

# Comparison of Metformin and Insulin in treatment of Gestational Diabetes Mellitus

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## Original Article

### Abstract

**Introduction:** Gestational Diabetes Mellitus (GDM) is one of the complications of pregnancy that has some maternal and neonatal outcomes. Some drugs such as insulin and oral agents (metformin, ...) are used for management of GDM. The aim of this study was to compare metformin and insulin in treatment of GDM

**Methods:** This clinical trial was carried out in 2009-2011. Sample size was 201 patients. Patients were selected with Block permutation and divided to two groups, including 156 women treated with insulin and 51 with metformin. Single-blind for physicians, women treated with metformin, (500mg one or two times in a day). Insulin administration was according to multi day injection program and starts with NPH and regular Insulin. Blood sugar status of mothers and neonates and neonatal complications in both groups were followed up after discharge by telephone or direct interview.

**Results:** There were no statistically significant differences between both groups in maternal oral glucose tolerance test and FBS, and risk factors. No significant differences were seen in birth weight, head circumference, chest circumference, height, neonatal trauma, incidence of dystocia, neonatal trauma, respiratory distress, sepsis, fetus anomaly. The prevalence of first six months and second six months were similar in both groups but the prevalence of third six months and fourth six months were significantly increased in the group of women treated with insulin compared to women treated with metformin ( $P < 0.001$ ).

**Conclusion:** Metformin therapy is clinically effective control of blood sugar in most of the women with GDM without any significant side-effects in the mother or in the fetus-neonate and it can be a safe alternative to insulin therapy.

**Key words:** Diabetes, Gestational, Insulin, Metformin

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### Introduction:

Diabetic women and their children are a lot exposed for different and sometimes dangerous complications. Sometimes these complications are

in direct interaction with intensity of maternal hyperglycemia. So the aim of pregnancy therapeutic programs is precise control of blood sugar before and through the pregnancy. The best way to do such thing is a group of different

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specialists and special education to the patients for controlling the diabetes (1). But the main problem is most of the pregnant women with GDM are asymptomatic and active screening should be done to prevent maternal and fetal complications (2).

One of the known characteristics of the diabetes in pregnancy is it has profound effect on maternal metabolism. These correlated differences with pregnancy in maternal body metabolism are needed for fetal needs. Studies on slim and healthy women have shown that the decreasing effect of glucose due to external usage of insulin in first trimester of pregnancy is more than the effect of insulin in last trimester of pregnancy.

#### Gestational diabetes mellitus

Gestational diabetes mellitus is a common complication and nearly 5% of pregnancies are involved in US. This disorder is seen in special subgroups such as individuals with positive family history of type 2 diabetes, increased maternal age, obesity, Hispanic races, uncontrolled GTT in black Americans, Spaniards, and American natives and Indian or middle eastern native women (3).

#### Staging of Diabetes:

Generally diabetes mellitus is divided in type 1 or insulin dependent (IDDM) or type 2 non-insulin dependent and gestational diabetes mellitus (GDM) (3). It is believed that most of the women in reproductive age are susceptible to type two diabetes as the reproductive age is increasing in these decades. GDM mainly is due to impairment of intolerance of carbohydrates by starting of the pregnancy. If impaired GTT is continued after pregnancy, patient may be diagnosed with diabetes type 1, type 2, or impaired glucose tolerance test (4).

#### Maternal Complications

Despite the recovery and improvement of pregnancy results and diabetes in gestational diabetes and prenatal gestational diabetes, these women are more susceptible for incidence of post partum diabetes. The complications are premature delivery, infectious complications, hydramnious and hypertensive disorders. Many of these disorders are correlated with uncontrolled blood sugar (5). Also women with prenatal gestation diabetes are prone to

acute diabetic complications because of diabetic metabolic complications and diabetic vascular complications, nephropathy, and retinopathy should be both precisely controlled (1).

#### Fetal Complications:

Risk of fetal complications increase in women with GDM which are fetal macrosomias, respiratory distress syndrome, metabolic disorders (6). Two of the main causes of perinatal mortality and morbidity are death of the fetus without cause and maternal malformations. Other unpredicted conditions are not completely understood.

