta = 80\% \quad d = 0.13$$

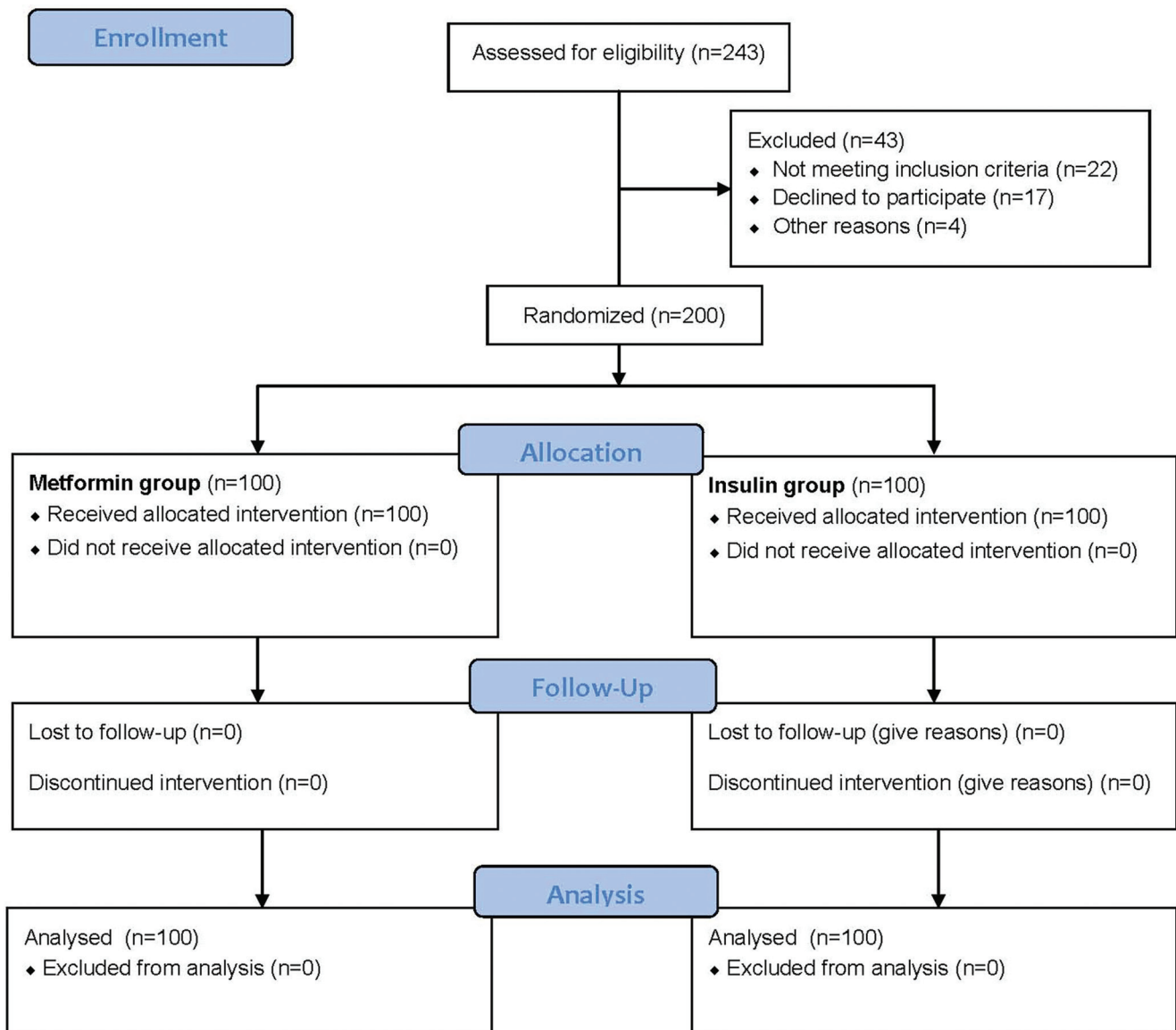
$$P_1 = 0.19 \quad P_2 = 0.06$$

Randomization was generated by a third party physician using tables of random numbers. Care providers and physician assessing outcomes were blinded in this study.

