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Original Research

Comparative efficacy and safety of oral anti-diabetic drugs and insulin in treating gestational diabetes mellitus

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ABSTRACT:
Introduction: Inadequate data are available on metformin therapy in gestational diabetes. The aim of the study was to compare maternal and neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin with those treated with insulin, or diet alone. **Material and Methods:** We conducted a retrospective study that included 45 GDM women treated with metformin, 45 women treated with insulin and 83 women with no pharmacological treatment. Subjects were matched for pre-pregnancy body mass index (BMI) and age. **Results:** There were no differences between the metformin-treated group and the other two groups in terms of maternal outcomes. In the diagnostic 2- hour oral glucose tolerance test, glucose values were slightly, but significantly, higher in the insulin group than in the metformin group ($p < 0.003$). No differences between the metformin-treated group and the other two groups (insulin, diet only) were observed in relation to mean birth weights, prevalence of macrosomia, or gestational weeks at delivery. The incidence of neonatal hypoglycemia was higher in the insulin group than in the metformin group ($p = 0.03$). There were no differences between the groups in other neonatal outcomes. **Conclusion:** These retrospective data suggest that metformin is effective in controlling gestational diabetes and is not associated with a higher risk of maternal or neonatal complications compared with insulin.
Keywords: Gestational diabetes, Insulin, Metformin

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INTRODUCTION

Pregnancy is a potentially glucose intolerant condition, and in all pregnancies, insulin sensitivity decreases as the pregnancy advances. This predisposes to the development of gestational diabetes mellitus (GDM), particularly in obese women with pre- existing insulin resistance. GDM develops if there is inadequate insulin secretion to compensate for the increased insulin resistance [1].GDM is diagnosed in approximately 3-7% of pregnancies [2, 3, 4]. In general, the number of studies reporting on the use of metformin in women with type 2 diabetes or GDM is still small. Theoretically, metformin is an alternative to insulin in the treatment of hyperglycemia during pregnancy. It decreases hepatic gluconeogenesis and improves peripheral glucose uptake [5-10]. It does not induce hypoglycemia and it is not associated with increased weight gain. Evidence supporting the use of metformin in pregnancy is available from studies in patients with polycystic ovary syndrome (PCOS). The syndrome is characterized by polycystic ovaries, oligo-amennorrhea, hyperandrogenism and insulin

resistance. Metformin has been used in the treatment of infertility secondary to PCOS [4, 11]. Although it crosses the placenta, there is no evidence of adverse fetal effects [12, 13] or increased risk of major malformations when metformin is used in pregnant women [14]. Some PCOS studies, where metformin was used, reported a reduction in spontaneous abortion in the first trimester [15, 16] and metformin also seems to reduce the risk of GDM in PCOS-mothers [17]. Growth, motor and social development in the offspring of mothers who conceived and continued on metformin did not differ from that of control babies over the first 18 months of life [1]. As previous retrospective studies on the use of metformin in GDM were not properly controlled, compare maternal and neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin with those treated with insulin, or diet alone.

MATERIALS AND METHODS

We conducted a retrospective analysis of all GDM pregnancies, where metformin was used at a tertiary health care facility. We included 45 metformin-treated women and the same number of insulin-treated GDM control patients after approval from the institutional ethics comittee. These patients were matched for pre-pregnancy body mass index (BMI, kg/m2) and age. We also had a reference group of GDM patients treated with diet alone (n = 83). We aimed for a ratio of two diet alone patients to each metformin patient, although seven metformin patients had only one control patient treated with diet alone. Data were collected retrospectively from the maternal and neonatal patient records. All women receiving metformin gave their informed oral consent. The initial dose of oral metformin varied from 500 mg once a day to 750 mg twice a day. Insulin treatment was usually started with intermediate-acting insulin. For patients treated with metformin, insulin was subsequently used as supplementary treatment if required. All patients had a third trimester ultrasound evaluation of fetal weight. Patients treated with metformin or insulin were scheduled several visits to an obstetrician at the clinic and to a diabetologist, if necessary. The following pregnancy and neonatal outcomes were recorded: pregnancy-induced hypertension (PIH; blood pressure elevation detected for the first time during pregnancy without proteinuria)[22], pre-eclampsia (increased blood pressure > 140/90 mmHg accompanied by proteinuria > 0.3 g/24 h)[22], birth weight (grams and SD for gestational weeks), macrosomia (birth weight > 4500g and/or >2 SD), the incidence of small for gestational age (SGA; birth weight < 2 SD), prematurity (birth < 37 weeks of gestation), Apgar score at the age of 5 min, umbilical artery pH <7.05 and base excess, hypoglycemia (s-gluc < 2.6 mmol/l, measured during the first two hours post-partum), hyperbilirubinemia (need for phototherapy), need for intensive care treatment, respiratory distress syndrome (RDS), the mode of delivery (spontaneous, assisted or caesarean section) and shoulder dystocia. We considered p-values lower than 0.05 to be statistically significant after the application of the appropriate statistical tools.

