THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13477 J. Obstet. Gynaecol. Res. Vol. 44, No. 1: 81–86, January 2018

Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study

Enrique Valdés[1], Alvaro Sepúlveda-Martínez[1], Paula Candia[2], Nancy Abusada[3], Rodrigo Orellana[3], Bárbara Manukian[1] and Eduardo Cuellar[2]

[1]Fetal Medicine Unit, Department of Obstetrics and Gynecology, [3]Pharmacy Unit, Hospital Clínico Universidad de Chile and [2]Department of Obstetrics and Gynecology, Hospital Barros Luco Trudeau, Santiago, Chile

Abstract

Aim: We aimed to assess the use of metformin (MTF) in the prevention of gestational diabetes mellitus (GDM) in patients with pregestational insulin resistance (PIR).

Methods: A double blind, multicenter, randomized trial was carried out in patients with a history of PIR and pregestational MTF treatment. Groups were allocated either to MTF 1700 mg/day or placebo. Patients were recruited between 12^{+0} and 15^{+6} gestational weeks, and treatment was extended until week 36. A multiple logistic regression analysis was applied to determine the relation between the use of metformin and the development of GDM.

Results: One hundred and forty one patients were randomized (68 patients in the MTF group and 73 in the placebo group). A total of 30 patients withdrew from the study during follow-up. Administration of MTF was not associated with a decrease in the incidence of GDM as compared to placebo (37.5% vs 25.4%, respectively; $P = 0.2$). Moreover, MTF administration was associated with a significant increase in drug intolerance as compared to placebo (14.3% vs 1.8%, respectively; $P = 0.02$).

Conclusion: The use of MTF is not effective in prevention of GDM in populations with PIR. The use of MTF shows a significantly higher frequency of drug intolerance than placebo.

Key words: gestational diabetes, insulin resistance, metformin, pregnancy, randomized controlled trial.

Introduction

Gestational diabetes mellitus (GDM) is a condition characterized by a disorder of carbohydrate metabolism, presenting with variable severity, with an onset or first detection during pregnancy. In Chile, its prevalence among pregnant women has been on the rise from 5–8% to 10–14% over a 10-year period. This is mainly due to the dramatic rise of pregestational overweight and to increased maternal age. In addition, risk factors, such as a family history of type 2 diabetes mellitus (DM2), a history of GDM during previous pregnancies, and belonging to the middle-lower socioeconomic status, are other causes of such an increase.[1–3]

On the other hand, progressive insulin resistance during pregnancy is recognized as a physiological effect, necessary to ensure fetal energy requirements. Evidence shows that higher degrees of this condition could negatively impact a mother's health and perinatal outcomes. Recent studies have shown a relation between polycystic ovary syndrome (PCOS), which is closely connected to insulin resistance syndrome and

Received: September 25 2016.
Accepted: July 17 2017.
Correspondence: Dr Enrique Valdés Rubio, Fetal Medicine Unit, Department of Obstetrics and Gynecology, Hospital Clínico Universidad de Chile, Santos Dumont 999 Primer Piso Sector A, Independencia, 8380000 Santiago de Chile, Chile.
Email: evaldes@vtr.net

© 2017 Japan Society of Obstetrics and Gynecology

a higher risk of developing GDM, pre-eclampsia (PE), and fetal growth restriction.[4–6]

Moreover, it has been proven that an increase in the severity of pregestational insulin resistance (PIR) during pregnancy, measured through disorders in biomarker concentrations in different stages of gestation (Sex Hormone Binding Globulin [SHBG], adiponectin, leptin, and tumor necrosis factor),[3,4] is closely related to first trimester miscarriage. Etiopathogenesis of such cases involves endothelial dysfunction and/or predisposing metabolic conditions, both having an anomalous placentation as such seen in intrauterine growth restriction and/or PE.[7]

Lastly, MTF is a second-generation biguanide with an insulin sensitizing effect. It has been widely used to treat DM2 patients and to optimize ovulation and to prevent first trimester miscarriage in PCOS patients. MTF is currently a US Food and Drug Administration-approved type-B drug.[8,9] However, the evidence that supports the use of MTF during pregnancy for GDM prophylaxis remains controversial. Because such studies have been carried out mainly on patients with PCOS, a syndrome showing insulin resistance in 70% of cases, results among such a population are quite dissimilar.[10–15] The present study aimed to evaluate the use of MTF as a preventive treatment for GDM in patients with PIR.

