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Association of Uncontrolled Glycemia with Periodontal, Urinary Tract and Cervical Vaginal Infections in a Group of Type 2 Diabetic Women during Pregnancy and during the Postnatal Period

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Abstract

Objective: To determine whether periodontal infections (PI), urinary tract infections (UTI) and cervical vaginal infections (CVI) are associated with the incidence of uncontrolled glycemia (UCG) in type 2 diabetics in the third trimester of their pregnancy and during the postnatal period.

Materials and methods: An observational, prospective, longitudinal, comparative study was carried out. Patient selection was carried out through consecutive non-probability sampling. The convenient sample consisted of 52 pregnant INPerIER users. Glycemic control and the presence UTI, CVI and periodontal infections PI were assessed through clinical and laboratory examinations in the third trimester of pregnancy and during the postnatal period. Informed consent was requested.

Results: The frequency of infections in the third trimester was: UTI 24, PI 22, and CVI 16. The incidence of uncontrolled glycemia (UCG) in the third trimester was 5 patients; PI was associated with the UCG. There was an increase in the frequency of PI associated with UCG; patients without PI maintained glycemic control (RR 6.14). The PI, the CVI and UTI are risk factors associated with uncontrolled blood glucose levels in the postnatal stage.

Conclusions: Periodontal disease is associated with the incidence of uncontrolled blood glucose levels in cases of type 2 diabetes in the third trimester of pregnancy and during the postnatal period.

Keywords

Type 2 diabetes mellitus, Periodontal disease, Urinary tract infection, Cervical vaginal infections

Introduction

Infections are one of the most common complications of diabetes. The relationship between diabetes and infection is twofold: diabetes favors infection and infection makes glycemic control difficult [1]. Several changes are known to occur in diabetes when related to the responsiveness to infection (from alterations in vascular permeability to those limiting the function of macrophages) that together explain this complex interrelationship. Diabetes and infection are closely related, being the most common infectious cause of metabolic decompensation. Similarly, the metabolic state of patients determines the risk of infections to occur, so the better the control, the lesser the risk of infections and vice versa. In fact, terminal disease complications are often exacerbated by infections [2]. Diabetes is the main endocrine disruption that occurs during human pregnancy. Although Mexico does not have recorded statistics showing the magnitude of this problem, the National Institute of Perinatology (INPerIER) in 2013 admitted 2,766 obstetric patients, where 358 were enrolled with diabetes mellitus during pregnancy. The fact that diabetes reaches epidemic proportions and is to some extent common care for pregnant women over 35 years, allows to assume that the frequency of any type of diabetes during pregnancy is high, estimated that about 2 to 3 and up to 10 of every 100 pregnancies are often complicated with gestational diabetes [3]. During pregnancy, blood volume expansion leads to an increase in glomerular filtration rate and urine output, as also urinary tract volume. The ureters suffer noticeable changes mainly secondary to the mass production of hormones by the growing trophoblast. The chemical composition of the urine itself is enriched by pregnancy such as glucose, amino acids and fragmented hormones, which could facilitate bacterial proliferation; bacteriuria increases the likelihood of symptomatic infection of the upper urinary tract, especially in the last trimester. The frequency of bacteriuria in pregnant women range from 4 to 7%; [4] in pregnant diabetics this ranges from 16 to 20% [5]. Moreover, diabetic women who become pregnant are more likely to have urinary tract and cervical-vaginal infections, which can alter their general welfare and even encourage changes in glycemic control. In the year 2000, [6] the American Academy of Periodontology noted that "the incidence of periodontitis increases in diabetics,

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increasing the frequency and severity of systemic complications". The increased susceptibility is not related to plaque levels or dental calculi. [7] Collective evidence supports the relationship between the two diseases, especially in poorly controlled diabetics [8]. Periodontal disease (PD) has been considered the sixth complication in diabetic patients [9], and has shown that this treatment can decrease HbA1 levels 0.4% - 0.5%. This metabolic effect is similar to that achieved by adding a second drug - a hypoglucemic drug in the treatment of diabetic patients [10].