RESULTS

The metformin dose varied from 500 mg to 2 g a day with a mean dose of 1 g a day. Eight out of 45 patients (18 %) required insulin in addition to metformin to maintain adequate glucose control (fasting glucose < 5.5 mmol/l, postprandial glucose < 7.8 mmol/l). In the insulin-treated group (n = 45), 13 patients were treated with short-acting insulin only, 9 patients were treated with intermediate-acting insulin only, and 23 patients were treated with both short- and intermediate-acting insulin. Two patients in the metformin group were treated with oral corticosteroids in the first trimester of pregnancy, one because of asthma and the other because of idiopathic thrombocytopenia. Two patients in the metformin group and one patient in the insulin group had pregnancy-induced cholestasis in the third trimester of their pregnancy. Glucose values (at 0, 1, 2 h) in OGTT were significantly higher (respective p-values 0.005, 0.006 and 0.003) and the proportion of primiparas was slightly higher (p-value 0.05) in the insulin group than in the metformin group. Compared with the diet only group, fasting and 1-h glucose values in OGTT and HbA1c levels were significantly higher in the metformin group (respective p-values 0.0005, 0.03 and 0.02), whereas gestational weeks at OGTT and the proportion of primiparas were significantly lower (p-values 0.004 and 0.02). There were no statistically significant differences between the metformin and the other groups with respect to maternal age, pre- pregnancy BMI, total weight gain during pregnancy or after the diagnosis of GDM, smoking, pre-existence of hypertension, PIH or pre-eclampsia. Table 1

Table 1: Maternal data

Parameter	Metformin (n = 45)	Insulin (n = 45)	Diet only (n = 83)	Overall p-value	Metformin vs. insulin p; OR (95%CI)	Metformin vs. diet only p; OR (95%CI)
Age (yr)	32.8 ± 5.0	32.7± 4.7	32.4 ± 5.3	NS	NS	NS
BMI (kg/m²)	34.0 ± 6.4	33.2± 6.2	33.7 ± 6.2	NS	NS	NS
Total weight gain (kg)	10.2 ± 6.7	9.7 ± 7.7	8.8 ± 4.8	NS	NS	NS
Weight gain GDM (kg)[1]	3.0 ± 3.6	3.5 ± 5.2	3.6 ± 2.4	NS	NS	NS
OGTT 0h (mmol/l)	5.9 ± 0.7	6.3 ± 0.8	5.5 ± 0.3	< 0.0001	0.005	0.0005
OGTT 1h (mmol/l)	11.7 ± 1.7	12.7± 2.0	11.0 ± 0.9	< 0.0001	0.006	0.03
OGTT 2h (mmol/l)	8.3 ± 1.8	9.5 ± 2.2	7.7 ± 1.1	< 0.0001	0.003	0.07
HbA1c at OGTT (%)	5.7 ± 0.4	5.7 ± 0.4	5.5 ± 0.3	0.001	NS	0.02
Gestat. wk at OGTT	24.8 ± 5.5	24.3± 5.7	27.1 ± 2.4	0.0002	NS	0.004
Gestat. wk at delivery	38.4 ± 1.4	38.1± 1.5	38.9 ± 2.0	0.015	NS	NS
Primipara, n (%)	10 (22.0)	19 (42.0)	38 (46.0)	0.06	0.05; 0.4 (0.2 - 1.0)	0.02; 0.4 (0.2 - 0.9)
Smoking, n (%)	7 (15.6)	7 (15.6)	10 (12.0)	NS	NS; 1.0 (0.3 - 3.0)	NS; 1.4 (0.5 - 3.7)
PPH, n (%)	2 (4.4)	4 (8.9)	2 (2.4)	NS	NS; 0.4 (0.1 - 2.8)	NS; 2.1 (0.3 - 15.9)
PIH, n (%)	0 (0.0)	1 (2.2)	3 (3.6)	NS	0.0*	0.0*
Pre-eclampsia, n (%)	4 (8.9)	4 (8.9)	2 (2.4)	NS	NS; 1.0 (0.2 - 4.5)	NS; 3.6 (0.6 - 20.8)
Induction of labor, n (%)	19 (42.2)	26 (57.8)	32 (38.6)	NS	NS; 0.5 (0.2 - 1.2)	NS; 1.2 (0.6 - 2.6)