As the patient needs to be trained how to inject the insulin and many of the patients come irregularly to the clinic or doctor's office to learn insulin injection, it's preferred that pregnant women use metformin for their own ease because it's use is simple and most patients prefer oral medications to injections. The aim of this study was to compare the efficacy of metformin with insulin in GDM in pregnant women.

#### Methods:

In this single blinded clinical trial which began from March 2009 till February 2011 in Shariati Women's hospital in Bandar Abbas, pregnant women with GDM were enrolled. The physicians were blinded in the study.

Inclusion criteria (according to Williams criteria for GDM i.e. impaired GTT)

Single pregnancy, age between 18-45 years, the patients had normal hospital criteria for initiation of insulin (7,8) and the patients were on a diet for 2 weeks and had exercise intervention, a capillary blood glucose after an overnight fast of 90 mg/dl or more than one 2hpp above 120mg/dl.

#### Exclusion criteria:

Pregestational Diabetes, intake of metformin, fetal anomalies, pregnancy induced hypertension, pre-eclampsia, IUGR, and ROM. In all groups the goal was FBS of less than 90mg/dl and 2hpp of lower than 120 mg/dl.

In this study, if the patients didn't respond to the diet or exercise they were candidate for either insulin or metformin treatment. The patients

themselves selected metformin, as it was a new alternate to insulin.

The patient has breakfast at 6 am, and at 8 am 2hpp was checked; the lunch is taken at 14 pm and blood sugar is checked at 16 hpp (2hpp).according to blood glucose charting for 48 hrs metformin's half life, Metformin is given every 6hrs i.e. 12am, 6 am, 12 pm, 6 pm.

In metformin group, metformin manufactured by Apotex® under brand name of Apo-metformin is administered once or twice daily 500mg with food and is increased during 48-72 hours till the appropriate blood sugar is achieved. Even the dose of metformin may be increased to 2000 mg/day.

In case that aim of treatment with metformin after 48-72 hours was not acceptable, insulin would be replaced.

Insulin administration was according to hospital routine (a 2hpp of 120, impaired FBS > 90 mg/dL) with a dose of 0.5-1 unit/kg according to gestational age. (0.5 IU/kg in first trimester, 0.7unit/kg in second trimester and 1 IU/kg in third trimester) according to multiday injection with (1/3) NPH and (2/3) regular.

Then the mother and newborn were followed up for 2 years by telephone after delivery and if required they were followed face to face.

Maternal glucose control, newborn complications (hypoglycemia, anemia), in both groups (insulin and metformin) and growth and development of the newborn was followed by telephone every 6 months.

The data were analysed by SPSS 16 using descriptive statistics, Chi-square and t-tests.

## Results:

The participants were grouped by number of pregnancies, number of previous pregnancies, number of abortions, body mass index, which were not significantly different, so the two groups were similar.

Fifty one (20%) patients had a gestational age of under 37 weeks. Forty five patients (88.2%) were taking insulin and 11.8% patients were taking Metformin. Between patients taking insulin FBS was 111.8±28.69 and 2hpp was 141.44±37.76. In patients taking metformin FBS was 96.44±23.7 mg/dL and 2hpp was 128.29±20.98 mg/dL.

In patients with preterm pregnancy no significant difference was observed between FBS in patients taking insulin or metformin ( $P=0.216$ ), also these two groups had no significant difference in 2hpp ( $P=0.410$ ).

From the all of the participants 207 (80%) had a gestational age of more than 37 weeks. 156 patients (75.3%) were under treatment with insulin and 51 patients (14.7%) were taking metformin. Insulin takers had an FBS and mean 2hpp of 137.71±37.39, though in patients taking Metformin, FBS was 12.8±95.77, and 2hpp was 120.83±22.12.

Between the patients receiving metformin and insulin with a gestational age of more than 37 weeks (term and post term pregnancy) there was statistical significant difference between fasting blood sugar according to gestational age ( $P=0.010$ ) and blood sugar levels in insulin group were more than in metformin group. There was also a significant difference between 2hpp of two groups ( $P=0.003$ ), insulin group 2hpp was higher than metformin group.

Among the group who took insulin ( $n=201$ ) FBS was 104.73±25.42 and 2hpp 135.44±37.51. Fasting blood sugar among patients who took metformin ( $n=56$ ), was 95.68±14.09 and 2hpp was 121.46±22.11. There was no significant difference between FBS among two groups ( $P=0.011$ ), and so was among 2hpp (0.008).