To date, the association of periodontal infections (PI) with the incidence of glycemic control during pregnancy and the postnatal stage has not been determined. The aim of this study is to determine whether PI are associated with the incidence of glycemic decontrol in type 2 diabetes in the third trimester of pregnancy and in the postnatal period, as well as to describe the frequency of PI in pregnancy and through the monitoring of women with and without UTI.

Methods

The cohort study was an observational, prospective, longitudinal, comparative study. Patient selection was carried out through a consecutive non-probability sampling. The convenience sample was 52 pregnant INPerIER patients. Patients were selected from diabetics seen at the Endocrinology Service at the INPerIER, who met the following inclusion criteria: pregestational type 2 diabetes, in their second trimester, and under glycemic control (A1c ≤ 6.5%) without urinary tract (UTI) or cervical-vaginal (CVI) infections. Glycemic control was assessed based on the concentrations of glycosylated hemoglobin A1C, collected in vacutainer tubes with K3 EDTA, using the commercial kit DCA 2000 and a Bayer 2000 T equipment [11]. Tests took place at the Laboratory of the Department of Endocrinology INPerIER. In order to standardize the technique, a study to determine the interobserver consistency was performed, internal and external checks were done to corroborate the reliability of the results. To ensure the quality of both test procedures, and the results, the DCA 2000 system performs 48 optical, electronic and mechanical systems check during the course of each of the determinations which include calibration verification exercises for each measurement [12]. The laboratory has ISO 9002 certification and external quality controls. The criteria for glycemic control were established considering the A1C ≤ 6.5%, according to the international standards as stated in the "Mexican Official Norm NOM-015-SSA 2-2007 for the prevention, treatment and control of diabetes mellitus" from the Ministry of Health). During the study, the following tests were performed: 1) baseline assessment in the second trimester. These A1c results provided the backbone for the study group; 2) during the third trimester, and 3) in the postnatal period (two months). The presence of PI was studied using the Löe and Silness gingival index (GI) [13]. The WHO periodontal probe (Hu-Friedy) was used to assess the angle to the tissues of the mesiovestibular papilla and lingual gingival margin, registering the highest value. The numerical value is associated with the degree of clinical gingivitis. + For probing the periodontal pocket, a force not exceeding 25 grams parallel to the longitudinal axis of the dental organ and then slide circumferentially around each tooth surface to detect its settings and areas of deeper penetration was used. The depth of the gingival sulcus is determined by observing the mark, the level gingival margin. The clinical attachment loss (CAL) was quantitatively determined, which is the distance in millimeters of the cement-enamel junction to the bottom of the pocket. Only non-smoking patients were included because smokers present increased susceptibility to periodontitis and greater severity and progression of periodontal disease compared with nonsmokers; smoking habit also contributes to an unfavorable clinical response to nonsurgical and surgical anti-infectious therapies [14]. To determine the existence of PI, moderate and severe periodontitis were considered, examinations were conducted by a trained and calibrated dental examiner [15]. To determine the presence of urinary and cervical-vaginal tract infections, a certified sexually transmitted disease specialist performed a clinical diagnosis. Cervical-vaginal swab exudates and urine culture samples were sent to the Research Laboratory for Sexually Transmitted Infections at the INPerIER. For obtaining samples, the patient was asked to provide the morning's first urine sample after cleaning the perineal area using sterile gauze moistened with soap and water, with from front to back. Soapy residue was removed using sterile gauze moistened with water. Once the cleansing was done, the sample was collected by separating the labia with one hand. The patient was asked to urinate the first few milliliters into the toilet to pull bacteria from the urethra and collect the following milliliters ("midstream") in a sterile wide-mouthed container that was provided at the laboratory.

