The Use of Oral Hypoglycemic Agents during Pregnancy: An Alternative to Insulin?

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Objective: Gestational Diabetes Mellitus (GDM) and Type 2 Diabetes Mellitus (DM2) are metabolic disorders characterized by increased insulin resistance. Although insulin is the treatment of choice in pregnant patients with DM, the prescription of oral hypoglycemic agents (OHA) has been increasing among practitioners. This study aimed to evaluate the maternal and neonatal outcomes when oral hypoglycemic agents were used in diabetic pregnant women.

Methods: Medical records from the Maternal-Infant Care Unit Clinics SoM-UPR (n=149) were reviewed. Patients that were treated with metformin, sulfonylurea or insulin were included. Maternal and neonatal outcomes were compared between groups.

Results: Patient's mean age was 28 ± 6 years. The majority had GDM (91%). The most common comorbidity was hypertension (9.9%). Lifestyle modification was used as treatment in 77% of patients during the second trimester, but its use decreased to 33% during the third trimester. Insulin was the treatment of choice. Among the OHA, sulfonylurea was preferred. Postprandial glucose levels were lower in patients who used insulin as compared to those without medications.

Conclusion: No significant differences were found in maternal outcomes such as C-section, induction of labor, episiotomy or preterm labor, or neonatal outcomes such as macrosomia, neonatal hypoglycemia or congenital abnormalities among treatment groups. OHA can be considered as an alternative to insulin for the treatment of DM during pregnancy in selected cases. [*P R Health Sci J 2021;40:162-167*]

Key words: Oral hypoglycemic agents, Diabetes Mellitus in pregnancy, Gestational Diabetes management, sulfonylureas, Metformin

Gestational Diabetes Mellitus (GDM) and Type 2 Diabetes Mellitus (DM2) are related metabolic disorders characterized by increased insulin resistance. The prevalence of both conditions are in increasing trend worldwide and are associated with complications during pregnancy and long term risk of diabetes in both the mother and the child (1-3). Patients with GDM have a higher risk for development of type 2 diabetes mellitus later in life (4). In both conditions, fetal complications include increased risks for: macrosomia, birth trauma, neonatal hypoglycemia, preterm birth, intrauterine growth retardation, hypercalcemia and hyperbilirubinemia (1-4). Maternal adverse outcomes include maternal weight gain, pre-eclampsia, gestational hypertension, increased risk for C-section and the need for labor induction (5).

Management options for these conditions during pregnancy include medical nutrition therapy, oral hypoglycemic agents (OHA), and/or insulin. Even though insulin is the preferred therapy during pregnancy, its use is associated with some disadvantages. Woman who are started on insulin regimen require adequate health literacy to ensure its appropriate administration (6). In addition, the use of insulin is associated with maternal weight gain and risk of hypoglycemia. Other important aspects are the inconvenience of repeated injections, high cost and storage problems (7-9). The latter being of particular relevance in countries exposed to atmospheric and natural disasters which causes loss of electricity for prolonged periods of time, making insulin use and storage difficult (10-11).

Oral hypoglycemic agents used during pregnancy include metformin and glyburide. There has been controversy about the efficacy and safety of OHA during pregnancy. Several guidelines had been published regarding this topic. The National Institute

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The authors have no conflict of interest to disclose.

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for Health and Care Excellence (NICE) recommends the use of metformin as an adjunct or alternative to insulin if lifestyle intervention does not achieve glycemic control in patient with GDM. In addition, NICE consider the use of glyburide in patients whom blood glucose targets are not achieve with metformin but who decline the use of insulin therapy or those patients that cannot tolerate metformin (12). The American College of Obstetricians and Gynecologists (ACOG) updated their guidelines in 2018 and recommends insulin as the preferred treatment for diabetes in pregnancy when a pharmacologic treatment is indicated. However in women who decline the use of insulin or when the physician believe the patient is unable to safely administer insulin or unable to afford insulin, metformin is a reasonable treatment alternative. Since in most studies glyburide do not yield equivalent outcomes when compared with insulin, ACOG recommends against using glyburide as a first-choice pharmacologic treatment (13). According to the Endocrine Society and the American Diabetes Association, glyburide and metformin are appropriate alternative to insulin therapy for glycemic control in gestational diabetes mellitus that cannot achieve glycemic control after a trial of lifestyle modification. They also agreed that these agents can be used when factors such as cost, language and/or cultural barriers among others, prevent the use of insulin safely (14). For other noninsulin antihyperglycemic medication, there are no enough evidence to support their use during pregnancy. Taken together, both medical associations preferred the use of insulin in women with diabetes during pregnancy (14-15).

