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Body Composition, Gynecologic-Obstetric Variables, and Prolactin Levels in Patients with Breast Cancer

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Abstract

Objective: The aim of this study was to determine body composition, gynecological, and obstetric data, sex hormones, and prolactin serum levels in pre- (PREW) and postmenopausal women (PMW) with breast cancer (BC) and compare them with a control group (CG) of healthy women. **Methodology:** BC patients without treatment or use of hormone replacement therapy, or hormonal birth control, and without data of metastasis were included. CG was matched for age, BMI, and menstrual cycle status. FSH, LH, E^2, progesterone, testosterone, and prolactin (PRL) were measured using radioimmunoassay kits. Comparisons between BC and CG were made with "*t*" tests, and with the Mann-Whitney U-test; χ^2 test was used to compare the qualitative variables between the groups. **Results:** Seventy-two patients with BC, and 74 CG women were evaluated. Both groups presented overweight data, BMI (kg/mt^2) = 27.21 ± 5.51 vs. 28.40 ± 4.66, p = ns, for BC patients and CG, respectively. In PREW, the age at menarche was later in BC patients compared to the CG (13.3 ± 1.36 years vs. 12.41 ± 1.27 years, p = 0.005). The PMW with BC presented a higher age at menarche and menopause compared to the women of the CG (13.51 ± 1.48 vs. 12.91 ± 1.41, p = 0.09, and 49.03 ± 2.86 vs. 45.5 ± 8.78, p = 0.03, respectively). PRL levels were significantly higher in PMW with BC, in comparison with the CG; median and minimum and maximum values (min-max) were: 14.7 ng/mL (3.6 - 52.7) vs. 5.9 ng/mL (1.9 - 33.3), p = 0.005). A higher percentage of PMW with BC (26.0% vs. 7.1%, χ^2 = 5.57, p = 0.01) presented hyperprolactinemia (PRL serum levels > 20 ng/mL), com-

pared to the GC. **Conclusions:** The higher levels of PRL in PMW with BC compared with CG, suggest a proliferative effect of this hormone in the affected breast tissue. This study demonstrates the need to use biological markers such as PRL to determine the risk of BC in PMW.

Keywords

Breast Cancer, Sex Hormones, Prolactin, Postmenopausal Women

1. Introduction

Evidence from the scientific literature shows that there are several factors involved in the etiology of breast cancer (BC) [1]-[6]. Some of these factors are, for example: 1) overweight, obesity, and excess body fat [1] (a significant increase in body weight, from the age of 18, has been shown to be a risk factor) [2]; 2) the reproductive status of the woman [1] (more than 77% of BC cases in the United States occur in postmenopausal women 50 years of age or older); 3) the woman's gynecologic and obstetric history (for example, the early age at menarche, the use of hormone replacement therapy, older age at first delivery, lower parity, and higher number of abortions) [1] [2]; 4) genetic and hereditary factors [3] [4]; 5) environmental factors [5]; and 6) endocrine factors, including sex hormones [6].

The mechanisms that involve hormonal factors in the origin of BC are not sufficiently clear. However, it is known that the sex hormones and prolactin (PRL) have an important role in the reproduction of cancer cells; since it has been shown that they stimulate cell mitosis, activating the receptors, and binding to specific deoxyribonucleic acid sites; thus inducing the transcription of structural genes that produce the synthesis of specific proteins, and modify cell activity for its transformation to a neoplastic [7] [8].

The role that estrogens play in breast cancer has been recognized in the past; some investigators have reported elevated serum levels of estradiol [9] [10] in women with BC. It has also been shown that women with BC have elevated levels of serum testosterone, in nipple discharge [11] [12].

Many studies carried out in different animal models show that PRL has an important role as a tumor-promoting hormone in tissues *in vitro*. In humans, however, the role that PRL has in the development of BC has not been clearly defined, due to contradictory results in different studies [13] [14] [15].

Olsson *et al*. have shown that men with a clinical and histopathological diagnosis of BC had higher serum levels of PRL than healthy controls [14]. However, Coskun *et al*. [15] did not demonstrate such elevations when measuring leptin, PRL, and vascular endothelial growth factor levels in women with BC.

Because there is controversy in the scientific literature regarding the sex hormones and PRL serum levels; and because of the role of PRL in BC in PREW and PMW with the diagnosis of BC. The objective of this research was to evaluate the

profile of sex hormones and PRL in a group of BC patients, and compare them with those of a control group of healthy women.