For the urine culture, the urine sample was seeded in the following culture media: 5% MacConkey and sheep blood agar. These means allow for the detection of most Gram-negative bacteria (*Escherichia coli, Proteus mirabilis, Klebsiella Enterobacter* spp), Staphylococcus (*Staphylococcus aureus*), streptococci (*Streptococcus agalactial*), enterococci (*Enterococcus feccalis*). Once the sample was obtained, a 0.01 ml urine sample was taken with a disposable sterile calibrated loop and massively seeded in the MacConkey Agar for isolating colonies. The same procedure is repeated in 5% sheep blood agar, and incubated at 37°C for 24 - 48 hours. Colonies from each plate were counted and multiplied by 100 for the total number of colony forming units per milliliter (CFU / ml). The microorganisms were identified using conventional international methods [16].

Urine samples which after 48 hours of incubation showed no growths were considered as negative urine cultures. Symptomatic patients with >100,000 CFU/ml were diagnosed UTI.

Cervical tissue samples were obtained by the physician by using a Cuzco vaginal sterile mirror to locate the cervix, taking the sample with a sterile swab scraping of the cervix and/or posterior fornix. The culture media were inoculated with the cervical-vaginal tissue sample to isolate *Streptococcus agalactiae* (5% sheep blood agar), potato dextrose agar to isolate Candida spp, chocolate agar (GC) to isolate Neisseria gonorrhoeae, and Human Blood agar (HB) to isolate Gardnerella vaginalis. HB and GC were incubated at 37°C in a partial 5% CO2 atmosphere for 72 hours, SC and PDA were incubated at 37°C for 72 h. Under aerobic conditions, those colonies that developed in each culture medium suggesting the microorganism sought were later identified by conventional biochemical tests to reach the final identification. Biochemical tests were performed simultaneously with the strains of the American Type Culture Center (ATCC). In order to perform the statistical analysis of the information obtained from instruments and laboratory tests, special formats were used. A database was created and analyzed using the Statistical Package for Social Sciences (SPSS) version 19.0 program. The information was validated by double uploading and simple frequencies. The study variables were described based on their level of measurement. Relative risks and confidence intervals were obtained; chi-square statistics and student t difference medians were used to determine associations between variables; with a level of statistical significance $p < 0.05$. The results are shown in the tables. At all times, the guidelines established by the 1975 Declaration of Helsinki and its 2000 Amendment were followed [17]. The protocol for this study was registered at the INPerIER Reasearch Direction and approved by the Research and Ethics Committees (number 212250 - 08181). Since patients were pregnant at the time of the study and because laboratory tests were performed, the risk is higher than minimum, as established by the general rules of ethics, the principles of the Declaration of Helsinki and the Regulations of the General Health Law on Research in Mexico. Patients were informed of the objectives and benefits of their participation, and given a few days to decide on whether they would take part in the study, while afterwards obtaining their written informed consent. They were referred to the specialist (endocrinologist, gynecologist or dentist) if treatment required.

Results

During the recruitment period, 150 pregestational type 2 diabetic women were invited to take part in the study, of which 13 (8.6%) were smokers. Seven patients refused to participate (4.6%), citing lack of time to attend appointments because they did not live in Mexico City

Table 1: Distribution of certain history variables of the exposed and non-exposed groups to PI

Variable	Exposed (n = 12)	Non-Exposed (n = 40)	p
Average Age (in years) (**)	33 ± 6	31 ± 5.4	0.255
Average Duration of the Disease (**)	4.3 ± 4.31	3.6 ± 3.1	0.895
Median- Pregnancies (***)	1	2	0.061
White Classification (*)	A (0.25), B (0.75), C 0)	A (0.15), B (0.77), C (0.25)	0.488
Type of Treatment (*)	Insulin and Diet (0.80), Diet (0.20)	Insulin and Diet (0.80), Diet (0.20)	0.580
Schooling ≤ Junior High (*)	0.75	0.57	0.229

Chi-square (*)
Student t (**)
Difference of medians (***)
The number in parenthesis means the proportion.