Even though insulin is the preferred therapy in patients with diabetes during pregnancy, metformin and glyburide are also reasonable therapies. Puerto Rico has the highest prevalence of Diabetes Mellitus when compared to USA (16). Data regarding the prevalence of GDM and DM2 during pregnancy are scarce as well as data regarding efficacy and safety of oral hypoglycemic agents during pregnancy in our population. This study aimed to evaluate the maternal and neonatal outcomes when oral hypoglycemic agents were used in our diabetic pregnant women.

Materials and Methods

This was a retrospective observational study. Medical records from patients between the ages 18 to 45 years old, who were evaluated at the Maternal-Infant Care Unit (MIC) clinics of the University of Puerto Rico School of Medicine from January 1st, 2013 to December 31st 2015, with Gestational Diabetes (ICD-9 code 648.8 or ICD-10 code O24) or Diabetes Mellitus Type 2 (ICD-9 code 250* or ICD-10 code E11*) that were treated with metformin, sulfonylurea or insulin were reviewed. Patients with Diabetes Mellitus Type 1, contraindications for the use of metformin or sulfonylurea, Type 2 Diabetes Mellitus who had previously failed to achieve glycemic control on metformin monotherapy before pregnancy, systemic disease that required systemic steroids during the pregnancy and patients with chronic kidney disease, in whom metformin is contraindicated, were excluded. Information obtained from maternal records include: patient age, height, weight, body mass index, type of diabetes mellitus, medications, medical comorbidities, obstetrical history, blood pressure, HbA1c, pre-meal and 1 hour post-prandial mean capillary glucose, use of insulin, and complications during labor. Information about post- partum follow up such as: blood pressure, weight, fasting plasma glucose test, HbA1c and if 75 g glucose tolerance test was done were also obtained.

Clinical data from neonatal medical records included: gestational week age at birth, weight at birth, length at birth, APGAR score at 1 minute and 5 minute, glucose level, bilirubin level, calcium level, complications including macrosomia, small for gestational weight, shoulder dystocia, neonatal hypoglycemia, congenital abnormalities, neonatal intensive care unit (NICU) admission, transient tachypnea, respiratory distress syndrome or intubation.

This study was approved by the Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus.

Statistical analysis

Linear mixed-effects regression models were performed to assess the effect of medications on pre-meal and post-meal glucose levels; models were adjusted for age, body mass index and repeated measures effect (i.e., glucose levels at different time points in pregnancy). Furthermore, multilevel logistic regression models were performed to estimate odds ratios (OR) and 95% confidence intervals (CI) of maternal and infants' outcomes, respectively, according to type of medication used during their pregnancy. These models were adjusted for age and the use of other type of medication (oral agents or insulin). Stata v15 (College Station, Texas 77845 USA) was used.

Results

From January 1st 2013 to December 31st 2015 a total of 149 medical records from the MIC were reviewed. Baseline characteristics of the study are shown in Table 1. The average age was 28 ± 6 years. The majority of patients had gestational diabetes mellitus (90.9%). Among the comorbid conditions, the most common was hypertension (9.9%) followed by hypothyroidism (8.5%). Obstetric history included previous history of gestational diabetes mellitus (30.3%), C-section (21.1%), miscarriage (28.9%) and macrosomia (8.5%).

