Gestational diabetes and thyroid disorders in pregnant women in a specialized maternal-child diagnostic center

Diabetes gestacional y alteraciones tiroideas en gestantes de un centro especializado de diagnóstico materno-infantil

Jhoalmis Sierra-Castrillo[1*], Yojanna Perdomo Dominguez[2], Jeferson Adrian Villamizar Carvajal[3], Adriana Muñoz-Bravo[4], Lyz Jenny Gómez Rave[5], Valmore Bermudez[6].
[1]Magister en Bioquímica Clínica Programa de Bacteriología y Laboratorio Clínico. Facultad de Salud, grupo Biogen, Universidad de Santander Campus Cúcuta. coordbacteriologia@cucuta.udes.edu.co. Autor de Correspondencia: Jho.sierra@mail.udes.edu.co
[2]Magister en Administración de proyectos. Programa de Bacteriología y Laboratorio Clínico. Facultad de Salud, Universidad de Santander Campus Cúcuta. naniapd@hotmail.com
[3]Estudiante del Programa de Bacteriologia y Laboratorio Clínica. Facultad de Ciencias de la Salud, Universidad de Santander Campus Cúcuta. Cuc16172022@mail.udes.edu.co
[4]Magister en Bioquímica Clínica; Programa de Bacteriología y Laboratorio Clínico. Grupo Biociencias, Facultad de Ciencias de la Salud, Institución Universitaria Colegio Mayor de Antioquia. adriana.bravo@colmayor.edu.co
[5]Magister en Bioquímica Clínica Programa de Bacteriología y Laboratorio Clínico. Facultad de Salud, Instituto Universitaria Colegio Mayor de Antioquia. liz.gomez@colmayor.edu.co
[6]Universidad Simón Bolívar, Facultad de Ciencias de la Salud, Barranquilla, Colombia.
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Resumen

Introduction: gestational diabetes mellitus (GDM) commonly appears between the second and third trimesters of pregnancy as a result of hormonal changes that induce a transitory state of insulin resistance (IR) in the mother, allowing a greater supply of glucose to the fetus. After GDM, thyroid disease is the most common endocrine disorder in obstetrics, with an incidence of 5-10%. Some studies speak of the existence of a relationship between diabetes and thyroid disorders (TA) but the results remain controversial, limiting the analysis of the effects that both diseases could have on the development of pregnancy. Therefore, the identification of patients at risk, prevention and timely treatment, constitute one of the priority issues in public health. **Objective**: in this study, the prevalence of GDM and AT in pregnant women attended in a specialized center for maternal and child diagnosis was analyzed. **Materials and methods**: retrospective research, based on the exploration of medical records in the period from 2016 to 2020, with a probabilistic sample of 388 pregnant women (n=388). For the diagnosis of GDM, the results of the O'sullivan test, oral glucose tolerance test (OGTT) and fasting blood glucose were taken into account. Thyroid alteration was identified from TSH values, but only 120 pregnant women reported results for this test (n=120). Descriptive measures and simple frequency distributions were calculated. To establish the relationship between GDM and AT, the chi-square test was applied with a statistical significance of p=0.05. **Results**:the prevalence of GDM was 10.6% (n=41) and of AT 17.5% (n=21). 19% of the pregnant women simultaneously presented GDM and AT with a predominance of a tendency to hyperthyroidism. No significant association was found between GDM and AT (p=0.537). **Conclusion**: This pilot study confirms that GDM and AT are conditions frequently present in pregnant women. Although there could be a risk of developing GDM in patients with AT, studies with a larger sample number are suggested to clarify this relationship.

Key Words: diabetes gestational, thyroid diseases, pregnancy, prevalence.