Table 2: Frequency of Infections during the third trimester

Type of Infection	Frequency	
	Yes	No
UTI	24 (0.46)	28 (0.54)
PI	22 (0.42)	30 (0.58)
CVI	16 (0.31)	36 (0.69)

UTI = Urinary Tract Infection
PI = Periodontal Infection
CVI = Cervical Vaginal Infection
The number in parenthesis means the proportion.

or close by. One hundred thirty (130) patients agreed to participate who underwent the initial assessment. Seventy-eight (60%) volunteers were excluded due to vaginal and urinary tract infections and/or uncontrolled glycemia at the time. The study sample consisted of 52 pregestational type 2 diabetics under glycemic control without cervical-vaginal or urinary tract infections diagnosed clinically and through laboratory tests. The cohort consisted of women under prenatal supervision at the INPerIER studied for seven months throughout their pregnancy and postnatal period. All patients were included during the same study period. The group was comprised by 52 patients who entered the study and had normal glycemia in the second trimester. The aim of the study was to determine whether PI was associated to the incidence of glycemic control in the third trimester of pregnancy and in the postnatal stage. We proceeded to analyze the demographic characteristics of the second trimester patients exposed to periodontal infections as a risk factor. We found 12 (0.23) patients to have PI, and 40 (0.77) others not exposed (as shown in table 1). The distribution of demographic variables is also shown, where we can observe that there are no statistically significant differences between groups. The White Classification used in table 1 distinguishes between gestational diabetes and diabetes that existed before pregnancy, in addition to being a prognostic classification used in gynecology-obstetrics to establish certain criteria for the well being of pregnant patients [18,19]. After this assessment, the patients continued with their regular monitoring visits at the INPerIER. All were advised to not miss their appointments with the obstetricians and endocrinologists, attend their nutritional consultations, follow directions on the dietary regimen recommended and continue general hygiene and oral cavity measures. During the third trimester, their glycemic condition was reassessed, finding an incidence of uncontrolled glycemia (UCG) in 5 (0.10) patients, whose average HbA1C was 7.4 (min 7% max 8%), and 47 (0.90) under glycemic control (CG) having an HbA1C averaging 5.6 (min 6.50% max 4.10%). The association of PI in the second trimester, with UCG during the third trimester. Five (0.42) women with PI had UCG had a risk of exposure of 42%. It is worth noting that of the forty women without

Table 3: Frequency of infections in the third trimester

Type of Infection		Uncontrolled Glycemia		RR	CI	p
		Yes	No			
PI	Yes	18 (0.84)	4 (0.16)	6.14	2.4-15.6	0.00
	No	4 (0.13)	26 (0.87)			
UTI	Yes	19 (0.80)	5 (0.20)	5,54	2.1-14.4	0.00
	No	4 (0.14)	24 (0.86)			
CVI	Yes	5 (0.31)	11 (0.69)	0.66	0.29-1.49	0.44
	No	17(0.47)	19 (0.54)			

UTI=Urinary Tract Infection
PI= Periodontal Infection
CVI= Cervical Vaginal Infection
The number in parenthesis means the proportion.

Table 4: Type and number of infections related to uncontrolled glycemia during the postnatal stage

Type of Infection	Uncontrolled Glycemia				Total
	Yes		No		
	Num	Proportion	Num	Proportion	
None	2	0.14	12	0.86	14
PI	0	0	4	1	4
CVI	0	0	9	1	9
UTI	2	0.4	3	0.6	5
UTI and PI	13	1	0	0	13
CVI and PI	1	1	0	0	1
CVI and UTI	0	0	0	2	2
CVI, UTI, PI	4	1	0	0	4

PI, none had uncontrolled glycemia, so that the risk in unexposed patients was zero (RR 18.00, 95% CI 2.36 - 136, χ^2 12.24, $p < 0.004$).