During the second trimester, 77% of the patients were initially treated with lifestyle modification. However, upon progression of pregnancy, during third trimester of pregnancy this percentage was reduced to 33% (Figure 1). On the other hand, insulin was the most common therapy used during the second trimester (18%) and its use was increased to 44% during third trimester. Among the oral hypoglycemic agents, sulfonylurea was preferred during pregnancy when compared to metformin. Amongst patient initially managed with metformin, 50% required the addition of insulin.

Table 1. Characteristics of patients with diabetes on oral hypoglycemic agents and/or insulin treatment attending the high-risk pregnancy clinics from 2013 to 2015. (n = 142)

Characteristics	n (%)	Mean ± SD
Age (in years)	-	28.7 ± 6.0
Gestational age at delivery (in weeks)	-	37.1 ± 2.9
Number of infants per patient*		
1	130 (91.5)	-
2	9 (6.3)	-
3	3 (2.1)	-
Classification of Diabetes		
GDM	129 (90.9)	-
T2DM	13 (9.2)	-
Co-morbid condition**		
Hypertension	29 (9.9)	-
Hypothyroidism	12 (8.5)	-
Hyperthyroidism	3 (2.1)	-
Obstetric History**		
History of GDM	43 (30.3)	-
Cesarean Section	30 (21.1)	-
Miscarriage	41 (28.9)	-
Infant with birth weight > 4,000g (8.8 lbs)	12 (8.5)	-

*Eight patients had twins; **Patients may have had more than one co-morbid condition and/or obstetric history (i.e., non-exclusive data)

Mean blood glucose of women who were managed only with lifestyle modification were 119 ± 4 mg/dL pre-meal and 185 ± 5 mg/dL post-prandial. After adjusting for age, BMI, and the effect of repeated measures, postprandial glucose levels were 12.42 mg/dL (95% CI: -22.10; -2.74) lower in patients who used insulin as compared to those without medications. Likewise, patients receiving oral agents had post-prandial glucose levels that were 8.54 mg/dL (95% CI: -20.24; 3.16) lower than from those without medications (Table 2).

None of the maternal and fetal outcomes showed an association to being treated with insulin or oral agents ($p > 0.05$; Table 3 and 4). The largest difference between women receiving insulin and oral agents, although not significant, was observed in the number of women who underwent C-section (% difference = 15.2, 95% CI: -4.5; 32.2). C-sections were also the most frequent maternal outcome for those receiving insulin and/or oral agents (Table 3).

The most common fetal outcome among women treated with insulin or oral agents was having their infants admitted at NICU (35.2% and 30.6%, respectively). About 13.9% and 19.2% (% difference = 5.3, 95% CI: -11.2; 18.4) of women that were treated with oral agents and insulin, respectively, had infants with macrosomia.

Discussion

Pharmacological interventions are generally initiated in the management of gestational diabetes mellitus and diabetes mellitus type 2 in pregnancy when dietary therapy fails to achieve desired glycemic level. In our study, a significant percent of patients (67%) required a pharmacological agent in addition to dietary intervention. Consensus exists about the use of insulin in such patients (13-15), however, the use of oral hypoglycemic drugs as an alternative treatment is becoming more acceptable. . In this cohort, the majority of patients were managed with insulin (47.1%) when compared with oral hypoglycemic agents (22%). Our institution is a tertiary medical care center and as such it receive a variety of complex cases with different comorbidities and complicated medical scenarios. Whether this increased in insulin use among these patients is an effect of clinical wisdom or it reflects the degree of complexity of our patients with less glycemic control during the third trimester, needs to be assessed.