Methods

Study design

This double-blind multicentric randomized clinical trial was carried out in patients with PIR, with or without the use of MTF until 12 gestational weeks (GW). Pregnancies under control in the two participant institutions (Hospital Clínico Universidad de Chile and Hospital Barros Luco Trudeau) were included. In patients with a pregestational treatment with MTF, the therapy was maintained until 12 GW. Patients were randomized at 12^{+0}–15^{+6} GW to receive either MTF 1700 mg/day or placebo. The therapy was used until 36 GW or until the diagnosis of GDM. Based on the absence of scientific evidence of an ideal dose of MTF in pregnant patients with pregestational insulin resistance, an intermediate dose of 1700 mg/day was chosen for better tolerance and pregnancy safety.

Multiple pregnancies, major congenital birth defects, aneuploidies, and genetic syndromes were excluded from the analysis. Patients with chronic diseases, such as DM1, DM2, and chronic nephropathy, or with incomplete perinatal data were also excluded.

All patients were evaluated with an oral glucose tolerance test (OGTT) at 24–28 GW and at 32 GW. The diagnosis of GDM was considered with a fasting glucose >105 mg/dL or a 2-h glucose >140 mg/dL. In patients with a diagnosis of GDM, the therapy was suspended and the management was performed according to the local guidelines. This study was approved by the local ethics committee in both institutions, and all the patients signed the informed consent before randomization.

Definitions

The diagnosis of PIR was performed in the preconceptional period, based on the presence of abnormal values in fasting insulinemia test (≥15 uUI/mL) and/or homeostatic model assessment–insulin resistance (>2.6) and at least one of the PIR-suggestive clinical signs, such as acrochordons, acanthosis nigricans, or the diagnosis of PCOS.[16–19]

To assess the general purpose of the present study, GDM was defined according to the criteria of the International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy[3] as any type of carbohydrate intolerance during pregnancy, diagnosed through OGTT, with an overload of 75 g carried out by the 26th GW. Additionally, recruited patients underwent an OGTT at GW 32. GDM was diagnosed with baseline glycaemia >105 mg/dL on two occasions or >140 mg/dL after 2 h.

PE was defined as new-onset hypertension after 20 GW, with proteinuria, according to the International Society for the Study of Hypertension in Pregnancy[20] as resting systolic and diastolic blood pressure ≥140 mmHg and 90 mmHg, respectively, in two measurements 6 h apart, or one measurement ≥160/100 mmHg. Proteinuria was defined as a qualitative value ++ or higher, and/or a quantitative value above 300 mg/day, without a urinary tract infection.[20]

Small for gestational age was defined as a birthweight below the 10th percentile according to the national reference neonatal curve.[21]

Sample size estimation

For the simple size estimation, a power of 80% and an alpha-error of 5% were used. According to an incidence of insulin resistance of 10% in fertile women, with an estimated rate of GDM of 30% in these patients, and a projected reduction until 10%, with a gastrointestinal intolerance of 10%, 72 patients per arm were needed.

© 2017 Japan Society of Obstetrics and Gynecology

Statistical analysis

For continuous variables, a Shapiro–Wilk test was performed to determine the variable distribution. A *t*-test or a Mann–Whitney *U*-test was performed in normal and non-parametric distribution, respectively, and expressed as mean (standard deviation) or median (interquartile range). Categorical variables were analyzed with the χ^2-test or Fischer's exact test and expressed as a percentage. A simple and a multiple regression model were performed to determine the correlation of the variables with the risk of developing GDM in patients with MTF. An intention-to-treat basis was used for the analysis. STATA 14.1 was used for all analyses and a *P*-value <0.05 was considered as significant.

The study was financed by Merck Laboratories and the Oficina de Apoyo a la Investigación Clínica of Hospital Clínico Universidad de Chile (Registration No. 494/11).

Results

During the study period, 144 patients agreed to be included in the study. Three of them withdrew from the study before randomization (Fig. 1). Metformin was assigned to 68 patients and 73 patients received placebo. A total of 22.9% (n = 33) of the patients were excluded from the final analysis because of missing data regarding the outcome of interest. Table 1 shows the maternal characteristics of the randomized patients with complete perinatal outcome. There were no differences in rates of nulliparity, GDM in previous pregnancy, or use of metformin before pregnancy.