The PI distribution based on the severity of UCG during the second and third trimester of pregnancy did not show a specific pattern. No demographic characteristics were found that may be different in patients with UCG. During the third trimester, the frequency of infections was again measured. These data were useful for determining the risks during the next stage (Table 2). In the postnatal stage, 22 (0.42) women were detected having uncontrolled glycemia, their mean HbA1c was 6.82% (4.80 - 11.80). Clinical data and laboratory test results shown in table 2 also include the frequency of infections seen during the third trimester considered as risk factors for postnatal glycemic problems.

Table 3 shows the increase in the frequency of PI associated with UCG, as well as the fact that 26 (0.87) patients without PI maintained glycemic control (RR 6.14, 95% CI 2.4 - 15.6, X2 1.6638, $p < 0.0000$ Yates correction). Similarly, we analyzed the association between urinary tract infections and UCG, It is shown that 19 (0.80) uncontrolled diabetics had UTI (RR 5.5 95% CI 5.5 - 14.04, 19.50 χ^2, $p < 0.000$

With respect to the distribution of cervical-vaginal infections, no association was found to UCG (RR 0.66, 95% CI 0.29 - 1.4, χ^2 0.59, $p > 0.44$).

It should be noted that the presence of infections was not necessarily isolated, since a patient could have one, two or even three infections while 14 patients had no infections (Table 4).

Table 5 shows the relative risks (employing the Wolf modification) [20] of the studied entities, having women whithout infections as a reference group. It should be noticed that the CI higher to one unit are placed in the three lower rows.

Discussion

The study allowed for observing the behavior of a group of pregnant diabetic women who enrolled while in glycemic control, with glycosylated hemoglobin levels under 6.5% without urinary and cervical-vaginal tract infections examined by a certified clinical infectious sexually transmitted disease expert and confirmed by laboratory tests. It is noteworthy that results on the incidence of uncontrolled glycemia associated with the most common infections

Table 5: Relative risks of the different types of infections related to uncontrolled glycemia

Type of Infection		Uncontrolled Glycemia		Relative Risk	CI 95%
		Yes	No		
CVI*		0	9	0.31	0.016 - 5.88
PI*		0	4	0.60	0.034 - 10.50
UTI*	CVI	0	2	1	0.06 - 15.98
UTI		2	3	2.5	0.57 - 10.93
CVI - PI*		1	0	4.5	1.12 - 17.99
UTI - CVI - PI*		4	0	5.4	1.67 - 17.37
UTI - PI*		13	0	5.7	1.85 - 18.01
None		2	12		

*Wolf Modification

Reference Group

UTI = Urinary Tract Infection
PI = Periodontal Infection
CVI = Cervical Vaginal Infection
The number in parenthesis means the proportion