A study by Beyuo et al. (2015) found that 2-hour post prandial blood glucose levels were significantly lower in patients randomized to metformin when compared to the insulin group (9). In our study we found that postprandial glucose levels were significantly lower in patients using insulin or OHA when compared to lifestyle modification. However, these changes were only significant in the insulin group when adjusted for age, BMI, and the effect of repeated measures. In addition, we found that patients treated with metformin often required the addition of insulin for better glucose control. This finding is similar to a meta-analysis by Poolsup at al. (2014) where they found that patients requiring insulin despite the use of metformin can range from 14% up to 46.3% (17). Liang HL et al. (2017) also found that even though metformin was the fastest in achieving glucose control, the

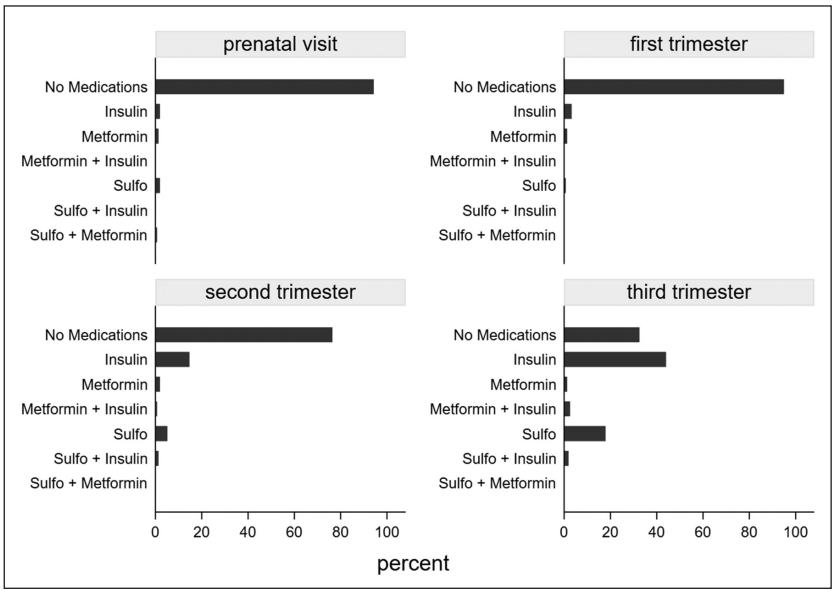

Figure 1. Treatment by trimester of pregnancy

rate of glucose control was the lowest among the groups (18). On the other hand, other studies have found that metformin had less therapeutic failure than glyburide, it is well tolerated by patients, and is associated with less maternal weight gain and less maternal adverse outcomes (19-20).

When maternal and fetal outcomes were evaluated no significant differences were found in our study which differs from studies that found adverse maternal and fetal outcomes such as macrosomia, preeclampsia, neonatal hypoglycemia, NICU admission, and neonatal distress when sulfonylureas or insulin were used (5, 17-20). In a meta-analysis done by Poolsup and colleagues in 2014, they included 13 studies for a total of 2151 patients with GDM and found a significant increased risk for macrosomia and neonatal hypoglycemia in patients using sulfonylureas when compared to patients using insulin (17). Another meta-analysis done in 2017 by Liang et al that included 4,723 patients with GDM also found an increased risk of macrosomia in patients treated with insulin when compared to patients treated with metformin, an increased risk of preterm delivery in patients treated with metformin and an increased risk of admission to NICU in patients treated with insulin (18). Hyer and colleagues (2018) evaluated a subgroup of 118 patients and found that patients treated with metformin had similar incidence of gestational hypertension, pre-eclampsia, induction of labor, and rate of C-section when compared to placebo (20).

Our study found no significant adverse maternal or fetal outcomes in patients that used metformin or sulfonylurea for the treatment of diabetes during pregnancy. The complexity of insulin therapy that requires more frequent glucose monitoring, multiple daily injections, and more frequent medical appointments can be challenging to some patients. These agents can be considered an alternative to insulin in these patients and in those at high risk for adverse events associated to insulin

Table 2. Effect of medications on pre-meal and post-meal glucose levels among patients with diabetes attending the high-risk pregnancy clinics from 2013 to 2015.