Resumen

Introducción: comúnmente la diabetes mellitus gestacional (DMG) suele aparecer entre el segundo y tercer trimestre del embarazo como consecuencia de cambios hormonales que inducen en la madre un estado transitorio de resistencia a la insulina (IR), permitiendo un mayor aporte de glucosa al feto. Después de la DMG, la patología tiroidea es la alteración endocrina más frecuente en obstetricia, con una incidencia de 5-10%. Algunos estudios hablan de la existencia de una relación entre diabetes y alteración tiroidea (AT) pero los resultados siguen siendo controvertidos, limitando el análisis de los efectos que ambas enfermedades podrían tener en el desarrollo del embarazo. Por ello, la identificación de pacientes en riesgo, la prevención y el tratamiento oportuno, constituyen uno de los temas prioritarios en salud pública. **Objetivo**: en este estudio se analizó la prevalencia de DMG y de AT en gestantes atendidas en un centro especializado de diagnóstico materno infantil. Materiales y métodos: investigación retrospectiva, a partir de la exploración de historias clínicas en el periodo de 2016 al 2020, con una muestra probabilística de 388 gestantes (n=388). Para el diagnóstico de DMG se tuvieron en cuenta resultados del Test de O'sullivan, prueba de tolerancia oral a la glucosa (PTOG) y glucemia en ayunas. La alteración tiroidea se identificó a partir de valores de TSH, pero sólo 120 gestantes reportaron resultados para esta prueba (n=120). Se calcularon medidas descriptivas y distribuciones de frecuencia simple. Para establecer la relación entre DMG y AT se aplicó la prueba chi-cuadrado con una significancia estadística p=0,05. **Resultados**: la prevalencia de DMG fue del 10,6% (n=41) y de AT 17,5% (n=21). El 19% de las gestantes presentaron de manera simultánea DMG y AT con predominio de tendencia a hipertiroidismo. No se logró evidenciar asociación significativa entre DMG y AT (p=0,537). **Conclusión**: este estudio piloto ratifica que la DMG y la AT son condiciones presentadas con frecuencia en gestantes. Aunque podría existir riesgo de desarrollo de DMG en paciente con AT, se sugieren estudios con mayor número de muestra que permitan esclarecer esta relación.

Palabras Clave: diabetes gestacional, enfermedades de la tiroides, embarazo, prevalencia.

Introduction

Pregnancy is a physiological condition that involves major changes in different systems and organs. Glucose metabolism may be affected more frequently as a consequence of the action of some hormones such as chorionic gonadotropin (hCG), placental lactogen (hPL), prolactin (PRL), progesterone (PR), cortisol and glucagon[1,2], which ensure energy supply to the fetus through anti-insulin effects and elevation of maternal catabolism. From the second trimester onwards, the decrease in insulin affinity for IR receptors is exacerbated, with a response of approximately one third of normal[1], negatively modifying the reaction to carbohydrate loading and therefore blood glucose levels[3,4].

In some pregnant women, the adaptive physiological mechanisms fail to compensate for insulin resistance (IR), resulting in gestational diabetes mellitus (GDM)[4,5]. This type of diabetes, of multifactorial etiology, is characterized by being identified for the first time during pregnancy and its risk factors include, among others: advanced age, high body mass index (BMI), genetic predisposition, hormonal alterations and family history[6-10].

In public health, this disease is of great interest due to its implications on fetal and maternal health, which have a high prevalence rate[11,12]. There is an increased risk of fetal macrosomia, preeclampsia, gestational arterial hypertension, cardiovascular disease and postpartum diabetes[13]. A global frequency is estimated between 1 and 28%, with frequencies for Latin America between 4.2% and 7.6%[14].

After GDM, thyroid pathology is the most frequent endocrine disorder in obstetrics, with a prevalence of 16.6%[15-18].

Previous studies have demonstrated the effect of HCG on the thyroid gland and the impact on thyroid stimulating hormone (TSH) levels. During the first trimester, when HCG concentrations are higher, a stimulus of this hormone similar to that exerted by TSH on the gland is observed, leading to an increase in free thyroxine (FT4) and free triiodothyronine (FT3), accompanied by a decrease in TSH which will be regulated with the evolution of pregnancy[17,19]. This behavior is explained by the high demand of thyroid hormones necessary for fetal and placental development. Failure to adapt to these changes or a major imbalance in maternal thyroid function could have adverse gestational effects. Placental abruption, preeclampsia and fetal growth retardation, irreversible neurocognitive deficit and thyroid impairment are common[20-23]. As for thyroid disorders in pregnant women, there is a predominance of subclinical forms, of which subclinical hypothyroidism (SCH) occupies the highest figures, with a prevalence of 8%[24].

Recent research has tried to elucidate the relationship between GDM and thyroid impairment (TA), but the results are still controversial, limiting the analysis of the effects that both diseases could have during pregnancy[12,25-28].

Some institutions, such as the World Health Organization (WHO), recommend screening for GDM in all pregnant women, others suggest carrying out diagnostic tests only if indicated by the risk profile[29]. In Colombia, although diagnostic tests for GDM are covered in the prenatal control program, the evaluation of thyroid function is neglected, being limited in most cases to the determination of TSH levels and applied in special situations. Additionally, there are few studies on these alterations in pregnant women, preventing the identification of high-risk patients, prevention and timely treatment.