GDM mothers were taught lifestyle modification initially. Plasma glucose levels of fasting and 2 h after breakfast, lunch and dinner were recorded within one week. If FBS > 95 or BS 2h > 120 were obtained, it was assumed that lifestyle modifications had not been sufficient and necessitated drug administration. At this point having received a written informed consent patient's entrance to study was registered.

All demographic data including age, body mass index (BMI), gestational age, family history of diabetes and Hb<sub>A1C</sub> were recorded.

Patients were grouped randomly as metformin or insulin groups. Sample size was calculated based



**Figure 1:** flow diagram of the progress through the phases of parallel randomised trial of two groups

on data in previous studies and GDM prevalence in Kashan city, Isfahan, Iran.

An important harm in metformin group was inefficient plasma glucose control and need of additional insulin. Of 200 women enrolled in this study, 100 women were treated with insulin and 100 were treated with metformin. In metformin group 22 women required supplemental insulin to achieve target values of plasma glucose. These patients were excluded and replaced with new patients. There after study was continued with 100 patients in metformin group.

Every GDM mother was admitted in obstetrics ward. Plasma glucose target levels were defined as FBS < 95 mg/dl and BS 2h < 120 mg/dl. Patients in the metformin group (100 patients) received metformin tablets with an initial dosage of 500 mg/d and if necessary, dose adjustments were made up to 2500 mg/d. In insulin group (100 patients), insulin was administered with an initial dose of 0.5 IU/kg/d divided as 2/3 of total dose injected in the morning and 1/3 in the afternoon. Two third of total Insulin dosage was injected as NPH insulin and 1/3 as regular. If target levels of BS were not obtained, as any 10 mg/dl of glucose level more than target levels, 1 IU of NPH or regular insulin (depending on the time of impaired glucose intolerance) was added to initial insulin dose. After achieving target levels of BS, the patients were discharged with written prescription of drug and follow-up schedule for every 2 weeks.

FBS and BS of 2 h after a meal were recorded every two weeks up to labor time. Any disturbance in glucose level control was observed and new dose adjustments were accomplished if required. Under this condition, follow-up visits were done on weekly basis. The newborns of GDM mothers had a follow up for 1 week.

Data related to demography, HbA<sub>1c</sub> after delivery, method of delivery, hypertension, pre-eclampsia, mean birth weight, shoulder dystocia, first and 5<sup>th</sup> min Apgar, neonatal sepsis, and jaundice, as well as hypoglycemia and respiratory distress, fetal anomalies and NICU admission were recorded. Umbilical blood samples for liver function tests of newborn babies were also obtained.

Results were analyzed with SPSS software version 11.5 using Fisher's exact test, Kolmogorov Smirnov test, Mann-whitney test, paired *t* test, Chi-square, Leven's test and Haenszel- Mantel test.

## Ethics

Having received a written informed consent approval by Kashan University of medical sciences ethics committee in medical research, Kashan, Iran, (based on World Medical Association Declaration of Helsinki regarding ethical conduct of research), patient's entrance to study was registered.

This study is registered in Iranian Registry of Clinical Trials (IRCT) as trial number: *IRCT201104162699N5*.

## RESULTS

Among 100 patients in the metformin group, 22 patients required supplemental insulin for glycemic control. These patients were excluded from the study.

Patients were carefully checked during the study and no cross-over effect was detected.

Considering demographic data, no statistical differences were observed between groups [Table 1].

Thirty two percent of newborns in group and 47% in metformin group had a birth weights between 3001-3500 grams. The insulin group contained more neonates with birth weight more than 4 kg rather than the metformin group but it revealed no statistical differences between groups.