	Pre-Meal		Post-Meal	
	Unadjusted β̂ (95% CI)	Adjusted Model β̂ (95% CI)	Unadjusted β̂ (95% CI)	Adjusted Model* β̂ (95% CI)
Glucose Levels**				
Mean ± SE	102.83 ± 1.78	119.18 ± 3.82	150.02 ± 2.48	185.11 ± 5.39
No medications	Reference	Reference	Reference	Reference
Insulin	-5.69 (-12.95; 1.58)	-2.01 (-9.11; 5.10)	-16.77 (-26.87; -6.68)†	-12.42 (-22.10; -2.74)†
Oral Agents	-7.51 (-16.57; 1.54)	-4.58 (-13.01; 3.85)	-13.23 (-26.11; -0.34)†	-8.54 (-20.24; 3.16)
Insulin + Oral Agents	-6.22 (-23.24; 10.80)	-1.33 (-17.35; 14.68)	-16.02 (-39.60; 7.56)	-11.39 (-33.26; 10.47)
Insulin	Reference	Reference	Reference	Reference
Oral Agents	-1.83 (-11.41; 7.75)	-2.57 (-11.55; 6.40)	3.55 (-9.58; 16.67)	3.88 (-8.28;16.03)
Insulin + Oral Agents	-0.53 (-17.73; 16.66)	0.67 (-15.33; 16.67)	0.76 (-22.95; 24.46)	1.03 (-20.78; 22.83)
Oral Agents	Reference	Reference	Reference	Reference
Insulin + Oral Agents	1.29 (-16.47;19.06)	3.25 (-13.11; 19.60)	-2.79 (-27.81; 22.23)	-2.85 (-25.30; 19.61)

Abbreviations: CI, Confidence Intervals; SE, Standard Error; *Models were adjusted for age, body mass index and repeated measures effect (i.e., glucose levels at different time points in pregnancy). All models were controlled for multiple testing using a Scheffé correction. **Mean of glucose levels among women not receiving medications. †Results were statistically significant ($p < 0.05$).

Table 3. Multilevel logistic regression model on maternal outcomes according to type of medication used among women with diabetes attending the high-risk pregnancy clinics from 2013 to 2015.

	Insulin		Oral Agents	
	No	Yes	No	Yes
Spontaneous Vaginal Delivery (n = 149)				
Yes	33 (42.9)	32 (44.4)	54 (69.4)	11 (30.6)
No	44 (57.1)	40 (55.6)	59 (52.2)	25 (69.4)
Crude OR (95% CI)	Ref.	1.09 (0.41; 2.86)	Ref.	0.31 (0.07; 1.36)
Adjusted OR (95% CI)*	Ref.	0.80 (0.27; 2.33)	Ref.	0.29 (0.06; 1.36)
C-section (n = 149)				
Yes	42 (54.6)	39 (54.2)	56 (49.6)	25 (69.4)
No	35 (45.5)	33 (45.8)	57 (50.4)	11 (30.6)
Crude OR (95% CI)	Ref.	0.96 (0.30; 3.14)	Ref.	4.63 (0.81; 24.48)
Adjusted OR (95% CI)*	Ref.	1.45 (0.40; 5.26)	Ref.	5.27 (0.83; 33.57)
Induction of Labor (n = 148)				
Yes	20 (26.0)	21 (29.6)	33 (29.5)	8 (22.2)
No	57 (74.0)	50 (70.4)	79 (70.5)	28 (77.8)
Crude OR (95% CI)	Ref.	1.26 (0.44; 3.65)	Ref.	0.62 (0.17; 2.21)
Adjusted OR (95% CI)*	Ref.	1.13 (0.37; 3.48)	Ref.	0.64 (0.16; 2.54)
Other MO** (n = 157)				
Yes	23 (28.4)	32 (42.1)	45 (37.5)	10 (27.0)
No	58 (71.6)	44 (57.9)	75 (62.5)	27 (73.0)
Crude OR (95% CI)	Ref.	2.49 (0.80; 7.75)	Ref.	0.47 (0.14; 1.60)
Adjusted OR (95% CI)*	Ref.	2.26 (0.72; 7.13)	Ref.	0.60 (0.17; 2.15)

Abbreviations: OR, Odds Ratios; CI, Confidence Intervals; MO, Maternal Outcomes. *Models were adjusted for age and the use of other type of medication (i.e., oral agents / insulin). **Other MO includes episiotomy and/or pre-term labor.