2. Methodology

2.1. Study Design

In this study participated 71 BC women and 74 control subjects: in ages from 24 - 70 years. This observational, case-control study; with a cross-sectional design was evaluated and approved by the Ethics Committee of the University of Guanajuato. It was performed following ethical principles for conducting research with human beings and in accordance with the criteria described in the Declaration of Helsinki [16]. The study objectives were explained to all participants, who signed informed consent forms to participate in the research.

2.2. Procedure

All the patients who attended the outpatient clinic of the Oncology Center of the Ministry of Health, in the city of León, Guanajuato, Mexico, were studied for a period of six months. To enter the study, patients should have a clinical and histopathological diagnosis of breast CA, and no history of prior treatment for the disease. All patients were matched for age, body mass index (BMI), and socioeconomic status (SES), with women without clinical data or a family history of BC. BC patients and control women who were at reproductive age (PREW) were evaluated on the same day of the menstrual cycle. Hysterectomized women were not included, nor were those with a history of hormone replacement therapy or sex hormone use.

The BC patients and women of the CG were evaluated through a clinical history that included the following data: 1) non-pathological and pathological antecedents; 2) gynecological and obstetric data; 3) anthropometric evaluation: weight (kg); height (cm), and with these data, the body mass index (BMI, kg/mt^2) was calculated. Waist, abdomen, and hip circumferences were also measured, and with them, waist/hip and abdomen/hip indices were calculated. To determine body composition, the measurements (in mm) of the following skinfolds were used: tricipital, subscapular, abdominal, supra-iliac, anterior thigh, and calf. With these variables and using the procedure previously described by us, fat weight and lean weight were calculated (the calculation was made in percentage data, considering the total weight in Kg, as 100%) [17].

2.3. Breast Cancer Patients

The following clinical data were obtained from each patient with a diagnosis of BC: time of evolution of the disease (from the moment the tumor is detected until the date of oncology consultation), the quadrant affected, the type of cancer, the size of the tumor (in centimeters), the discharge through the nipple, the ulceration of the skin of the affected breast, the presence of pain, the clinical stage of the disease, the type of biopsy performed and the histopathological

diagnosis.

2.4. Blood Samples

All BC patients and CG women were asked to present in a fasting state for 8 to 12 hours. The PREW of the CG were scheduled to present on the day of the menstrual cycle that corresponded to the same day as the woman with BC.

A 10 mL blood sample was taken from all the women in both groups from the antecubital vein. The serum was separated by centrifugation and kept frozen at −70˚C in aliquots, to determine the serum levels of estradiol (E^2), prolactin (PRL), progesterone (P_4), testosterone (T), follicle stimulating hormone (FSH), and luteinizing hormone (LH). The procedure for the determination of sex hormones was carried out following the methodology similar to that used in previous studies [18]. Through radioimmunoassay (RIA) kits procedures, the sex hormonal determinations and prolactin were performed in duplicate using a solid phase system, and the average of the results of each hormone was obtained; with a range of variation coefficients from 1.7% to 7.1%, indicating that the results are reliable (CV < 10%).

2.5. Statistical Analysis

All quantitative variables were tested for normality using the Kolmogorov-Smirnov & Lilliefors test for normality. Continuous variables with normal distribution (ND) were reported as mean values and standard deviation (X ± DE) and were compared between BC patients and CG with the *t-test* for independent samples. Variables without ND were reported as median and minimum-maximum values and were compared between patients and controls with Mann-Whitney U-test. The associations between clinical variables, with the presence of BC, were determined with the χ^2 test. In all cases, a significance level was established when the p-value was <0.05.

3. Results

3.1. Study Subjects

A total of 178 subjects were evaluated (76 with BC and 102 of the CG). Twenty-eight women were excluded from the CG for the following reasons: 10 patients had undergone hysterectomy; six had a family history of some type of cancer; eight, PMW did not attend the day of their appointment to take the blood sample; and four, were using contraceptives. Of the BC group, in two patients, the collected blood sample was not sufficient to process sex hormones and prolactin; two patients had hysterectomies and one was being treated at the time of the study. In the statistical analysis, 145 women were included: 71 patients with BC and 74 women in the CG.