Taking into account these shortcomings, it was considered necessary to identify through a retrospective pilot study, the prevalence of GDM and TA in pregnant women attended in a specialized maternal and child center of the city, in order to make a local epidemiological contribution and provide information strategies to health professionals on the management of these endocrine diseases.

Materials and methods

Type of study
Retrospective, descriptive study, based on the exploration of clinical histories of pregnant women who received their prenatal consultation at the Specialized Center for Maternal and Child Diagnosis (CEDMI), in Norte de Santander, Colombia, in the period from 2016 to 2020.

Population and sample
Population: made up of N=10,000 pregnant women between the ages of 20 and 45 years who attended the Specialized Center for Maternal and Infant Diagnosis (CEDMI) in Cúcuta from 2016 to 2020.

Sample: a probability sample of 388 patients was calculated, with an error of 5% and a confidence level of 95%.

Inclusion criteria
Pregnant women, between 20 and 45 years old, primigravid or multigestational, with complete medical history.

Exclusion criteria
Diagnosis of diabetes mellitus 1 or 2 prior to pregnancy, history of thyroid disease, pre-existing endocrine, autoimmune or metabolic disorders, in treatment with hormone therapy, hemoglobinopathies, hepatic or renal complications.

Data collection
Information on age, gestational week, fasting blood glucose, PTOG, O'sullivan test, thyroid function and important medical history were extracted from the clinical history.

Diagnosis of DMG (30)
It was established following the guidelines of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (31), applied to pregnant women without a previous diagnosis of diabetes, between the 24th and 28th week.

One-step strategy
PTOG
After an 8-hour fasting period, a venous blood sample is taken, then a 75g glucose load is administered under standard procedure and consecutive postload blood samples are taken at 1 and 2 hours. The cut-off point for GDM is to have at least one blood glucose result equal to or greater than the following; fasting 92 mg/dL (5.1 mmol/L), 1 hour 180 mg/dL (10.0 mmol/L) and 2 hours 153 mg/dL (8.5 mmol/L).

Two-step strategy
O'sullivan test
After administration of a 50 g glucose load, with prior fasting of 8 hours, venous blood sample is taken after 1 hour. Results above 140 mg/dL (7.8 mmol/L) are positive for GDM. For results between 130 (7.2 mg/dL), 135 (7.5 mg/dL) or 140 mg/dL (7.8 mmol/L), apply Carpenter and Coustan test.

Carpenter and Coustan test
Following the previous protocol described in the previous tests, a 100g glucose load is administered. It will be positive for GDM to present at least two of the following criteria, with values equal to or above the cut-off; fasting blood glucose 95 mg/dL (5.3 mmol/L), 1 hour 180 mg/dL (10.0 mmol/L), 2 hours 155 mg/dL (8.6 mmol/L), 3 hours 140 mg/dL (7.8 mmol/L).

DIAGNOSIS OF AT
TSH levels were quantified in serum samples, obtained by standard procedure and treated with sandwich enzyme immunoassay test. The reference values provided by the manufacturer were adopted for the analysis of the hormone and the different thyroid disorders; hyperthyroidism with TSH <0.4 mIU/L, euthyroid TSH of 0.4-4.5 mIU/L, subclinical hypothyroidism TSH 4.5-10 mIU/L, clinical hypothyroidism TSH >10 mIU/L.

Bioethical considerations
This project is carried out under the endorsement of the institution's bioethics committee, guaranteeing the handling of data by suitable and trained personnel, with exclusive purposes for the study and respecting the confidentiality of the information, in accordance with resolution 8430 of the Colombian legislation, the Helsinki declaration and the Council for International Organizations of Medical Sciences (CIOMS)[32-35].

Statistical analysis
The information was represented based on the calculation of descriptive measures in numerical variables corresponding to laboratory tests, simple frequency distributions, contingency tables and graphic representations according to the levels of measurement. To establish the relationship between GDM and AT, the hypothesis contrast was performed using the chi-square test with a statistical significance of p=0.05. The SPSS© package for Windows™ version 2.0 and Microsoft® Excel® 2019 were used for this analysis.

Results

The sample consisted of 388 pregnant women attended during the period 2016 - 2020. The average number of care was 78 pregnant women per year, with 2018 being the year with the highest number (n=83). Overall, 10.1% were evaluated during the first trimester of pregnancy, 56.4% in the second trimester and 33.5% in the third trimester.

Table 1. Descriptive measures of tests for glycemia and TSH in pregnant women, according to year of care.

