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THREATENED ABORTION AND GESTATIONAL DIABETES CASES IN MEXICAN PREGNANT WOMEN DOES NOT CHANGE WITH THE FTO RS9939609 PRESENCE

Martínez Martínez M.A.[1], Camarillo Romero E.S.[2], González Santana A.[3], Mendieta Zerón H.[3,4], Santillán Benítez J.G.[5], Garduño García J.J.[2,6]

[1] Faculty of Behavioral Sciences, Autonomous University of the State of Mexico (UAEMex), Toluca, Mexico.
[2] Multidisciplinary Clinic, Autonomous University of the State of Mexico (UAEMex), Toluca, Mexico.
[3] Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), Toluca, Mexico.
[4] Ciprés Grupo Médico S.C. (CGM), Toluca, Mexico.
[5] Faculty of Chemistry, Autonomous University of the State of Mexico (UAEMex), Toluca, Mexico.
[6] Regional General Hospital 251, Mexican Social Security Institute (IMSS), Metepec, México.

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Abstract

The Obesity-associated fat mass (FTO) gene has been associated to a higher risk of obstetrical complications.

The aim of this prospective, cross-sectional and comparative study was to determine if there are clinical or laboratorial differences in pregnant women with the presence/absence of FTO rs9939609 focused on threatened abortion.

Pregnant women between 18 to 35 years of age were invited to participate. In all cases, it was obtained the sociodemographic information, anthropometry, clinical laboratories for obstetrical routine check-up, FTO rs9939609 positive expression, and the homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) indexes were also calculated.

Comparisons of this type of variables between both groups were performed through Student´s T-test. Chi-Square Tests were used to contrast the GDM and threatened miscarriages percentages of cases between both groups. Pearson correlation was performed among the quantitative variables of all the study population.

57 women positive and 52 negative for the FTO rs9939609 presence were included in the study with a Gestational Diabetes Mellitus prevalence of 19.3%. When contrasting the variables by the presence/absence of FTO rs9939609 the p-values were far from being significant. As such, Chi-Square Tests did not show significant statistical difference neither for GDM nor for threatened miscarriage between both groups.

Based on these results, the FTO rs9939609 presence did not reflect difference either in GDM or in threatened miscarriage. It was demonstrated in parallel, the utility of the QUICKI index in the metabolic evaluation during pregnancy. In conclusion, in Mexican women, pregnancy evolution and possible appearance of complications is not so determined by the FTO rs9939609 presence but by the overweight with which this physiological state is faced.

Keywords: *fat mass and obesity-associated gene, chromosome 16 (16q12.2), abort, Gestational Diabetes Mellitus*

Introduction

The fat mass and obesity-associated gene (*FTO*) is located on chromosome 16 (16q12.2) [*Fang H, et al, 2010*] and has been determined to encode the production of a nuclear protein with nucleic acid demethylase activity [*Chen J, Du B, 2019*]. Its action has been related to various biochemical and physiological processes, including influence on body composition through playing a role in cellular nutrient sensing [*Gulati P, et al, 2013*], DNA repair [*Jia G, et al, 2008*], regulation of lipid storage and adipose tissue [*Zhao X, et al, 2014*], etc.

Address for Correspondence:
Hugo Mendieta Zerón, MSc, PhD.
Faculty of Medicine, UAEMéx. Felipe Villanueva sur 1209, Col. Rancho Dolores, C.P. 50170. Toluca, México.
Telephone: +52-722-2194122.
E. mail: drmendietaz@yahoo.com

The *FTO* presence has been associated to a higher risk of metabolic syndrome parameters in adolescence as well as with weight gain/obesity [*Martínez-Martínez MA, et al, 2018; Kalantari N, et al, 2018*]. *FTO* mutations lead to extensive phenotypic modifications including various congenital malformations and delay in physical and psychomotor growth [*Rohena L, et al, 2016; Howard SR, 2019*]. *FTO* polymorphism (SNPs) have been investigated extensively in populations with obesity [*Zhang Q, et al, 2018; Daya M, et al, 2019*], and specifically, the rs9939609 variant has also been linked to the increased risk of diabetes mellitus [*Jiménez-Osorio AS, et al, 2019*]. Table 1 shows some diseases associated with the presence of this last SNP.