BMI: body mass index. GDM: gestational diabetes mellitus. OGTT: oral glucose tolerance test. PPH: Pre-pregnancy hypertension. PIH: Pregnancy-induced hypertension. OR: odds ratio. CI: confidence interval. NS: not significant. [1] Total weight gain after diagnosis of GDM. * OR could not be calculated because of zero cell values.

The incidence of neonatal hypoglycemia (s-gluc < 2.6 mmol/l) treated with intravenous glucose was significantly higher in insulin-treated patients (p = 0.03) compared with those treated with metformin (at our hospital, all the neonates born to diabetic mothers, including those with GDM, are tested for plasma glucose value during the first two hours post partum). There was no significant difference in the proportion of neonates sent to our neonatal intensive care unit (NICU) and no difference in the number of treatment days at NICU. There were also no statistically significant differences between the groups in relation to birth weight (grams or SD in gestational weeks), incidence of macrosomia or SGA, Apgar score at 5 min, asphyxia (umbilical artery pH < 7.05), base excess in umbilical artery and neonatal hy- perbilirubinemia needing phototherapy. Table 2

Table 2. Neonatal data and mode of delivery

Parameter	Metformin (n = 45)	Insulin (n = 45)	Diet only (n = 83)	Overall p-value	Metformin vs. insulin p; OR (95%CI)	Metformin vs. diet only p; OR (95%CI)
Birth weight (g)	3761 ± 598	3759 ± 642	3671 ± 573	NS	NS	NS
Birth weight (SD-units)	0.7 ± 1.3	0.9 ± 1.6	0.3 ± 0.9	0.08	NS	NS
Apgar score at 5 min	8.6 ± 0.8	8.7 ± 1.2	8.9 ± 0.6	NS	NS	NS
UA pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	NS	NS	NS
UA base excess (mmol/l)	-2.3 ± 4.8	- ± 3.3 3.3	- ± 2.8 3.1	NS	NS	NS
Neonate at NICU (days)	2.4 ± 8.1	3.9 ± 5.7	2.8 ± 7.0	NS	NS	NS
Macrosomia, n (%)[1]	7 15.6) (	10 22.2) (	10 12.0) (	NS	NS; 0.6 (0.2 - 1.9)	NS 1.3 3.6) (0.5 -
SGA (< 2 SD), n (%)	1 (2.2)	1 (2.2)	3 (3.6)	NS	NS; 1.0 (0.1 - 16.0)	NS; 0.6 5.6) (0.1 -
UA pH < 7.05, n (%)	2 (4.4)	1 (2.2)	0	NS	NS; 2.0 (0.2 - 22.1)	0.0*
Neonates transferred to NICU, n (%)	19 42.2) (	28 62.2) (	26 31.1) (	0.01	0.08; 0.5 (0.2 - 1.1)	NS; 1.5 3.0) (0.7 -
Hyperbil., n (%)[2]	12 26.7) (	11 24.4) (	17 20.5) (	NS	NS; 1.1 (0.4 - 2.9)	NS; 1.5 3.4) (0.6 -
Hypoglycemia, n (%)[3]	15 34.1) (	26 57.8) (	16 19.3) (	0.0004	0.03; 0.4 (0.2 - 0.9)	0.07; 2.2 5.1) (0.9 -
RDS, n (%)	0 (0.0)	1 (2.2)	2 (2.4)	NS	0.0*	0.0*
Spontan. delivery, n (%)	27 60.0) (	30 66.7) (	62 74.7) (	NS	NS; 0.8 (0.3 - 1.8)	NS; 0.5 1.2) (0.3 -
Assisted delivery, n (%)	5 11.1) (	5 (11.1)	6 (7.2)	NS	NS; 1.0 (0.3 - 3.7)	NS; 1.5 5.1) (0.4 -
Caesarean section, n (%)	14 31.1) (	10 22.2) (	15 18.1) (	NS	NS; 1.6 (0.6 - 4.2)	NS; 2.2 5.2) (0.9 -
Prematurity, n (%)	2 (4.4)	5 (11.1)	6 (7.2)	NS	NS; 0.4 (0.1 - 2.0)	NS; 0.6 2.9) (0.1 -