3.2. General Characteristics of the Study Subjects

When analyzing the occupation and marital status of women, some differences

were found. In patients with BC, there is a higher proportion of housewives and single women than in the CG (where there are more economically active and married women). No differences were found in SES when comparing the two groups (monthly income less than 10,000 Mexican pesos). A significantly higher percentage of women in the CG consumed tobacco and alcohol, when compared with patients with BC (Table 1).

3.3. Results of Anthropometrical Variables

No significant differences were observed in age, BMI, and body composition (body fat, and lean body mass); however, the women of the CG, presented greater measurements in the waist and abdomen circumferences in comparison with the patients with BC (Table 2).

3.4. Gynecologic and Obstetric Characteristics of Premenopausal Women (PREW)

The age at menarche of the women with BC was significantly higher than that of the CG (13.33 ± 1.36 years vs. 12.41 ± 1.27 years, p = 0.005). The onset of active sexual life occurred at older age in the BC group in comparison with the CG (21.82 ± 6.16 years vs. 18.54 ± 6.58, p = 0.06). Although, it is interesting to observe that in the group with cancer, 29% (n = 10) of the cases reported being nubile, so there is no chance of pregnancy in this subgroup of patients. No differences were found in the number of pregnancies (5.34 ± 4.0 vs. 5.6 ± 3.6, p = 0.79);

Table 1. General characteristics and sociodemographic variables of breast cancer patients and control subjets.

Variables	BCP[a] (n[c], %)	CG[b] (n[c], %)	χ^2	p
Occupation				
Homemaker	70 (47.6)	62 (42.2)	9.5	0.05
Small Business Owner	0 (0)	4 (2.7)		
Blue Collar Workers	1 (0.7)	5 (3.4)		
Professional	2 (1.4)	1 (.7)		
Students	0 (0)	2 (1.4)		
Marital Status				
Single	27 (18.5)	10 (6.9)	12.0	0.007
Married	35 (24.0)	51(34.9)		
Free Union	1 (0.7)	0 (0.0)		
Divorced	10 (6.9)	12 (8.22)		
Family Income (Monthly, Mexican Pesos)				
<10,000	60 (41.1)	45 (30.8)	9.6	0.008
1000 - 2500	10 (6.9)	21 (14.4)		
>2500	2 (1.4)	8 (5.5)		
Smokers	3 (2.04)	8 (5.44)	2.4	0.01
Occasional Alcohol Consumption	6 (8.22)	10 (13.5)	1.1	0.03

a: BCP = Breast Cancer Patients; b: CG = Control Group; c: (n) = number of subjects.

Table 2. Anthropometrical characteristics of breast cancer patients and control groups.

Variable	n[c]	BCP[a] (X ± SD)	n[c]	CG[b] (X ± SD)	p
Age (years)	73	50.88 ± 13.40	74	47.79 ± 13.58	0.17
BMI[d] (Kg/Mt^2)	71	27.21 ± 5.51	69	28.40 ± 4.66	0.17
HC[e] (cm)	67	85.10 ± 11.70	71	86.60 ± 9.67	0.41
WC[f] (cm)	67	98.32 ± 10.48	71	102.70 ± 12.05	0.02
AC[g] (cm)	62	92.74± 14.81	69	97.98± 10.26	0.01
W/H[h]	67	0.86 ± 0.08	71	0.85 ± 0.06	0.52
A/H[i]	62	0.95 ± 0.07	69	0.95 ± 0.07	0.82
% BF[j]	65	26.09 ± 5.23	68	26.36 ± 4.81	0.75
% LBM[k]	60	73.6 ± 5.22	67	73.33 ± 4.95	0.47

a: BCP = Breast Cancer Patients; b: CG = Control Group; c: n = number of subjects; d: BMI = Body Mass Index; e: HC = Hip circumference; f: WC = Waist Circumference; g: AC = Abdomen Circumference; h: W/H = Waist to Hip Ratio; i: A/H = Abdomen to Hip Ratio; j: % BF = Percent of body fat; k: % LBM = Percentage of Lean Body Mass.

deliveries (3.8 ± 3.42 vs. 3.9 ± 3.6, p = 0.9); caesareans sections (0.34 ± 0.9 vs. 0.9 ± 1.14, p = 0.06); and abortions (0.78 ± 1.53 vs. 0.81 ± 1.1, p = 0.9). The time of contraceptive use (in months) was higher in BC patients in comparison with the GC (71.33 ± 66.9 vs. 13.0 ± 16.0, p = 0.12), although the data was not statistically different. The percentage of women who breastfed their children was significantly higher in the control group than in the BC patients (χ^2 = 7.3, p = 0.007).