Table 4. Multilevel logistic regression model on neonatal outcomes according to type of medication used among women with diabetes attending the high-risk pregnancy clinics from 2013 to 2015.

	Insulin		Oral Agents	
	No	Yes	No	Yes
Macrosomia				
Yes	9 (11.5)	14 (19.2)	18 (15.7)	5 (13.9)
No	69 (88.5)	59 (80.8)	97 (84.4)	31 (86.1)
Crude OR (95% CI)	Ref.	1.94 (0.63; 6.03)	Ref.	0.96 (0.24; 3.73)
Adjusted OR (95% CI)*	Ref.	2.14 (0.59; 7.79)	Ref.	1.25 (0.29; 5.37)
Intubation				
Yes	2 (2.7)	4 (5.8)	4 (3.6)	2 (6.1)
No	73 (97.3)	65 (94.2)	107 (96.4)	31 (93.9)
Crude OR (95% CI)	Ref.	2.25 (0.40; 12.67)	Ref.	1.72 (0.30; 9.86)
Adjusted OR (95% CI)*	Ref.	3.49 (0.48; 25.12)	Ref.	3.09 (0.42; 22.88)
Congenital abnormalities (n = 81)				
Yes	3 (8.6)	1 (2.2)	3 (4.8)	1 (5.3)
No	32 (91.4)	45 (97.8)	59 (95.2)	18 (94.7)
Crude OR (95% CI)	Ref.	0.23 (0.02; 2.38)	Ref.	1.09 (0.11; 11.14)
Adjusted OR (95% CI)*	Ref.	0.16 (0.01; 1.92)	Ref.	0.53 (0.04; 6.33)
NICU				
Yes	25 (33.3)	25 (35.2)	39 (35.5)	11 (30.6)
No	50 (66.7)	46 (64.8)	71 (64.6)	25 (69.4)
Crude OR (95% CI)	Ref.	1.09 (0.55; 2.15)	Ref.	0.80 (0.36; 1.80)
Adjusted OR (95% CI)*	Ref.	1.00 (0.48; 2.07)	Ref.	0.79 (0.33; 1.88)
Neonatal distress				
Yes	3 (4.0)	9 (13.0)	9 (8.1)	3 (9.4)
No	71 (96.0)	60 (87.0)	102 (91.9)	29 (90.6)
Crude OR (95% CI)	Ref.	3.78 (0.88; 16.30)	Ref.	1.16 (0.27; 4.93)
Adjusted OR (95% CI)*	Ref.	5.57 (0.98; 31.65)	Ref.	2.66 (0.47; 15.23)
Transient Tachypnea				
Yes	6 (8.1)	1 (1.5)	5 (4.5)	2 (6.3)
No	68 (91.9)	68 (98.5)	106 (95.5)	30 (93.8)
Crude OR (95% CI)	Ref.	0.17 (0.02; 1.42)	Ref.	1.41 (0.26; 7.65)
Adjusted OR (95% CI)a	Ref.	0.16 (0.02; 1.43)	Ref.	0.85 (0.15; 4.86)

Note: None of the infants had respiratory distress syndrome whereas two infants had dystocia (mothers from these two patients were treated with insulin). Abbreviations: OR, Odds Ratio; CI, Confidence Interval; NICU, Neonatal Intensive Care Unit
*Models were adjusted for age and the use of other type of medication (i.e., oral agents / insulin)

use or which have contraindications to insulin. In addition, the high cost of insulin makes OHA a suitable alternative in patients who cannot afford insulin cost (7-8). Even more, in countries where there is an increased risk of having natural disasters, a treatment alternative that does not require refrigeration is reassuring. However, these agents cross the placenta which raises concern about the long-term effects in the offspring (21-22). There are limited data about the long-term effects of these agents but some studies suggest that metformin alter the cellular programming of the offspring resulting in the development of metabolic diseases later in life (23). Glyburide has been shown to contribute to changes in glucose transporter expression which can affects the transport of nutrients to the developing fetus contributing to overgrowth and macrosomia. Nevertheless, due to the different approaches used in the available studies there is still a controversy about which oral agent is better for the management of DM during pregnancy (21,24).