YEAR	Descriptive measure	Blood glucose fasting mg/dL	Test de O'sullivan		PTOG				TSH mUI/L
			Blood glucose fasting mg/dL	Blood glucose 2 hours mg/dL	Blood glucose fasting mg/dL	Blood glucose 1 hours mg/dL	Blood glucose 2 hours mg/dL	Blood glucose 3 hours mg/dL	
2016	n	29	2	2	17	17	17	16	43
	Mean	83,24	72,50	92,50	88,71	125,88	111,29	97,44	2,81
	Standard deviation	8,50	12,02	2,12	27,04	44,71	48,19	58,67	1,88
	Median	84	72,5	92,5	82	115	106	78	2,5
	Minimum	67	64	91	68	81	61	55	0,6
	Maximum	100	81	94	182	252	232	297	8,9
2017	n	11	5	6	10	9	10	6	29
	Mean	80,63	80,00	104,33	78,31	133,56	96,60	63,67	1,80
	Standard deviation	8,71	12,06	39,97	11,48	44,98	27,90	13,84	1,21
	Median	79,8	78	82	75	128	94	60	1,7
	Minimum	70	68	74	66	85	56	49	0,1
	Maximum	100,1	99	166	97,1	221	132	90	4,7
2018	n	37	2	2	11	11	11	11	31
	Mean	84,65	93,65	131,50	82,42	124,00	110,27	84,18	2,85
	Standard deviation	13,35	17,18	58,69	6,25	26,97	21,68	20,79	2,20
	Median	84,6	93,65	131,5	81,3	125	115	89	2
	Minimum	65	81,5	90	73	74	60	53	0,6
	Maximum	112	105,8	173	92	172	136	110	8,7
2019	n	67	---	---	1	1	1	1	9
	Mean	89,00	---	---	85,00	160,00	86,00	71,00	4,46
	Standard deviation	8,47	---	---	---	---	---	---	1,86
	Median	88	---	---	85	160	86	71	5
	Minimum	63	---	---	85	160	86	71	0,7
	Maximum	109	---	---	85	160	86	71	6,2
2020	n	1	---	---	16	16	16	15	8
	Mean	93,00	---	---	89,56	106,06	98,37	80,53	3,45
	Standard deviation	---	---	---	14,40	39,32	31,08	13,26	1,29
	Median	93	---	---	85,5	95	93,5	81	3,9
	Minimum	93	---	---	76	64	60	50	1,53
	Maximum	93	---	---	139	215	188	100	4,8
GLOBAL	n	145	9	10	55	54	55	49	120
	Mean	86,13	81,37	107,40	85,74	121,54	104,20	84,61	2,74
	Standard deviation	10,27	13,65	38,15	17,97	40,20	34,98	36,82	1,91
	Median	87	81	90,5	84	115	102	78	2,1
	Minimum	63	64	74	66	64	56	49	0,1
	Maximum	112	105,8	173	182	252	232	297	8,9

Conventions: PTOG: oral glucose tolerance test; TSH: thyroid stimulating hormone. --- No data

A prevalence of GDM of 10.6% was recorded, where the years with the highest prevalence were 2016 (13.7%) and 2017 (13.5%). For the vigencies 2018 to 2020, a decrease in prevalence per year was evidenced, being below 10.0% as shown in Table 2.

Tabla 2. Prevalence of GDM in the period of years 2016 - 2020.

YEAR	n	Evaluation of blood glucose	
		GDM n (%)	NORMAL n (%)
2016	80	11(13,8)	69(86,3)
2017	74	10(13,5)	64(86,5)
2018	83	8(9,6)	75(90,4)
2019	77	5(6,5)	72(93,5)
2020	74	7(9,5)	67(90,5)
Período (2016 - 2020)	388	41(10,6)	347(89,4)

Conventions: GDM: gestational diabetes mellitus.

Regarding the prevalence of TA, a TSH test was obtained in 120 pregnant women. A total of 17.5% presented TSH values outside the cut-off points. In this group, a prevalence of subclinical hypothyroidism of 2.5% was determined. A decrease in TSH values was also detected, which was established as possible hyperthyroidism, with a prevalence of 15.0% (Table 2).

Table 3. Prevalence of TA in the period of years 2016 - 2020..