3.5. Gynecologic and Obstetric Characteristics of Postmenopausal Women (PMW)

PMW with BC presented older ages at menarche, and menopause, compared to the CG (13.51 ± 1.48 years vs. 12.91 ± 1.41 years, p = 0.09, and 49.03 ± 2.86 years vs. 45.5 ± 8.78 years, p = 0.03, respectively); the onset of their active sexual life was at a higher age when compared to the CG (21.82 ± 6.16 vs. 18.54 ± 6.58, p = 0.06).

PMW with BC also had fewer pregnancies (7.7 ± 5 vs. 8.9 ± 4.8, p = 0.4) and deliveries (5.87 ± 4.1 vs. 7.8 ± 4.31, p = 0.09); and more abortions than the CG (1.66 ± 1.68 vs. 0.94 ± 1.13, p = 0.05); and their age at first pregnancy was an older age than for the CG (23.87 ± 6.69 years vs. 20.57 ± 6.02 years, p = 0.05). PMW with BC also had more years of reproductive life than the CG (35.09 ± 4.05 vs. 32.71 ± 6.75, p = 0.08). Even though, only one patient in the BC group, compared to nine women in the CG, mentioned of having used contraceptives.

3.6. Clinical Data of Patients with Breast Cancer (BC)

Seventy-two patients had BC (35 were PREW and 37 PMW). Sixty (89.6%) had a sporadic type of cancer and seven (10.4%) had a family history of breast cancer; 97% reported having palpated the tumor, which is why they went to the consul-

tation. The mainly affected breast was left; the right breast was affected in 31 patients (46.3%). In two patients, there was an affection bilateral.

In the group of patients with BC, no significant differences were observed in clinical data when comparing PREW with PMW. Only in the presence of skin ulceration which was bigger in PMW (5.71% vs. 27.03%, $\chi^2 = 5.88$; p = 0.01, data for PREW and PMW respectively). Most of the patients did refer a slow growing of the cancer tumor. To the palpation, the tumor was hard in consistence, irregular edges, and no adhered to deep levels in most of the cases. The average size of the tumor at the diagnosis time it was 6.03 ± 3.1 cm, and a 15.5 months of evolution time. The predominant clinical stage in both PREW and PMW was 3b with N1 and M0.

3.7. Sex Hormones and Prolactin Serum Levels of PREW

In Table 3, we demonstrated that in the PREW (evaluated during the follicular phase of the menstrual cycle), the LH, FSH and PRL serum levels were lower in BC patients when compared to PREW of the CG. Although, statistical differences were only observed in serum LH levels (p = 0.03).

3.8. Sex Hormones and Prolactin Serum Levels of PMW

The most relevant finding of this study was to demonstrate that the serum levels of PRL were significantly higher in PMW with BC when compared to PMW from the CG (p = 0.005) (see Table 4).

Table 3. Sex hormne profile in premenopasal women with breast cancer (PREW-BC) and control group of healthy women (PREW-CG).

Variable	PREW-BC	PREW-CG	*U*	*Z*	p
	Medium Min - Max	*Medium* Min - Max			
LH mUI/ml	3.08 1.1 - 22.9	7.0 2.2 - 25.9	19.0	−2.12	0.03
FSH mUI/ml	4.95 2.9 - 7.4	6.3 2.4 - 67.1	25.0	−1.63	0.10
P_4 ng/ml	0.42 0.09 - 2.5	2.5 0.17 - 10.2	40.0	−0.40	0.68
PRL ng/ml	8.17 3.3 - 16.7	6.4 4.29 - 23.4	43.0	−0.16	0.87
T ng/ml	0.35 0.03 - 0.61	0.3 0.13 - 0.90	35.5	−0.69	0.48
E_2 ng/ml	48.1 12.1 - 119.9	28.3 20.9 - 37.1	40.0	−0.40	0.68

U = Mann-Whitney U-test result; Min - Max = Minimum and Maximum values; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; P_4 = Progesterone; PRL = Prolactin, T = Testosterone; E^2 = Estradiol.

Table 4. Sex hormne profile in postmenopasal women with breast cancer (PMW-BC) and control group of healthy women (PMW-CG).

