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REVIEW ARTICLE

Metformin Versus Insulin in The Management of Gestational Diabetes Mellitus

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ABSTRACT

Background: Insulin and metformin have been used extensively in the management of gestational diabetes mellitus (GDM). Insulin has been the primary medical treatment if maternal glucose targets are not achieved by dietary therapy. Insulin is safe for the fetus because it does not normally cross the placenta. Oral antidiabetic agents, glibenclamide, and metformin are the most studied agents to treat GDM patients.

Objective: To examine if oral metformin is as effective as insulin in the prevention of fetal macrosomy in pregnancies complicated with GDM.

Method: In this prospective randomized controlled study, 100 women with GDM who did not achieve euglycaemia with dietary regulation were enrolled. Women were randomized to receive either insulin (n=50) or oral metformin (n=50). Incidence of macrosomia in infants and neonatal morbidity was measured.

Results: There were no statistically significant differences in the incidence of macrosomia (16°/o versus 20°/o), and neonatal morbidity between insulin and metformin groups. Around 15 (30°/o) of the metformin-treated women needed supplemental insulin. They were more obese, (36.2 versus 30.6) kg/m^2 bad higher fasting blood sugar levels (7.4 mmol/L versus 6.1 mmol/L) and required medical therapy for GDM earlier (27 versus 32 weeks) than women who were normoglycemic with metformin only. Higher rate of caesarean sections in the metformin than in the insulin arm.

Conclusion: Metformin might prevent fetal macrosomia, especially in lean or overweight women developing GDM in late pregnancy Women with significant obesity, high fasting blood sugar, and an early need for medical treatment may be a candidate for insulin treatment.

INTRODUCTION

Basal and postprandial glucose metabolism is altered in pregnancy. Eating causes stronger insulin secretion during pregnancy, but postprandial glucose concentrations are still higher than in nonpregnant individuals. Although fasting glucose is decreased, basal hepatic glucose production increases because hepatic insulin sensitivity and glucose suppression are reduced. This, in turn, leads to increased insulin production. GDM is classically defined as “a state of impaired glucose tolerance recognized during pregnancy in women not known to have had impaired glucose tolerance before pregnancy.[1]

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Fasting glucose concentrations are higher in pregnancies complicated by GDM than in normal pregnancies, while basal hepatic glucose production is similar. Insulin sensitivity is lower in pregnancies of lean and obese GDM patients compared with normal pregnancies. Insulin resistance is increased by 40% in late pregnancy in patients with severe GDM compared with normal pregnancies.[2] GDM occurs when the pancreatic b-cells do not produce enough insulin to combat the increased insulin resistance. Obesity and chronic insulin resistance are the most common factors that predispose to b-cell dysfunction during pregnancy.

Insulin has been the primary medical treatment if maternal glucose targets are not achieved by dietary therapy. Insulin has several disadvantages since its use needs training; subcutaneous injections administrate it, cause hypoglycemia, and increase appetite and weight.[3] However, oral antidiabetic agents, glibenclamide, and metformin are the most studied agents to treat GDM patients. A meta-analysis of 6 studies with 395 GDM patients on metformin, 291 on glibenclamide, and 702 on insulin reported no differences between maternal fasting and postprandial glycemic control groups. The use of metformin or glibenclamide compared to insulin did not increase the rate of neonatal hypoglycemia, birth weight, the incidence of LGA-babies, or cesarean deliveries.[4]

According to the literatures, identification of high-risk group (GDM) women and offering them oral metformin treatment could improve both the morbidity and mortality for pregnant women and their fetuses in our community because most of our diabetic pregnant mothers are relactating for using subcutaneous insulin injections during their pregnancies. So our goal or our aim of the study was to investigate the efficacy of metformin in the prevention of fetal macrosomy and its influence on neonatal and maternal morbidity in women with GDM in comparison with insulin therapy.

METHODOLOGY

A target number of 100 women with GDM was obtained in the study from Basra maternity and children hospital. Gestational diabetes was diagnosed by measuring the concentration of serum blood glucose before breakfast and 1.5 hours of the main meals. The target concentration was <5.3 mmol/L for fasting and >6.7 mmol/L for postprandial glucose. The women with singleton pregnancies diagnosed with GDM between 12;34 weeks of gestation were asked to participate. The study was randomized to treatment with either metformin (n=50) or insulin (n=50).