In this study no case of small for gestational age babies (SGA) was observed. But, LGA was explored in 24% of insulin group babies and 16% in the metformin group, although no difference was vivid statistically.

Considering the Apgar score of first and 5<sup>th</sup> min after birth, shoulder dystocia, neonatal hypoglycemia, and sepsis, fetal anomalies and

**Table 1:** Clinical characteristics

Characteristic	Insulin N=100	Metformin N=100	Statistical significance
Age (year)	30.2±5.9	29.6±5.3	NS
BMI of pregnancy beginning (kg/m <sup>2</sup> )	28.46	27.6	NS
Hb <sub>A1c</sub> at the time of entering the study (mg %)	6.3±1.1	6.2±1.6	NS
Gestational age at the time of entering the study (week)	28.9±3.8	27.9±3.22	NS
Familial history of diabetes mellitus	12	9	NS

NS=Not significant, BMI=Body mass index

umbilical cord blood sample for liver function tests of newborns, no significant statistical differences were seen between groups.

Neonatal respiratory distress was more prevalent in the insulin group rather than the metformin group. (15 vs. 6) ( $P=0.038$ ).

Neonatal jaundice and hyper bilirubinemia showed significant statistical differences between groups. (13 in the insulin group vs. 4 in the metformin group –  $P=0.02$ ).

NICU admission was more in the insulin group. (33 vs. 14) ( $P=0.002$ ) main causes of hospitalization were hyper bilirubinemia in need of photo therapy, respiratory distress, and hypoglycemia.

Eight cases of preterm labor occurred in insulin group, but the metformin group had none ( $P=0.007$ ) [Table 2].

At the delivery time, HbA<sub>1c</sub> was checked once more in order to assess glycemic control. Significant statistical difference was observed between groups ( $4.86 \pm 0.70$  in the metformin group vs.  $5.12 \pm 0.84$  in the insulin group –  $P=0.021$ ).

## DISCUSSION

It was proved in this study that metformin could be an efficient and practical alternative for insulin in GDM treatment. Without any influence on intrinsic production of insulin, metformin increases peripheral sensitivity to insulin and also reduces the plasma insulin level.

**Table 2:** Neonatal outcomes in trial groups

Neonatal outcome	Metformin N=100	Insulin N=100	Statistical significance
Birth weight (g)	3512±484	3528±563	NS
Birth weight >4 kg	11	18	NS
LGA	16	24	NS
Jaundice	4	13	$P=0.02$
Hypoglycemia	10	15	NS
Respiratory distress	6	15	$P=0.038$
NICU admission	14	33	$P=0.002$
Anomaly	0	3	NS
Shoulder dystocia	2	0	NS
Prenatal mortality	0	0	NS
Sepsis	4	3	NS
5 <sup>th</sup> min. apgar <7	0	0	NS
Preterm labor	0	8	$P=0.007$

LGA=Large for gestational age, NS=Not significant, NICU=Neonatal intensive care unit

In our study no significant differences were observed between metformin and insulin groups related to birth weight and macrosomia. Balani *et al.*, and Terti *et al.*, showed similar findings in their studies.<sup>[12,15]</sup>

Small for gestational age (SGA) is defined as birth weight less than 10% of normal value. We recorded no case of SGA infants. On the other hand, large for gestational age, (LGA), defined as birth weight more than 90% of normal weight, was observed in 24 patients of insulin group versus 16 in the metformin group, although not statistically significant. Rowan *et al.* and Terti *et al.* also reported similar.<sup>[15,18]</sup>

First and 5<sup>th</sup> min apgar scores revealed no difference between the 2 groups statistically, of similar results were reported by Rowan and Terti.<sup>[15,18]</sup>

The statistical significance of preterm labor between metformin and insulin groups (8 in the insulin group versus 0 in the metformin group-  $P=0.007$ ) in this trial is similar to findings in Balani *et al.*, study.<sup>[12]</sup> But, Rowan *et al.*, mentioned that preterm labor in metformin group is higher than insulin group.<sup>[18]</sup> This could be due to phenomenon of chance or an unknown effect of metformin on labor cycle.