The use of metformin did not correlate with a reduction of GDM as compared to placebo (37.5% vs 25.4%; P = 0.17). Moreover, metformin was associated with a significant increase in the rate of gastrointestinal intolerance (14.3% and 1.8% for metformin and placebo, respectively; P = 0.017). The obstetric and perinatal outcomes are presented in Table 2. There were no differences in C-section rates (61.4% and 64.3% for placebo and metformin, respectively; P = 0.9) or deliveries of large-for-gestational-age newborns (10.3% and 16.3% for placebo and metformin, respectively; P = 0.4). Despite the similar gestational age at birth in the two groups (38.4 GW [38–39.1] and 38 GW [37.4–39.4] for metformin and placebo, respectively; P = 0.5), the median birthweight percentile demonstrated a non-significant trend to be lower in the offspring of patients treated with metformin compared to placebo (47 [25–83] and 57 [39–80], respectively; P = 0.5).

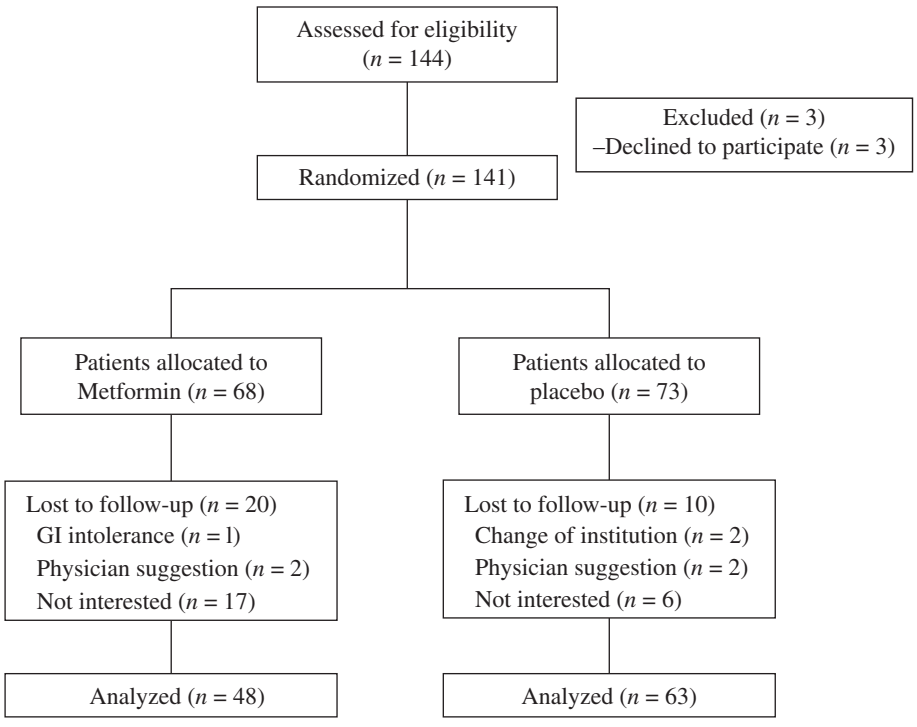

Figure 1 Flow diagram of the randomization process, according to the CONSORT guidelines. GI, gastrointestinal intolerance.

© 2017 Japan Society of Obstetrics and Gynecology

Table 1 Maternal characteristics at randomization

Variable	Placebo (n = 73)	Metformin (n = 68)	P-value
Maternal age, years	31 (27–34)	31 (26.5–35.5)	0.7
Maternal height, m	1.58 (1.55–1.63)	1.59 (1.56–1.62)	0.6
Pre-pregnancy BMI, kg/m^2	31.1 (27.4–34.8)	31.6 (28.9–34.2)	0.3
Metformin before pregnancy	20/39 (51.3)	15/32 (46.9)	0.7
Nulliparity	33/65 (50.8)	20/50 (40)	0.3
Previous gestational diabetes	3/48 (6.25)	4/40 (10)	0.5
First trimester fasting glucose, mg/dL	83.2 (±8.7)	84.4 (±7.4)	0.4

Quantitative variables expressed as mean (± standard deviation) or median (interquartile range) for parametric and non-parametric distribution, respectively. Categorical variables expressed as *n/total (%).* BMI, body mass index.