in pregnancy is shown and is similar to what has been reported as the prevalence of infectious diseases through cross-sectional studies [21]. Few authors have used cohort designs as the one used here. It was important to know the impact of UCG, and the enormous value in the study of causality. These women are in full reproductive stage, newly diagnosed with the disease, which is representative of the user profile of an INPerIER diabetic, according to data reported from the Social Work Department. According to White's classification, 42 (0.80) women were rated B, (pre-gestational diabetes, age of onset at any age, without vascular disease, or dietary treatment); seven (0.14) were classified as A (onset after age 20 and length < 10 years, without vascular disease), and three (0.6) as C (onset before age 20 and length of disease for 10 years, without vascular disease). It is worth noting that the diabetic patients seen more often are those classified as A, B and C. Similar results have been reported by other gyneco-obstetric tertiary care centers [22]. Regarding family history: six (0.12) patients denied a family history of diabetes, 46 (0.88) reported a family history-six reported having diabetic siblings (0.11), 15 (0.29) a diabetic father, 15 (0.29) reported having a diabetic mother, while 10 (0.20) women reported that both parents were diabetics. The lack of glycemic control and/or infectious processes in diabetics was very common in six out of 10 of the women invited to take part in the study. Patient characteristics were strict and often less frequent. However, these were the only ones that allowed us to reach our objectives of whether PIs were associated to the incidence of UCG in the third trimester. This is the reason why we looked for demographic differences in the second trimester at the beginning of the study in women with PIs as shown in the exposed and non- exposed groups where no statistical differences were found. The strategy used to divide the group of pregnant women in the second trimester in exposed and unexposed to PI, was aiming to assess whether this risk factor could be associated to glycemic control in the third trimester. As seen in table 1, the general characteristics (chronological age, duration of illness, number of pregnancies, White classification, schooling and type of treatment showed no significant statistical differences. In this study we saw that in the third trimester, uncontrolled glycemia occurred in five patients (42% exposure risk), all of which were part of the group exposed to PI since the second trimester. This is consistent with the results by Ruiz et al. [23] where levels of inflammation and periodontal destruction were significantly higher in a group of Brazilian patients who were enrolled with gestational diabetes and type I diabetes mellitus during pregnancy compared with non-diabetic pregnant patients. On the other hand, Bullon et al. [24] observed the relationship between PI and certain biochemical parameters such as cholesterol, triglycerides and blood sugar in patients diagnosed with gestational diabetes finding these higher parameters in patients with periodontitis than in patients without periodontitis. They were also positively related the probe depth and level of attachment. Notably, seven patients did not have UCG despite having a history of severe or moderate PD, consistent with the findings by Esteves et al. [25] who found no association between periodontitis and gestational diabetes, which allows us to assume there are other factors involved. It is important to note that of the 40 diabetics with continued glycemic control in the third trimester, 36 had gingivitis often associated with pregnancy with no deterioration in the supporting dental tissues. Factors associated with UCG considered in this study were periodontal disease, urinary tract and cervical vaginal infections. We noticed that although there were different proportions in the cases with infection and lack of glycemic control, it is rare to have uninfected women, as was observed. Infections increased in the postnatal stage. A probable explanation may be that woman must now take action related to the baby's care, which in most cases are by leaving aside the daily task of disease control due to the additional demands where diabetics minimize their personal care for the care of the newborn [26]. Hence the promotion of educational aspects in all pregnant women with diabetes allows for the activation of different behaviors and ways of solving problems, which benefits patients [27]. UTI, CVI and PD are common infections found in type 2 diabetic pregestational patients. In the group studied, the frequency during the third quarter was UTI 46%, PI 42% and CVI 31% during pregnancy while increasing during the postnatal period. This could tentatively explain the associations of the loss of glycemic control in PD (RR 6.14, 95% CI 2.4 - 15.6, χ^2 1.6638, $p < 0.0000$) and in UTI (RR 7.4, 95% CI 2.49 - 22.0, 22.08 χ^2 $p < 0.000$). It is interesting to note that only two women did not have infections during the postnatal stage and that the highest number of infections was in those women who had had UTI and PI - all of which were uncontrolled, (RR 5.7, 95% CI 1.85 - 18.01). The relative risks of the factors studied were higher than the unit when patients had both CVI/PI (RR 4.5, 95% CI 1.12-17.99), UTI/ PI / CVI (5.4 95 % 1.67-17.37), and UTI / PI (5.7, 95% CI 1.85-18.01).

One of the limitations of this study was the sample size and this is due to the strict inclusion criteria taken into account. However despite this limitation, the fact that women without PI or who only had gingivitis in the third trimester did not have uncontrolled glycemia, is a worthy contribution to be taken into account to support preventive programs during the prenatal stage. On the other hand, knowing that postnatal relative risks with confidence intervals greater than the unit arose when diabetics had urinary tract and/or cervical-vaginal infections in association with the PI is important. This study's approach is original in the sense that it could follow a group of type 2 diabetic women, from the second trimester to the postnatal stage. The frequency of infections studied here is similar to the data reported by other authors. We believe that would suggest that there is a need for conducting similar studies with different approaches. It would be interesting from a microbiological perspective, knowing which microorganisms colonize periodontal pockets both in controlled patients as those found in uncontrolled glycemic circumstances. Also worthwhile would be to consider increasing the number of participants to obtain data from different obstetric care centers.

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