Randomizations were achieved using numbered selected envelopes containing randomization on e-generated manually in blocks of ten. Exclusion criteria were pre-eclampsia, essential hypertension requiring antihypertensive drugs. Metformin 850 mg once daily for the first week, twice daily for the second week, and three times daily from the third week onward. Medication was discontinued if significant side effects were achieved or if normoglycemia was not achieved within 1-2 weeks and supplement. Insulin was added. While in the second group, along acting insulin was used to normalize fasting, and rapid-acting was used to normalize postprandial glucose concentration.

The women continue to measure the daily profiles of capillary glucose concentration twice a week. The women were followed at the outpatient maternity clinics of the hospital at 4 weeks intervals between 12–32 weeks of gestation, at 2 weeks intervals between 32–36 weeks of gestation.and once or twice weekly after 36 weeks of gestation. The primary outcome was macrosomia incidence, and secondary outcomes included neonatal complications such as admission to the neonatal intensive care unit, neonatal hypoglycemia requiring intravenous glucose treatment, hyperbillirubinaemia treated with phototherapy, and birth injuries; the Apgar score in 1 and 5 minutes were recorded.

Maternal outcomes included a need for supplemental insulin in the metformin group, incidence of premature delivery before 37 weeks of gestation, a hypertensive complication of pregnancy, weight gain during pregnancy and mode of delivery. The significance of the difference between the groups studied was assessed by Chì-square test and t-tests as appropriate, statistical significance was defined as $p<0.05$, $p<0.01$, $p<0.001$.

RESULT

During the study period, 239 women were referred to the outpatient clinics of the study hospital for the consideration of pharmacological treatment for GDM, 128 were eligible for the study and follow up till birth, and only 100 of them can be followed and agreed to participate and were randomized in two equal groups~ each of 50 patient. Table 1 shows the

Table 1: Maternal Baseline characteristics

Character	*N=50*	*N=50*	*P*
Age in year	33.1 ± 5.1	33.6 ± 5.4	N.S
Parity	2.4 ± 1.2	2.1 ± 1.8	N.S
Nulliparous	16(32.0)	18(36)	N.S
BMI at the first antenatal visit	30.8 ± 1.2	32.2 ± 6.5	N.S
Fasting glucose serum level mmol/L	5.7 ± 0.6	6.2 ± 0.9	N.S
Length of gestational enrollment-WK	30.1 ± 3.2	30.2 ± 3.3	N.S
Education No%	6(122}%	5(10}%	N.S
HBA1c% at randomization	5.8 ± 0.2	5.9 ± 0.5	N.S

Data or means ± SDs or n (%)

maternal baseline characteristics. The mean gestational age at delivery did not differ between the study group. There were no significant differences in the mean birth weight of the newborn, or the macrosomia and neonatal complications, as shown in Table 2.

There were no perinatal deaths in this trial, also the incidence of pregnancy complications did not differ between the two study groups. Five women in both study groups had mild pre-eclampsia, while the incidence of cesarean section was significantly higher in the metformin group compared with the insulin group (P=0.04) Table 2, Around 15 out of 50 (30%) women randomized to metformin therapy did not reach normoglycemia and needed supplemental insulin. After starting supplemental insulin, three of the women discontinued metformin because of its gastrointestinal side effects. The women needing supplemental insulin had greater BMI, high fasting glucose concentration, and needed pharmacological treatment of earlier gestational age than women who were normoglycemic with metformin (Table 3).

DISCUSSION

The prevalence of GDM has considerably increased in recent years. At the same time, the number of patients for whom lifestyle modification alone failed in achieving adequate postprandial glucose targets and, therefore, requiring drug therapy for GDM, also rose.[5] This development awakens interest in gaining more information on antidiabetic drug therapy in pregnancy, which was the present study's focus. Glucose levels directly influence maternal and neonatal outcomes and even glucose values lower than normally diagnostic for diabetes seem to have an adverse effect, such that strict glycemic control is necessary. Several studies have compared the efficiency and tolerability of different antidiabetic gents, such as insulin and metformin.