Table 2 Maternal and perinatal outcomes

Variables	Placebo (n = 73)	Metformin (n = 68)	P-value
Perinatal outcome			
GA at birth, weeks	38 (37.4–39.4)	38.4 (38–39.1)	0.5
Birthweight, g	3325 (3050–3650)	3220 (3000–3640)	0.7
Birthweight percentile	57.1 (38.7–79.6)	47.2 (25.1–83.4)	0.5
Large for gestational age	6/58 (10.3)	7/43 (16.3)	0.4
Small for gestational age	4/58 (6.9)	2/43 (4.65)	0.6
5-min Apgar ≤ 7	0	2/40 (4.6)	0.1
Maternal outcome			
OGTT at 24–28 GW, mg/dL			
Basal	79 (73–87)	79 (75–85)	0.6
2-h	110.5 (94–133)	125 (113–135)	0.1
Gestational diabetes	16/63 (25.4)	18/48 (37.5)	0.17
Gastrointestinal intolerance	1/57 (1.8)	6/42 (14.3)	0.016
Pre-eclampsia	3/57 (5.3)	4/40 (10)	0.38
Preterm delivery	8/55 (14.6)	3/41 (7.3)	0.27
Mode of delivery			0.9
Cesarean section	35/57 (61.4)	27/42 (64.3)	—
Vaginal	21/57 (36.8)	14/42 (33.3)	—
Forceps	1/57 (1.8)	1/42 (2.38)	—
Lost to follow-up	10 (13.7)	20 (29.4)	0.002

Quantitative variables expressed as mean (standard deviation) or median (interquartile range) for parametric and non-parametric distribution, respectively. Categorical variables expressed as *n/total (%).* GA, gestational age; OGTT, oral glucose tolerance test.

Discussion

MTF is an insulin sensitizer widely used in DM2 treatment. Its use improves tissue sensitivity to insulin, inhibiting glucose synthesis by the liver, increasing the intake of peripheral glucose, and decreasing insulin concentrations.[11] The physiopathology of GDM is similar to that of DM2, with an increased insulin resistance, poor control of hepatic gluconeogenesis, and a decreased pancreatic beta cell response. Based on such information, it could be inferred that MTF would be useful as a prophylactic treatment to prevent GDM in patients with PIR.[9] However, evidence regarding this subject is controversial, as several studies either support or reject this treatment.[7,8,12] On the other hand, such studies were carried out only in patients with PCOS, which is a syndrome that occasionally presents PIR. Consequently, conclusions are not extrapolable.[10–15]

Our study supports the results of two recent meta-analyses that concluded that prophylactic administration of MTF to PCOS patients during pregnancy was not effective in prevention of GDM.[14,22] Hence, the present experience demonstrated that the use of MTF in the PIR population was not able to prevent GDM, PE, small for gestational age, or the delivery of a macrosomic fetus. Besides, the administration of MTF during pregnancy appears to be safe, as there were no malformations or deleterious effects on the fetus, considering that subsequent follow-up of newborns is not available.

In the current study, it is important to highlight that because the analysis was post-hoc, it was possible to

© 2017 Japan Society of Obstetrics and Gynecology

state that MTF might have had a beneficial effect by reducing newborn weight. Even though in our results the reduction in birthweight was not significant, we believe that this could be solved with a larger recruited cohort. This information might be useful in further studies specifically designed to prevent fetal macrosomia. However, the explanation of a reduced birthweight is not well understood. Several studies have demonstrated that, in patients with PCOS, the use of MTF during pregnancy reduces the rates of maternal complications, such as GDM and hypertensive diseases, but without a significant impact on birthweight.[12,23]

A possible explanation of the similar birthweight in newborns of patients with PCOS with and without MTF during pregnancy was raised in a recent secondary analysis of a previous randomized controlled trial. Even though this randomized study showed a similar rate of GDM in patients with MTF and placebo, insulin levels in maternal blood were reduced in the MTF arm (259 ± 209 vs 361 ± 261 pmol/L; $P = 0.020$). However, this treatment was not associated with a reduction of insulin in cord blood,[24] which may be secondary to the secretion of insulin of placental origin to the fetus.

Regarding the latter, a recent randomized study concluded that treatment with MTF in populations with body mass index greater than 35 is unable to prevent macrosomia or GDM, while it just decreases late-onset PE.[25] In this study, weight gain by the pregnant patient was lower in the treated population; this might explain the decrease in PE that would therefore be unrelated to the use of MTF. On the other hand, while it is true that adverse drug reactions were more frequent, and all were related to gastrointestinal intolerance, such effects were significant enough to interrupt the treatment in just one patient.

Although this study is the only published clinical trial that has evaluated the preventive effect of MTF on patients with a clear-cut PIR diagnosis, it has a limitation: There was a high percentage of recruited patients lost to follow-up. This might have affected the variable analysis, as for a correct result, interpretation compliance with the previously calculated sample size is critical. Hence, further studies with a larger sample size are essential either to support or to reject such therapeutic indication. In conclusion, MTF does not seem to have an impact on GDM prevention; however, its association with a newborn's weight warrants further studies.