In this study overall 1.9% information about pregnancy was lost.

Weight of infants of mothers taking insulin was 602±111.83 gr and weight of infants of mothers Taking metformin was 3024.18±564.38, and there was no significant difference between patients taking insulin or metformin ( $P=0.336$ ). Mean height of newborn of insulin taking mothers was 49.246.995 and in metformin taking mothers was 48.61±3.76 which was not significantly different ( $P=0.525$ ).

Mean head circumference of the newborns of the mothers taking insulin was 33.86±2.23 and was 33.44±2.25 in women taking metformin which was not statistically significant ( $P=0.235$ ). Mean of chest circumference of newborns of mothers taking metformin was 32.30±2.23 which is not statistically significant ( $P=0.184$ ).

**Table 1. Mean No of Pregnancies, previous deliveries, history of abortion, body mass index and gestational age in group receiving Insulin and Metformin**

Mean	Metformin group	Insulin group	P-value
No of pregnancies	2.63±1.4	2.95±1.93	0.239
No of previous deliveries	1.27±1.14	1.56±1.66	0.288
History of abortion	0.39±0.95	0.39±0.81	0.967
Body mass index	26±4.3	30.27±52.58	0.493
Gestational age	37.26±1.79	36.95±3.5	0.567

**Table 2. Mean FBS and 2hpp in groups receiving Insulin and Metformin**

Group	FBS (mg/dl)	(mg/dl)2HPP
Insulin	28.69±111.8	37.76±141.44
Metformin	23.7±96.44	20.98±128.29
P-value	0.216	0.410

In mothers taking insulin, complications (hypoglycemia, nausea) was seen in 16 (8%) newborns, and in newborns of mothers taking metformin complications (hypoglycemia, nausea) was seen in 10 (17%) of the newborns. Which had no significant difference (P=0.37)

Only 23 newborns (8.7%) had respiratory distress of which 16 (8.1%) were born to mothers taking insulin and 7 (13%) were born to mothers taking metformin which was not significant (P=0.2).

Sepsis was seen in only one (0.4%) of the newborns born to a mother taking metformin, which had no significant difference (P=0.218).

Nearly 51 (19.4%) of newborns required phototherapy of which 41 (20%) were born to women receiving insulin and 10 (17.2%) were born to women receiving metformin, and no significant difference was observed (P=0.413)

No significant malformations were observed between newborns of two groups (P=0.516). Six of the newborns in insulin group (3.1%) and one newborn (1.8%) in metformin group had abnormal growth and development.

Growth of development disorders in every first semester, second semester, third semester and fourth semester is as following: in every first semester in insulin group 15 (8.1%) and in metformin group 1 (1.9%) had malformation which had no significant difference (P=0.091).

In second semester, 21 (12%) of insulin group and 1 (2%) of metformin group had malformation which had no significant difference (P=0.026)

In third semester 32 (23%) of insulin group and 0 (0%) of metformin group had malformation which had significant difference (P<0.001).

In 4<sup>th</sup> semester 38 (29.7%) of insulin group and 0 (0%) had malformation which had significant difference. (Malformations consist of growth and development disorders).

**Table 3. Comparison of complications in groups receiving Insulin and Metformin**

No	Complication	Insulin	Metformin	P-value	Missed data
1	Respiratory distress	(8.1%) 16	(13%) 7	0.2	11
2	Sepsis	(0.4%) 1	(0%) 0	0.218	10
3	Phototherapy	(20%) 41	(17.2%)	0.413	10
4	Trauma	(7.1%) 14	(5.5%) 3	0.470	10
5	Fetal anomalies	(3.1%) 6	(1.8%) 1	0.516	14
6	1 <sup>st</sup> Semester malformations	(8.1%) 15	(1.9%) 1	0.091	24
7	2 <sup>nd</sup> Semester malformations	(21%) 12	(2%) 1	0.026	38
8	3 <sup>rd</sup> Semester malformations	(23%) 32	(0%) 0	0.001 > P	90
9	4 <sup>th</sup> Semester malformations	(29.7%) 38	(0%) 0	0.001 > P	101

## Conclusion:

Gestational diabetes mellitus is the most common metabolic disorder during pregnancy, characterized by different levels of glucose intolerance. This disease is first time diagnosed

during pregnancy and resolves in sometime after delivery (9).