Variable	PREW-BC	PREW-CG	*U*	*Z*	p
	Medium Min - Max	*Medium* Min - Max			
LH mU/ml	21.0 4.5 - 35.7	13.4 2.1 - 41.6	161	1.89	0.05
FSH mU/ml	55.8 15.4 - 113.1	43.9 7.3 - 84.3	201	0.95	0.34
P_4 ng/ml	0.11 0.01 - 0.95	0.08 0.0 - 0.67	171	1.65	0.09
PRL ng/ml	14.7 3.6 - 52.7	5.9 1.9 - 33.3	124	2.76	0.005
T ng/ml	0.12 0.0 - 0.6	0.17 0.0 - 1.1	233	−0.19	0.84
E_2 ng/ml	6.4 0.0 - 29.9	3.9 0.0 - 38.9	226	0.36	0.71

U = Mann-Whitney U-test result; Min - Max = Minimum and Maximum values; FSH = Follicle Stimulating Hormone; LH = Luteinizing Hormone; P_4 = Progesterone; PRL = Prolactin, T = Testosterone; E^2 = Estradiol.

However, no differences were observed in the serum levels of LH, FSH, P_4 and T, when compared with those of the PMW in the CG. A relevant fact was that a higher percentage of PMW with BC (26.0% vs. 7.1% χ^2 = 5.57, p = 0.01) presented hyperprolactinemia (serum levels > 20 ng/mL, **Figure 1**), when comparing them with the PMW of the CG.

4. Discussion

In this investigation, no significant differences were found in some sociodemographic data such as occupation, monthly family income, and marital status of women with clinical and histopathological diagnosis of BC when comparing with women from the control group.

The results of anthropometrical variables of the patients with BC and the women from the control group, demonstrated that subjects had overweight (BMI > 27 kg/mt^2); their waist circumferences greater than 80 cm, and their waist/hip index greater than 0.8, indicate that both groups of women had risk factors for BC [1]. Blair *et al.* demonstrated that obese women had a 1.7- and 1.8-fold increased risk of stage III/IV disease [19]. In this investigation, we demonstrated that the clinical stage that predominated in both PREW and PMW with BC was stage 3b with N1 and M0, respectively. In the study of Blair *et al.*, it was also demonstrated that obese women with Luminal A- and Luminal B-like BC were 1.8 (95% CI: 1.3 - 2.5) and 2.2 (95% CI: 0.9 - 5.0) times more likely to die from their cancer compared to normal weight women [19]. In our study, we also demonstrated that hip

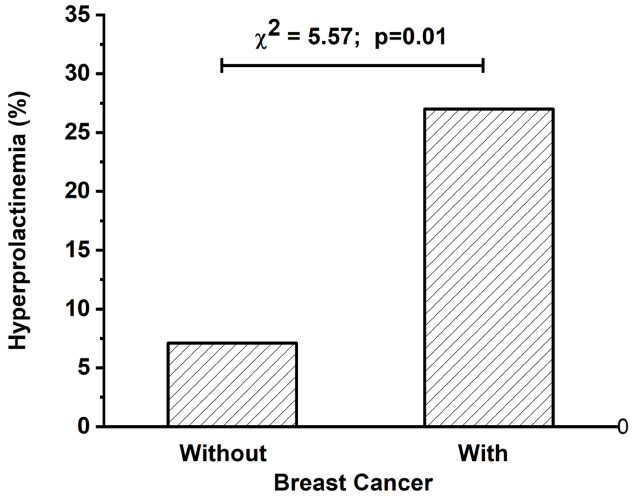

Figure 1. Hyperprolactinemia (prolactin serum levels > 20 ng/mL) in postmenopausal women (PMW).

and abdomen circumferences were significantly greater in the control group of healthy women than in the group of patients with BC; possibly the presence of cancer plays an important role in producing metabolic changes; causing a greater consumption of fats due to the catabolic effects of the disease. This could also be related to the lower food consumption of women with BC, since these women affected with BC were in the active stage of the disease. Another reason for the lower abdominal fat of the women with BC (from this study) could be that a higher percentage of them did not have children, which may also explain why these women have a less round abdomen and probably less intra-abdominal fat.