YEAR	n	TSH evaluation		
		> 4,5 mUI/L n (%)	0,4-4,5 mUI/L n (%)	<0,4 mUI/L n (%)
2016	43	0(0,0)	39(90,7)	4(9,3)
2017	29	3(10,3)	24(82,8)	2(6,9)
2018	31	0(0,0)	26(83,9)	5(16,1)
2019	9	0(0,0)	4(44,4)	5(55,6)
2020	8	0(0,0)	6(75,0)	2(25,0)
Período (2016 - 2020)	120	3(2,5)	99(82,5)	18(15,0)

Conventions: TSH: thyroid-stimulating hormone; TSH: thyroid-stimulating hormone.

Additionally, the relationship between TSH and glycemia results was established (Table 4).

However, the results observed did not show a statistically significant association between the two (p = 0.537).

Table 4. Relationship of TSH values with glycemia.

TSH evaluation	n	Glycemia		valor p*
		GDM n (%fila)	NORMAL n (% fila)	
HIGH	3	1(33,3)	2(66,7)	0,537
NORMAL	99	6(6,1)	93(93,9)	
LOW	18	3(16,7)	15(83,3)	
TOTAL	120	10(8,3)	110(91,7)	

Conventions: * Chi-square test, linear by linear association.

Discussion

Our study, carried out in 388 pregnant women, reported a prevalence of GDM of 10.6%. This figure is not very different from those reported worldwide, where it occurs as a complication in about 7% of pregnancies, resulting in more than 200,000 cases per year[36]. Similarly, in Colombia, a similar prevalence of around 7% is estimated, associated, in turn, with the obesity epidemic in young women and women of childbearing age[37].

It has been reported that this prevalence may vary according to the established diagnostic and screening criteria, type of population, race and body composition. In a study by Cortés et al.[38], a comparison in the diagnosis of GDM using different tests is shown. A frequency of GDM of 1.43% was established with the NDDG (National Diabetes Data Group) criteria and 2.03% with the Carpenter and Coustan criteria. Changes could also be observed in relation to ethnic groups, with a prevalence of 5.0 - 8.7% of GDM in Caucasian women and 5.7 - 9.7% in African-American women[39].

More than 50 years ago, the first criteria for the diagnosis of GDM were established by O'Sullivan & Mahan[40]. Although they have undergone modifications over time, they are still widely used. Although the main purpose is to identify women at high risk of developing GDM or adverse perinatal outcomes, they can also be used for screening subjects at risk of postpartum diabetes[41]. Opinions on these criteria are often divided, with some claiming that the current criteria may be restrictive in some respects, overlooking minor hyperglycemic states that increase the risk of maternal and fetal complications[29].

Regarding the biochemistry of the emergence of GDM, although the hormonal influence associated with pregnancy in the appearance of IR is clear, cell signaling exerted by components of the fetoplacental unit and maternal adipose tissue deposits is also linked, being markedly seen between 20 and 24 weeks of gestation and reestablishing itself with delivery[42,43]. Elevated BMI is a major contributor to disease progression; adipocytes can produce adipocytokines involved in maternal metabolic regulation and IR. Leptin, adiponectin, tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), resistin, visfatin, and apelin, carry out the modification of insulin sensitivity through pathways that include altering glucose metabolism, attenuating insulin signaling mechanisms, and favoring a proinflammatory state[44].

In the 120 pregnant women with reported TSH, a prevalence of 17.5% of alteration was obtained, defined as the presentation of values above or below the cut-off points. In this sense, it was possible to determine a frequency of TSH elevation, compatible with subclinical hypothyroid-

ism, of 2.5% and a frequency of TSH decrease of 15.0% for apparent hyperthyroidism. As mentioned, it has been found that hCG elevation during pregnancy appears to have several effects on thyroid gland function, increasing the expression of iodothyronines, improving their bioavailability and decreasing TSH levels[17,19]. It is likely that the decrease in TSH values evidenced in our study, which led to high prevalences of possible hyperthyroidism, are a reflection of the action of hCG on the pituitary and thyroid, so it would be advisable in further research to relate the gestational week with hCG, TSH and iodothyronine levels, since it is not known to what extent hCG concentrations affect thyroid function.

Molecularly, TSH and hCG belong to a group of hormones called glycoprotein hormones, together with luteinizing hormone (LH) and follicle stimulating hormone (FSH). All are constituted by the same α-subunit and a specific β-subunit that varies depending on the hormone and that confers differentiation in its effect[45]. Although the affinity of these ligands for their respective receptors is high, it has been described that, of all, the TSH receptor (TSHR) has the lowest specificity allowing hCG binding[46]. This condition, which intensifies during pregnancy, is responsible in many cases for the appearance of clinical hyperthyroidism attributable to the development of gestational thyrotoxicosis, to the secretion of hCG variants with higher TSHR activation capacity or to the expression of TSHR with higher affinity for hCG[47], it also seems to vary with factors such as BMI, fetal sex and maternal parity[10].