More recently the association of this SNP with a higher risk to develop Gestational Diabetes Mellitus (GDM) has also been studied in several surveys with contrasting results [*He H, et al, 2018; Lin Z, et al, 2018*]. The aim of this study was to determine if there are clinical or laboratorial differences in pregnant women with the presence/absence of *FTO* rs9939609 with focused on threatened abortion.

MATERIAL AND METHODS

This was a prospective, cross-sectional and comparative study performed at the "Mónica Pretelini Sáenz" Maternal Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, Mexico.

Patients; Pregnant women between 18 to 35 years of age were invited to participate, explaining them in detail the project, and asking to sign the consent form according to the current Clinical Practice Guideline. Those women with a history of smoking or alcoholism, chronic or autoimmune diseases were excluded from the final analysis.

Sampling: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 45 pregnant women per group were necessary for a percentage of threatened abortion of 5% in the GDM group [*Pacora Portella P, et al, 1991*] and a hypothetical 25% in the *FTO* rs9939609 group.

General data: General data including hereditary-family history was collected by means of a medical history comprising and personal interview; as well as complementary data of nutritional habits and physical activity.

Anthropometry Weight (kg), fat mass (kg), muscle mass (*kg*), corporal water (%) and metabolic age (ages) were calculated using Tanita (model BC-533, Tanita, Tokyo, Japan), height (*m*) was measured with conventional stadiometer and the Body Mass Index (BMI) was calculated as standard (kg/m^2). The gestational BMI classification was done according to World Health Organization (WHO) cutoffs (underweight [<18.5 kg/m^2], normal weight [18.5–24.9 kg/m^2], overweight [25.0–29.9 kg/m^2], and obesity [≥30.0 kg/m^2]) [*WHO, 2019*].

In addition, more clinical parameters, including gestational weight gain (*kg*) and blood pressure (*mmHg*) were also registered. Hand grip strength (HGS) was measured by a dynamometer (Takei Scientific Instruments Co., Ltd., Niigata-City, Japan).

Laboratory: Venous blood samples were taken after an 8-hour fasting period to process glucose and insulin curves. The GDM diagnosis was based on an abnormal 75 *g* oral glucose tolerance test (OGTT) where either one or more blood glucose values were above the values of 5.1 *mmol/L* (92 *mg/dL*) at fast-

TABLE 1.

Some diseases associated with the presence of *FTO* rs9939609

Source	Disorder
Khella MS *et al.*, (2018)	Malignant Pleural Mesothelioma
Huang X *et al.*, (2017)	Cancer
Yu JH *et al.*, (2017)	Biological aging
Castellini G *et al.*, (2017)	Eating disorders susceptibility
Barton SJ *et al.*, (2016)	Fetal growth trajectories
Gesteiro E *et al.*, (2016)	Lipoprotein profile at birth

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

ing, 10.0 mmol/L (*180 mg/dL*) at 1 h, and 8.5*mmol/L* (153 *mg/dL*) at 2 h. At the same time, the insulin curve was quantified and with this information, the homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) indexes were calculated for all women.

Genotyping: In the Genetics Laboratory of the Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), DNA was extracted, quantified with a spectrophotometry (NanoPhotometer, Implen), and kept at -70°*C* until SNP identification.

Genotyping was performed by real-time polymerase chain reaction (qPCR) in the Research Laboratory of Ciprés Grupo Médico (CGM) in a PrimeQ (Techne, UK) equipment. The *FTO* rs9939609 oligonucleotides used in this study were those described previously by Yan Q [*Yan Q, et al, 2009*], forward primer 5'-CAAAACTGGCTCTTGAATGAA-3' and the reverse primer 5'-TGTCCAAACAGTAGGTCAGGA-3'; requested at the DNA Synthesis and Sequencing Unit of the National Autonomous University of Mexico (UNAM), Institute of Biotechnology (Cuernavaca, Morelos, Mexico) with a previous BLAST search to verify the correct hybridization and following the conditions of the same author.