UA: Umbilical artery. SGA: small for gestational age. NICU: neonatal intensive care unit. RDS: respiratory distress syndrome. OR: odds ratio. CI: confidence interval. NS: not significant. [1] >2 SD-units and/or >4500 g. [2] Hyperbilirubinemia (need for phototherapy). [3] n = 44 in metformin group. * OR could not be calculated because of zero cell values.

Thirteen patients gave birth prematurely (<37 weeks of gestational age): two in the metformin group (4.4 %, gestational ages 35 and 36 weeks), five in insulin group (11.1 %, gestational ages 34, 35 and 36 weeks), and six in the diet only group (7.2 %, gestational ages 30 to 36 weeks).

DISCUSSION

We found significantly fewer neonates with hypoglycemia during the first two hours post partum in the metformin-treated group compared with the insulin- treated group (p = 0.03), whereas no difference in this respect was observed between the metformin and the diet only group. There was no significant difference in birth weight or neonate macrosomia between the three groups. Furthermore the rate of pre-eclampsia, caesarean section or neonatal RDS was similar in all three groups. These data are consistent with observations in PCOS patients treated with metformin [1], but are inconsistent with the results obtained by Hellmuth *et al*. in a combined cohort of GDM and T2DM mothers [18]. In the latter study, increased rates of pre- eclampsia and perinatal loss were observed in mothers treated with metformin. A common problem in retrospective studies is that control groups are inadequately matched, as was the case in the study performed by Hellmuth *et al*. [18]. The metformin group had other increased risk factors for pre-eclampsia unrelated to metformin use, i.e. they were older and more obese. In addition, their anti-hyperglycemic medication was started seven weeks later than in the women treated with insulin. To our knowledge, our study is the first retrospective case-

control study where control patients for metformin patients were matched for pre-pregnancy BMI and age. As a consequence, there were no significant differences in BMI or age of the patients between the groups. However, in the insulin group, the disturbance in glucose metabolism was slightly more severe according to the glucose values obtained in the diagnostic OGTT. This difference in maternal hyperglycemia, which may have also prevailed during delivery, may explain the higher rate of neonatal hypoglycemia in this group.

Until May 2008, only one small randomized study comparing metformin to insulin in GDM patients had been published [19]. In this study, patients' BMI, which may influence maternal and neonatal outcomes, differed significantly between the groups. Very recently, a larger prospective randomized study comparing metformin and insulin in the treatment of GDM was published. No differences were found in the composite endpoint of neonatal complications or birth weight, but the rate of preterm delivery was higher in metformin-treated mothers [20]. In our study, the incidence of preterm delivery was very low, but the study was not powered to detect differences in prematurity. In the study by Rowan *et al*., the rate of overall neonatal hypoglycemia was similar but the rate of severe hypoglycemia was lower in the metformin group compared to the insulin group [20]. Consistent with this result, the incidence of neonatal hypoglycemia was higher in insulin treated patients in our study. The caesarean section rate was not reported by Rowan *et al*. [20]. In our study, there was no difference in caesarean section rate between the metformin and the insulin group. The need for supplemental insulin was more frequent (46%) in the study by Rowan *et al*. than in our study (18%).

The limitation of our study lies in the selection and assignment of patients. Our study was not randomized and it is probable that insulin-treated patients were slightly more hyperglycemic than metformin-treated patients as judged by the glucose values in diagnostic OGTT. We had no strict criteria for assigning patients to metformin or insulin among those whose self-monitored glucose values did not exceed the limits for compulsory insulin treatment (fasting glucose above 7.0mmol/l or postprandial glucose above 10.0 mmol/l). The study had limited power to detect differences in many of the outcome variables, especially in those with low incidence.

CONCLUSION

We conclude that metformin appears to be effective in the treatment of GDM patients and does not seem to be associated with higher risks for maternal or neonatal complications compared with insulin. However, further sufficiently powered and randomized clinical studies are still needed, including long-term follow-up of children, in order to determine the role of metformin as an alternative treatment to insulin in GDM patients.

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