Additionally, thyroid disorders are common in young women of reproductive age; their frequency may be around 10%, where subclinical hypothyroidism occurs in approximately 2.5% of pregnant women, a figure in agreement with our results. Subclinical hyperthyroidism occurs in 1.7% and clinical forms are considered infrequent, with an approximate incidence of 0.2% to 0.36%; however, alterations and symptoms that are masked by the metabolic changes inherent to pregnancy are often overlooked[48,49]. Some complications of thyroid disorders in pregnancy include: threatened miscarriage, preeclampsia, oligohydramnios, hyperemesis gravidarum and urinary tract infection[50].

It is worth noting that for the last two decades the study of physiological changes of the thyroid gland in pregnancy has gained importance, and there have been discussions about its management that have made it impossible to reach a consensus on universal screening. Some experts advise the measurement of serum TSH in pregnant women with risk factors for the development of thyroid disease such as: family history, symptoms suggestive of hypothyroidism, atypical findings during physical examination of the gland, personal history of autoimmune disease, type 1 diabetes mellitus (DM1) and history of early fetal loss[51].

Authors point out that the lack of knowledge of the variations in thyroid function during the stages of pregnancy and the lack of specific ranges has led to some erroneous diagnoses in health care practice, resulting in the non-prescription of treatment or overtreatment of pregnant women, with repercussions for them and for fetal development[23]. However, other researchers defend the position that these reference values should be established according to the population studied and the local diagnostic methods available[23]. Table 5 presents the reference intervals for TSH concentration during gestation published by the American Thyroid Association (ATA), with the purpose of facilitating clinical decision making in the management of the disease[52].

Table 5. TSH reference values by gestational trimester[52]

Gestational trimester	TSH concentration (µUI/mL)
First	0,1 – 2,5
Second	0,2 – 3,0
Third	0,3 – 3,0

Conventions: AT: TSH: Thyroid stimulating hormone.

Regarding the prevalence of GDM with simultaneous thyroid alteration, our pilot study found that 3.33% of pregnant women present this condition and although there was no association between these variables (p=0.537), a meta-analysis showed that the incidence of diabetes mellitus in pregnant women with subclinical hypothyroidism is 1.35 times higher than the incidence in control groups without the disease[8].

Thyroid hormone levels at the beginning of pregnancy are determinant in the assessment of the risk of GDM. In a study performed by Yang et al, the protective effect of free tetraiodothyronine (FT4) on the development of GDM was demonstrated by regulating glucose metabolism, reducing the half-life of insulin, promoting the expression of GLUT 2 transporter proteins in the liver and activating beta adrenergic receptors that accelerate glycogenolysis[8,53,54]. Parham et al.[54] evaluated thyroid function in pregnant women with GDM and without GDM as a control. When comparing serum FT4 and TSH levels of the two groups, they found that TSH in pregnant women with GDM was at statistically significantly higher levels than in the control group (P=0.023), compatible with subclinical and clinical hypothyroidism disorders. However, so far the association between FT4 levels and GDM is not conclusive, since in some studies this behavior is not evidenced[55-58]. A high prevalence of elevated antithyroid antibodies has also been documented in situations where IR states predominate, so it is speculated that thyroid autoimmunity could be a risk factor for GDM[50,54].

Conclusions

Nowadays, it is increasingly important to closely monitor endocrine disorders during pregnancy in order to avoid maternal and fetal complications. This pilot study confirms that GDM and TA are conditions that occur frequently in pregnant women. Although there could be a risk of developing GDM in patients with TA, studies with a larger number of samples are suggested to clarify this relationship, contemplating the measurement of TSH, FT4, hCG levels and their association with gestational week.

Authors' contribution:

Jhoalmis Sierra Castrillo; Conceptualization, methodology, validation, formal analysis, research, writing: revision and editing, project administration.

Yojanna Perdomo Dominguez: Conceptualization, methodology, validation, formal analysis, research, writing: revision and editing.

Jefferson Villamizar: formal analysis, research, writing: proofreading and editing.

Adriana X. Muñoz Bravo: validation, formal analysis, research, writing: review and editing, project management.

Lyz J. Gómez Rave: validation, formal analysis, research, writing: proofreading and editing, project administration.

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