Bioethical implications: The Research Committee and the Ethics in Research Committee of the HMPMPS (2017-06-S29) as well as by the Research and Ethics Committee of the Medical Sciences Research Center (CICMED), UAEMéx (CIE2018-1), authorized this protocol.

The procedures were carried out under the deontological norms of the Declaration of Helsinki (2013 Fortaleza, Brazil) and of the General Health Law (Mexico), regarding health research. All participants were informed about the purpose of the study, risks and benefits and were given the informed consent letter for their signature.

Statistical analysis: Quantitative variables were represented in mean ± Standard deviation (SD). Comparisons of this type of variables between both groups were performed through Student´s T-test. Chi-Square Tests were used to contrast the percentages of cases of GDM and threatened miscarriage between both groups. Pearson correlation was performed among the quantitative variables of all the study population. The one-way ANOVA test was used to contrast the values of the quantitative variables per BMI classification of the patients and inde-

Table 2.

General characteristics of the patients

Variable (n=109)	FTO present (n=57)	FTO absent (n=52)	P
Age (years)	26.46 ± 6.59	25.60 ± 6.90	0.924
Gestational age (weeks)	26.4 ± 2.6	27.0 ± 2.3	0.155
Cardiac frequency	84.21 ± 11.45	85.42 ± 10.13	0.554
Weight (*kg*)	71.16 ± 14.23	68.58 ± 13.24	0.332
Height (*m*)	1.55 ± 0.06	1.54 ± 0.06	0.771
BMI (kg/m^2)	29.45 ± 5.24	28.54 ± 5.01	0.525
Fat mass (*kg*)	36.82 ± 7.29	35.19 ± .80	0.231
Muscle mass (*kg*)	41.78 ± 4.23	41.42 ± 4.43	0.668
Bone mass (*kg*)	2.22 ± 0.20	2.21 ± 0.23	0.828
Glucometry (*mg/dL*)	84.87 ± 10.89	86.48 ± 11.45	0.768
Basal glucose (*mg/dL*)	82.31 ± 16.81	81.36 ± 17.43	0.773
Glucose 60 min (*mg/dL*)	132.61 ± 37.03	133.55 ± 44.21	0.904
Glucose 120 min (*mg/dL*)	105.14 ± 30.67	107.36 ± 36.39	0.730
Basal insulin (*μU/mL*)	13.30 ± 6.40	16.03 ± 12.10	0.139
Insulin 60 min (*μU/mL*)	50.91 ± 57.62	53.70 ± 45.98	0.782
Insulin 120 min (*μU/mL*)	43.24 ± 46.53	46.84 ± 36.41	0.656
HOMA-IR	2.85 ± 1.59	3.44 ± 3.04	0.203
QUICKI	0.33 ± 0.02	0.33 ± 0.4	0.613
SBP (*mmHg*)	107.7 ± 10.52	104.32 ± 9.98	0.088
DBP (*mmHg*)	65.57 ± 9.57	64.28 ± 7.57	0.440
HGS right (*kg*)	24.07 ± 5.74	24.75 ± 4.71	0.503
HGS left (*kg*)	22.49 ± 6.01	22.69 ± 4.10	0.840

Notes: Data are expressed as mean ± SD., ***BMI:*** Body Mass Index, ***DBP:*** Diastolic Blood Pressure, ***HGS:*** Handgrip strength testing, ***SBP:*** Systolic Blood Pressure.

pendent sample Student's t-tests or the Mann Whitney U tests were used to do multiple comparisons between groups for all BMI classes. In all cases it was used the SPSS v21 statistical package with a level of significance of $p \leq 0.05$.

RESULTS

57 women positive and 52 negative for the *FTO* rs9939609 presence were included in the study with a prevalence GDM of 19.3%. The general characteristics of included patients are depicted in Table 2. After performing the Kolmogorov test, all the quantitative variables were confirmed to have parametric distributions.