Theoretically it is accepted that pre term neonates are at higher risk for respiratory distress and hospitalization.

Neonatal ICU admission up to 1 week after birth has been of significant statistical value among groups. Insulin group infants were admitted in NICU about 2 folds more than metformin group infants. (RR = 2.35) Balani *et al.*, reported similar results<sup>[12]</sup> but Rowan *et al.*, showed no statistical significance between groups related to admission.<sup>[18]</sup> It is assumed that higher rate of NICU admission in the current study and Balani *et al.*, study could be due to higher prevalence of preterm labor in these studies.

Neonatal hyperbilirubinemia was significantly more in the insulin group in our study. Balani *et al.*, have also reported as such.<sup>[12]</sup> But Terti *et al.*, showed no statistically significant difference between groups.<sup>[15]</sup> This is believed to be related to higher rates of preterm labor in the current study, as well as study done by Balani *et al.*

Respiratory distress of newborns among infants of the insulin group were more rather than the

metformin group infants in the current study and revealed a statistically significant difference between groups. ( $P = 0.038$ ) (RR = 2.5) this could be due to more preterm labors in the insulin group. Rowan *et al.*, reported no statistically significant difference between groups on this topic.<sup>[18]</sup> This may be due to more immature lungs among preterm neonates in our study rather than study done by Rowan *et al.*

Neonatal hypoglycemia revealed no statistical significance between groups in our trial. Terti *et al.*, reported no statistical significance either.<sup>[15]</sup> But, Rowan *et al.*, reported lower rate of hypoglycemia in metformin group rather than insulin group. ( $P = 0.008$ )<sup>[18]</sup> This could be due to considering hypoglycemia as BS less than 28.8 mg/dL in the study of Rowan *et al.*, and less than 35 mg/dL in current study.

Although, higher rates of anomalies were observed in the insulin group rather than metformin group neonates (3 vs. 0), but it revealed no statistical differences between groups in our study. Terti *et al.*, concluded in their trial that metformin does not result in great fetal anomalies but due to its passage via the placenta, it would be of concern.<sup>[15]</sup> This statement has been documented by Hawthorne, Rowan and Balani either.<sup>[12,18,21]</sup>

No statistical difference were observed among study groups related to infantile sepsis in this trial, as well as study performed by Rowan *et al.*<sup>[18]</sup>

No case of stillbirth was observed in the current study, as well as Balani *et al.*, study.<sup>[12]</sup>

Due to hepatic metabolism of metformin and its passage via the placenta, it could be doubtful whether it alters hepatic function of a newborn baby or not. Statistical analysis revealed no significant difference among groups related to umbilical blood samples of AST, ALT and ALP levels. So, metformin may be of no danger to the liver in the fetus.

Evaluating degree of glucose control in days before delivery necessitated measuring HbA<sub>1c</sub> at the time of delivery. Although, statistical difference was observed between groups and metformin receivers had better glucose control, but mean values of both groups were within normal range of glucose control. This elucidates that metformin is as effective as insulin in controlling blood sugar level.

Long term side effects of metformin on newborns may be of great concern either. Recent data regarding this aspect show that after 2 years

follow-up of children whose mothers had taken metformin or insulin for GDM control in Australia and New Zealand, children exposed to metformin had larger measures of subcutaneous fat, but overall body fat has been the same as in children whose mothers were treated with insulin.<sup>[22]</sup>

Main limitation of this study are believed to be some patient's non compliance for routine follow-up, and some difficulties in laboratory tests such as inadequacy of instruments and low technical experience of some laboratory technicians.

## CONCLUSION

Regarding the results of the current study, it is concluded that metformin can be an excellent alternative for insulin in the treatment of GDM. It is associated with fewer complications for fetuses and maternal acceptance may be better.

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