Fasting blood sugar was statistically different in patients taking insulin or Metformin (P=0.011), there was also statistically different 2hpp between two groups (P=0.008), which was similar to

different studies such as Janet A. Rowan et al (10,11), Moore LE et al (12), and e Hellmuth et al (13). But according to Lavanya Rai's study et al (14). Metformin controls blood sugar better than insulin.

Weight of newborns of mothers under treatment with insulin was  $602.653 \pm 111.83$  while the weigh of newborns of mothers taking Metformin was  $3024.18 \pm 564$  (15) (it means that in group taking insulin mean weight is more than in group taking metformin) and no significant difference was observed between weights of newborns in mothers taking metformin and insulin ( $P=0.336$ ). Mean height of the newborns in two groups (metformin and insulin) had no significant difference ( $P=0.525$ ).

In Elahe Mesdaghinia et al s study (16) and H Ija et al's study (17) weight of newborns in metformin group was more than weight of newborns in insulin group which is controversial with our results., but results of Lavanya Rai et al (14), Kristina Terti et al (18,19), Janet A Rowan et al (11) were similar to our study; but in all these studies there was no statistically significant difference between birth of two groups.. In Jaya Saxena Dhulkotia et al study, (20) also showed that there was no statistically significant difference between metformin and insulin.

Between two groups there was no statistical difference between head circumference, mean thoracic circumference, which is similar to Janet A Rowan et al (11). Kristinia Terri et al (19) showed in their study that duration of insulin or metformin intake was not that much enough that could effect on head circumference, chest circumference, newborn's height and weight and macrosomia, but the group that received metformin maternal BMI was 30 from beginning which could conclude higher amount of dystocia in insulin group. Between two groups receiving insulin or metformin no significant difference was seen.

Jaya Saxena Dhulkotia et al (21) and Kristiina Terti et al (19) showed that there was no significant difference between newborn respiratory distress, but Elahe Mesdaghinia et al (16) and Janet A. Rowan (11) showed that insulin group had more respiratory distress.

In our study, sepsis was only seen in one of the newborns of the mother which had been taking

metformin. There was no significant difference between incidence of neonatal sepsis between two groups ( $P=0.218$ ) which is similar to results of Elahe Mesdaghinia et al (16) and Janet A. Rowan et al (11). In our study there was no need for photo therapy in both groups ( $P=0.413$ ), but in Mesdaghinia et al (16) and J. Balani (18) jaundice Was more seen in insulin group; while Mark B. Landon et al (22) study's results were similar to our study, and there was no significant need for phototherapy.

Our study showed no significant maternal complications between two groups which coincided with Janet A. Rowan et al study (11) and E. Hellmuth et al study (13). In our study some of the neonatal complications (sepsis, birth trauma, respiratory distress, jaundice and need of phototherapy) were same in both groups and, in case of following up of, 6 month complications in newborns, complications were the same in first and second semester but complications in third and fourth semester were more in group under taking insulin compared with metformin. This difference was statistically significant which is in contrast with E. Hellmuth's study (13) which shows high amount of perinatal morbidity and mortality in women taking metformin.

J. Balani et al (18) show prenatal complications are more in patients taking metformin, also E. Hellmuth et al showed in their study (13) that in women taking metformin perinatal complications are more seen in comparison to women treated with insulin, because metformin pass the placenta easily and this predict metformin causes more perinatal complications than insulin, and many physicians consider insulin a safe medication for controlling GDM. In our study, during first and semester the results are the same but results of third and fourth are controversial. Although insulin can be a safe medication for the patients is expensive in comparison to oral hypoglycemic agents (20).

Elahe Mesdaghinia and co workers (31) have shown in their study that metformin can be used more because of less neonatal complications Janet A. Rowan, and coworkers (11) have shown that metformin alone or in combination with insulin could be a suitable treatment for GDM. Kristiina Terti and coworkers (19) and Moore LE et al (12)

have shown that metformin can be a suitable alternative for treatment of GDM.

From the results of our study it can be concluded that metformin can be a suitable alternative for insulin in GDM.

According to the results of this study and similarity of maternal complications and difference between two groups of insulin and metformin consumers and presence of complications in third and fourth trimesters, regarding the high of cost of medications, it is up to the physician to select the medication for the patient (23).

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