Puerto Rico has one of the highest prevalence of Diabetes Mellitus when compared to the USA which confers an increased risk for DM complicating pregnancies in our population (16). This study provides important information about the safety of using OHA in our patients.

With regard to limitations of this study; (i) due to the retrospective design, some information was not available in the medical records, and (ii) as a tertiary medical care center, clinical features may reflect a degree of complexity that is not typical of other health settings. Further studies that includes other institutions and clinics should be considered.

Conclusions

Oral hypoglycemic agents are arguably more convenient than insulin to treat woman with gestational diabetes and type 2 diabetes mellitus during pregnancy, but these agents must show no inferiority or superiority to the standard of care, insulin in this case, before we consider their use. In this patient cohort, the use of metformin required the addition of insulin for appropriate glycemic control. In fact, we noticed that there was a better glucose control post-prandial in the patient treated with insulin. Our study did not show significant differences in the maternal and neonatal outcomes among the pharmacological agents. Oral hypoglycemic agents can be an alternative for patients that do not want to use insulin, have a higher risk of insulin side effects such as severe hypoglycemia, or cannot have the proper insulin storage or availability. Prospective studies are still needed to evaluate the impact of oral hypoglycemic agents in glucose control during pregnancy, its maternal and fetal outcomes and the long-term effects of these agents in the offspring.

Resumen

Objetivo: La Diabetes Mellitus Gestacional (DMG) y la Diabetes Mellitus tipo 2 (DM2) son desórdenes metabólicos que se caracterizan por un aumento en resistencia a la insulina. A pesar de que la insulina es el tratamiento de elección en mujeres embarazadas con DM, el uso de agentes hipoglucemiantes orales (AHO) ha ido en aumento. El objetivo de este estudio fue evaluar los resultados maternos y neonatales cuando se utilizaron AHO en mujeres diabéticas embarazadas. Métodos: Se revisaron expedientes médicos de las Clínicas de la Unidad Materno-Fetal de la Escuela de Medicina de la UPR (n=149).

Pacientes que fueron tratadas con metformina, sulfonilureas o insulina fueron incluídas en este estudio. Los resultados maternos y neonatales fueron comparados entre los grupos. Resultados: La edad promedio de las pacientes fue 28 ± 6 años. La mayoría tenían DMG (91%). La comorbilidad más común fue hipertensión (9.9%). La modificación en estilos de vida se utilizó como tratamiento en 77% de las pacientes durante el segundo trimestre, pero su uso disminuyó a 33% durante el tercer trimestre. La insulina fue el tratamiento de elección. Entre los AHO, las sulfonilureas fueron preferidas. Los niveles de glucosa luego de las comidas fueron menores en las pacientes que utilizaron insulina cuando se compararon con las pacientes que no utilizaron medicamentos. Conclusión: No se encontraron diferencias significativas en los resultados maternos tales como cesáreas, inducción de parto, episiotomía o parto prematuro, o en los resultados neonatales tales como macrosomía, hipoglucemia neonatal o anomalías congénitas entre los grupos de tratamiento. Los AHO pueden ser considerados una alternativa a insulina para el tratamiento de DM durante el embarazo en casos específicos.

Acknowledgments

Research reported in this publication was supported in part by Hispanic Center of Excellence - University of Puerto Rico School of Medicine Grant Number: D34HP24463 U.S. Department of Health and Human Services Health Resources and Services Administration Bureau of Health Workforce. The authors acknowledge Dr. Juan C. Jorge for providing feedback to an earlier version of this manuscript and to the Hispanic Center of Excellence - University of Puerto Rico School of Medicine staff for their support during this process. Participation of LGS in this study was supported by PRCTRC grant number 2U54MD007587 from the National Institute on Minority Health and Health Disparities of the National Institutes of Health.

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