Historically, insulin was used for GDM as it does not cross the placenta (from maternal to fetal circulation),[6] and because only limited data on oral antidiabetics were available. Insulin was the most often prescribed agent in GDM. However, insulin holds several disadvantages, such as the requirement of intensive educational instruction at the beginning of therapy, its subcutaneous application, the necessity of ideal storage conditions, close and frequent stringent blood glucose monitoring, and the fact that it is much costlier than oral metformin. Therefore, patients prefer metformin to insulin,[7] moreover oral metformin has good compatibility with pregnancy, for example, in various studies, the metformin discontinuation rate was found to range between just 2 and 6%, which was mainly due to intolerable gastrointestinal side effects.[5,7,8]

Our randomized controlled study showed that metformin is a safe and clinically relevant medical alternative for treating GDM, the incidence of adverse pregnancy or neonate outcomes were not increased with metformin compared with women treated with insulin. Metformin was especially suitable for

Table 2: Neonatal data and the mode of delivery

Character	*N=50*	*N=50*	*p*
Gestational age at delivery in WK	39.3 ± 1.1	38.4 ± 1.6	N.S
Macrosomia	8(16)%	10(20)%	N.S
Apgar score at			
lM)	7.2 ± 0.3	7.6 ± 0.7	N.S
SM)	8.9 ± 0.7	9.0 ± 0.6	N.S
Neonatal transferral to NICU	11(22)%	8(16}%	N.S
Neonatal hypoglycemia	8(16)%	6(12)%	N.S
Neonatal hyperbillirubinaemia	16(32)%	14(28)%	N.S
Spontenous V.O	21(42)%	34(68)%	(S)
Labour induction	25(50)%	22(44)%	N.S
c.s	11(22)%	19(38)%	0.001

Data or mean ± SDs or n (%)

Table 3: The baseline characteristics and neonatal outcomes in the metformin group

Character	*M alone=35*	*M+l=15*	*p*
BMI at the first anti-natal visit	30.6 ± 1.4	36.2 ± 3.4	0.002
Fasting glucose serum level	6.1 ± 0.S	7.4 ± 1.2	0.001
G-estational age at randomization	32 ± 3.4	27 ± 6.2	0,001
Birth weight (g)ms	3923 ± 412	4179 ± 600	N.S
Macrosomic	8(16)%	10(20)%	N.S
Apgar score at			
1 M	7.4 +1.2	7.6+0.9	N.S
SM	9.3+0.7	9.1+ 1.2	N.S

Date or mean ± SD or n (%)
Relative risk in the metformin with supplemental insulin group compared with the metformin - only group.

lean and moderately overweight women with postprandial hyperglycemia in the later half of pregnancy. The mean birth weight of the newborns did not differ significantly between the metformin and insulin groups, which is in line with both earlier cohort studies and a prospective study (MIG trail),[9] in our study the incidence of birth weight over 4000GM was 20% in the metformin and 16%in insulin group which was less than the figures of 26.8% in a study in Finland 2008.[10]

ln our study, the frequency of neonatal hypoglycemia, neonatal hyperbillirubinaemia, and the need for treatment in Neonatal Intensive Care Unit (NICU) was slightly but not significantly higher in the insulin group. It is in line with one but not all previous studies in the MIG trial, which found that severe neonatal hypoglycemia was significantly higher in the insulin-treated group than in the metformin-treated group.[11] Although metformin crosses the placenta leading to a concentration similar to those present in maternal circulation, it neither increase the rate of congenital malformations nor harms fetal or neonatal growth, however it has advantages such as significantly lower incidence of neonatal hypoglycemia, and maternal pre-eclampsia and fewer admissions to the NICU than in the insulin group.

Other beneficial effects encompassed a reduction in macrosomia rate, which is probably attributed to decreased rate of cesarean deliveries. While in our study, the cesarean section rate (38%) was more than that in the insulin group, which may be attributed to a higher rate of macrosomia. In this study, 30% of the women on metformin required additional insulin to achieve normal blood sugar. In the MIG trial,[12] the percentage of the metformin-treated women requiring additional insulin was even higher 46.3%, by contrast. In the two retrospective studies, only 18 and 13% of the women required insulin therapy,[13] could be due to selection bias.

Women who required additional insulin were more obese, had higher fasting blood sugar levels, and needed medical treatment sooner than women who achieved normal blood sugar with metformin suggesting higher insulin resistance. They also needed higher insulin doses to reach normoglycemia than the women in the insulin group. Newborns in the supplemental insulin group had significantly higher mean birth weight when compared with the metformin-only group, but these differences were not statistically significant, possibly due to the smaller sample size. It is possible that women needing additional insulin had more severe altered glucose metabolism.

The glycemic level in those women was also unsatisfactory over a longer period, which is supposed to accelerate the growth of the fetus before reaching normoglycemia. So, in summary, our study was the first that confirmed in Basra that GDM treated with metformin can be a safe and effective alternative to insulin and that it is especially suitable for women with mild GDM. However, it will be the task of future follow-up studies to assess the possible differences in childhood between children exposed to metformin and those exposed to insulin in utero, which might lead to further changes in the prescription manner in GDM.

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