One of the most widely studied risk factors related to BC is nulliparity (the clinical antecedents of not having had children). In this study "nulliparity" was significantly more frequent among BC patients than in the control group. The mammary gland of women who have not had children (and therefore have not breastfed) have the most undifferentiated structures, compared to the mammary glands of women who have had children and had breastfed. Terminal pregnancy has been described as giving the mammary gland less susceptibility to carcinogenesis, while an interrupted pregnancy does not give it this protective effect; so, this is possibly the pathogenic relationship with BC [20].

A very interesting fact to point out, which could point to ovarian dysfunction or hormonal disorder of ovarian, hypothalamic, or other etiology, apart from the smaller number of pregnancies of PMW with BC and without the use of contraceptives, is their higher number of abortions ($p = 0.05$) when compared with the CG. BC patients present their first pregnancy at an older age than the control group ($p = 0.05$), although in both cases, the average age at first pregnancy is not a later age to be considered as a risk factor. BC patients presented their menopause later than women in the control group 49.03 ± 2.86 years vs.45.5 ± 8.78 years, $p = 0.03$, respectively.

The comparisons between BC patients with the women of the CG, demon-

strated, no significant differences in the serum levels of E^2, P_4, testosterone, and FSH; but higher serum levels of PRL were found in the PMW with BC when compared to the control group. High concentrations of PRL can influence mammary gland tumor growth. In a review carried out by Clevenger *et al.* [21] provided insight into the roles of PRL receptors and PRL in tumorigenesis and tumor progression. According to these investigators, there is evidence that the opposing actions of PRL in the mammary gland are mediated in part by the different isoforms of the PRL receptor; the investigators suggest that homomeric complexes of the long isoform of the PRL receptor promote mammary gland differentiation, while the heteromeric complexes of the intermediate and long isoforms of the PRL receptor trigger mammary oncogenesis. However, results like those of the present study were described by Love *et al.* [22], who demonstrated that there are no differences in PRL levels in PREW with and without BC; these investigators also found no differences in patients with a family history of cancer.

The changes that occur in a woman's mammary gland during their reproductive life have important repercussions on the development of breast cancer. Early age at menarche, late age at menopause, and a history of nulliparity are factors that exemplify the influence of endogenous sex hormones on mammary gland tumorigenesis [23]. Although, in this investigation, a measurement of sex hormones in the tissue of the mammary gland was not carried out; the serum profile of sexual hormones guides the knowledge of hormonal alterations in patients with BC [24].

In a meta-analysis carried out by Aranha *et al.*, it was shown that PRL has an important role in the development and growth of some carcinomas of the mammary gland [25]. At present, it has been shown that the expression of PRL and its receptor in the carcinoma tissues of the mammary glands. Although Hilton *et al.* describe the mechanisms by which estrogens, progesterone, and their receptors (ER and PR), have a role both in driving breast cancer, and both are favorable prognostic markers regarding the outcome. Therefore, these investigators present the current knowledge of the mechanisms of action of ER and PR in the normal breast and the implications for the development and management of breast cancer [26].

In this study, the elevated serum levels of PRL found in PMW with BC lead us to assume the effect that this hormone has on the mammary gland with cancer; however, more research is needed to understand the metabolic pathways, and other pathways that PRL uses to promote tumorigenesis in mammalian tissues [8] [25] [27]. In addition, it is necessary to monitor patients with BC, detected in situ, and in advanced stages of the disease, to guide specific antihormonal treatments and to reduce the possible effect of PRL, and thus change the course of the disease.

5. Conclusion

In this investigation, it was shown that the significantly elevated serum levels of prolactin in PMW with BC suggest that this hormone could contribute to the

proliferation of neoplastic tissue in the mammary gland in this group of patients. In this study, it was also confirmed that PMWs with BC had fewer deliveries and more abortions than the control group; the former also presented their first pregnancy and menopause at an older age when compared with the control group. Therefore, more longitudinal studies are required, in which these variables are controlled, especially in PMW.

Authors' Contributions

María-del-Corazón-de-Jesús Huerta-Franco and María-Raquel Huerta-Franco: Participated in the original idea, carried out an interview with patients and collected samples, captured data, and made the first draft of the manuscript.

Luis-Alfredo Jiménez-Huerta, Ángel-Haziel Vargas-Huerta, and Francisco-Miguel Vargas-Luna: Participated in study's design, statistical analysis, and manuscript revision.

Luis-Alfredo Jiménez-Huerta and Ángel-Haziel Vargas-Huerta: Participated in hormones' immunoassay realization and manuscript revision.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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