The nutritional classification in the first medical visit reported the following distribution: Undernutrition = 8, Normal weight = 37, Overweight = 34, Obesity =30. When contrasting the variables per classification of BMI, besides the expected differences in fat, muscle and bone masses, there were differences in the HGS of both hands between underweight and overweight women ($p = 0.008$ left, $p \leq 0.001$ right), observed only in the right HGS between underweight and obese women ($p \leq 0.05$) and in both sides again between normal-weight and overweight pregnant women ($p \leq 0.05$).

When contrasting the variables by the presence/absence of *FTO* rs9939609 the p-values were far from being significant. As such, Chi-Square Tests did not show significant statistical difference neither for GDM nor for threatened miscarriage between both groups.

Generally speaking, Pearson correlation showed that BMI, fat mass, muscle mass, body water, bone mass and metabolic age were positively correlated with capillary glucose, systolic blood pressure, HGS (both sides), kcal, basal glucose and glucose in the 1st and 2nd hour post 75 g oral glucose test (Table 3). It calls the attention that the QUICKI index had a significant negative correlation with 12 parameters, while HOMA index had positive correlation with only seven (Table 4).

DISCUSSION

Adding to what has been reported repeatedly [*He H, et al, 2018; Guo F, et al, 2018*] our study did not show a correlation between the *FTO* rs9939609 presence and GDM development. Although *FTO* has been associated with high gestational weight gain in obese black women who have either risk variant [*Groth SW, et al, 2018*] in our community black women are few and no one was attended in the Hospital during our screening phase.

Whereas some authors have shared information about an association between *FTO* (or variants) with lipid parameters [*Franzago M, et al, 2018*]; nevertheless, our study evidenced a lack of association of these variables. In a similar way, it has been demonstrated that some polymorphisms related to the adipocyte's ability to store fat are re-

TABLE 3.

Pearson correlation

Variable	BMI (kg/m^2)	Fat mass (kg)	Muscle Mass (kg)	Body water (%)	Bone Mass (kg)	Metabolic Age (years)
Fat mass (*kg*)	0.871$^{\Upsilon}$					
Muscle Mass (*kg*)	0.780$^{\Upsilon}$	0.725$^{\Upsilon}$				
Body Water (%)	-0.858$^{\Upsilon}$	-0.997$^{\Upsilon}$	-0.676$^{\Upsilon}$			
Bone Mass (%)	0.788$^{\Upsilon}$	0.715$^{\Upsilon}$	0.961$^{\Upsilon}$	-0.670$^{\Upsilon}$		
Metabolic Age (years)	0.785$^{\Upsilon}$	0.912$^{\Upsilon}$	0.673$^{\Upsilon}$	-0.913$^{\Upsilon}$	0.658$^{\Upsilon}$	
CG (*mg/dl*)	0.359$^{\Upsilon}$	0.314$^{\Upsilon}$	0.230	-0.317$^{\Upsilon}$	0.233*	0.251†
SBP (*mmHg*)	0.326$^{\Upsilon}$	0.354$^{\Upsilon}$	0.342$^{\Upsilon}$	-0.344$^{\Upsilon}$	0.330$^{\Upsilon}$	0.299†
HGS Left (*kg*)	0.192*	0.252†	0.339$^{\Upsilon}$	-0.240*	0.304$^{\Upsilon}$	0.242*
HGS Right (*kg*)	0.207*	0.280†	0.348$^{\Upsilon}$	-0.268*	0.307$^{\Upsilon}$	0.271†
kcal	0.676$^{\Upsilon}$	0.688$^{\Upsilon}$	0.891$^{\Upsilon}$	-0.641$^{\Upsilon}$	0.860$^{\Upsilon}$	0.592$^{\Upsilon}$
Glucose (*mg/dl*)	0.393$^{\Upsilon}$	0.299†	0.205	-0.302$^{\Upsilon}$	0.226*	0.241*
Glucose H1 (*mg/dl*)	0.403$^{\Upsilon}$	0.358$^{\Upsilon}$	0.216	-0.369$^{\Upsilon}$	0.243*	0.351$^{\Upsilon}$
Glucose H2 (*mg/dl*)	0.417$^{\Upsilon}$	0.357$^{\Upsilon}$	0.225	-0.366$^{\Upsilon}$	0.252†	0.372$^{\Upsilon}$