Disclosure

All authors declare no conflicts of interest with the pharmaceutical industry or with any process of the development of this study.

References

1. Tras el Cumplimiento del 5° Objetivo del Milenio: Mortalidad Materna, Chile 2011 (Editorial). *Rev Chil Obstet Ginecol* 2014; **79**: 5–8.
2. Sepe SJ, Connell FA, Geiss LS, Teutsch SM. Gestational diabetes: Incidence, maternal characteristics, and perinatal outcome. *Diabetes* 1985; **34** (Suppl 2): 13–16.
3. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG *et al*. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33**: 676–682.
4. Valdés E, Sepúlveda-Martínez A, Manukian B, Parra-Cordero M. Assessment of pregestational insulin resistance as a risk factor of preeclampsia. *Gynecol Obstet Invest* 2014; **77**: 111–116.
5. Solomon CG, Seely EW. Brief review: Hypertension in pregnancy: A manifestation of the insulin resistance syndrome? *Hypertension* 2001; **37**: 232–239.
6. Roberts JM, Gammill HS. Insulin resistance in preeclampsia. *Hypertension* 2006; **47**: 341–342.
7. Valdés ER, Lattes KA, Muñoz HS, Barja PY, Papapietro KV. First-trimester adiponectin and subsequent development of preeclampsia or fetal growth restriction. *Gynecol Obstet Invest* 2011; **72**: 152–156.
8. Al-Biate MA. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. *Taiwan J Obstet Gynecol* 2015; **54**: 266–269.
9. Valdés RE, Soto-Chacón E, Lahsen MR, Barrera HC, Candia PP. Effectiveness of oral hypoglycemic drugs in the metabolic control of patients with gestational diabetes. *Rev Med Chil* 2008; **136**: 915–920.
10. Lautatzis ME, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: A systematic review. *Metabolism* 2013; **62**: 1522–1534.
11. Ghazeeri GS, Nassar AH, Younes Z, Awwad JT. Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: An overview. *Acta Obstet Gynecol Scand* 2012; **91**: 658–678.
12. Glueck CJ, Wang P, Kobayashi S, Phillips H, Sieve-Smith L. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril* 2002; **77**: 520–525.
13. Vanky E, Stridsklev S, Heimstad R *et al*. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: A randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010; **95**: E448–E455.
14. Zhuo Z, Wang A, Yu H. Effect of metformin intervention during pregnancy on the gestational diabetes mellitus in

© 2017 Japan Society of Obstetrics and Gynecology

women with polycystic ovary syndrome: A systematic review and meta-analysis. *J Diabetes Res* 2014; **2014**: 381231.
15. Glueck CJ, Pranikoff J, Aregawi D, Wang P. Prevention of gestational diabetes by metformin plus diet in patients with polycystic ovary syndrome. *Fertil Steril* 2008; **89**: 625–634.
16. Zavaroni I, Bonini L, Gasparini P *et al*. Hyperinsulinemia in a normal population as a predictor of non-insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: The Barilla factory revisited. *Metabolism* 1999; **48**: 989–994.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
18. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27**: 1487–1495.
19. Acosta A, Maíz A, Leighton F, Pollak F, Castilo O. Determinación del índice de resistencia insulínica mediante HOMA en una población de la RM de Chile. *Rev Med Chile* 2002; **130**: 1227–1231.
20. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.
21. Juez G, Lucero E, Ventura-Junca P, Gonzalez H, Tapia JL, Winter A. Intrauterine growth in Chilean middle class newborn infants. *Rev Chil Pediatr* 1989; **60**: 198–202.
22. Tan X, Li S, Chang Y *et al*. Effect of metformin treatment during pregnancy on women with PCOS: A systematic review and meta-analysis. *Clin Invest Med* 2016; **39**: E120–E131.
23. De Leo V, Musacchio MC, Piomboni P, Di Sabatino A, Morgante G. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. *Eur J Obstet Gynecol Reprod Biol* 2011; **157**: 63–66.
24. Helseth R, Vanky E, Stridsklev S, Vogt C, Carlsen SM. Maternal and fetal insulin levels at birth in women with polycystic ovary syndrome: Data from a randomized controlled study on metformin. *Eur J Endocrinol* 2014; **170**: 769–775.
25. Syngelaki A, Nicolaides KH, Balani J *et al*. Metformin versus placebo in obese pregnant women without diabetes mellitus. *N Engl J Med* 2016; **374**: 434–443.

© 2017 Japan Society of Obstetrics and Gynecology