NOTES: ***BMI:*** *Body Mass Index,* ***CG:*** *Capillary Glucose,* ***HGS:*** *Handgrip strength testing,* ***SBP:*** ***Systolic*** *Blood Pressure.* ****≤ 0.05 †≤ 0.01 ϒ≤ 0.001***

Table 4.
Significant correlation of HOMA and QUICKI indexes with all the variables

	HOMA	QUICKI
BMI (*kg/m²*)		-0.249†
Muscle Mass (*kg*)		-0.202*
Bone Mass (*kg*)		-0.198*
Capillary Glucose (*mg/dl*)	0.380ϒ	-0.366ϒ
Basal Glucose (*mg/dl*)	0.589ϒ	-0.671ϒ
Glucose H1 (*mg/dl*)	0.411ϒ	-0.445ϒ
Glucose H2 (*mg/dl*)	0.349ϒ	-0.414ϒ
Basal Insulin (*IU*)	0.959ϒ	-0.764ϒ
Insulin H1 (*IU*)	0.439ϒ	-0.436ϒ
Insulin H2 (*IU*)	0.372ϒ	-0.415ϒ
FATMSKg		-0.205*
HOMA		-0.766ϒ

Notes: ***BMI:*** *Body Mass Index,* ***H1:*** *1st hour after 75 g of oral glucose,* ***H2:*** *2nd hour after 75 g oral glucose,* ***HOMA:*** *homeostasis model assessment,* ***QUICKI:*** *quantitative insulin sensitivity check index.* *≤ 0.05, †≤ 0.01, ϒ≤ 0.001

lated to the HOMA-IR marker of insulin resistance [*Smith CE, et al, 2012; De Luis DA, et al, 2016*] but in the two groups studied there was not a difference.

Research concerning mothers' *FTO* rs9939609 has confirmed an impact on birth weight and newborns' BMI of this SNP, a role in the newborns' nutritional status [*Mărginean C, et a, 2016*]. Unfortunately, it was not possible to attend all women in our Hospital so the information of the babies' weight and height was missing to make any association with the SNP presence.

A previous study controlling for important factors such as BMI, diabetes and cardiovascular disease showed that *FTO* rs9939609 SNP was associated with recurrent miscarriage [*Andraweera PH, et al, 2015*] and two more putative undesired effects of *FTO* rs9939609 SNP are an association with lower fetal growth [*Marsh JA, et al, 2012*] and spontaneous preterm birth [*Andraweera PH, et al, 2016*].

SNPs have been reported that depending on the interaction with environmental and nutritional factors are considered responsible for the onset of various diseases such as obesity and diabetes, or are the trigger for the development of such diseases. But this genetic interaction is most often not specific to a single SNP, but is the result of the interaction of various genes and individuality of each person [*Wang YT, et al, 2015*]. To make it more difficult, some effects can be discreet, indirect and identifiable in the long term, for example, *FTO* rs9939609 has been linked to systemic inflammation, which is related in processes of diabetogenesis and insulin resistance [*Saucedo R, et al, 2017*].

The present study has some limitations. First, the sample size for the SNP was relatively small. Second, abdominal fat of pregnant women was not measured. However, the results may be relevant to the extent of knowledge about the handicap of Mexican women since the beginning of pregnancy attributed to overweight/obesity [*Díaz Montiel JC, et al, 2019*].

Further studies are required to explore the specific association of the *FTO* rs9939609 alleles with all the variables studied or even consider more genes with their variants and of course additional analyses, such as epigenetic studies, to elucidate the role of the own fetal genes and alleles in the development and prognosis of metabolic diseases and obstetrical complications.

Conclusion

FTO rs9939609 presence did not lead to a higher percentage of cases neither of GDM nor of threatened miscarriage. Another important observation was that QUICKI index seems to be more useful than HOMA index to check-up the metabolic status during pregnancy.

Conflict of Interest: *All of the authors declare that there are no competing interests regarding the publication of this paper.*

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