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Gestational Weight Gain Influences the Adipokine-Oxidative Stress Association during Pregnancy

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Keywords
Gestational weight gain · Adipokines · Oxidative stress

Abstract

Introduction and Objective: The weight gained during pregnancy could determine the immediate and future health of the mother-child dyad. Excessive gestational weight gain (EGWG) due to abnormal adipose tissue (AT) accumulation is strongly associated with adverse perinatal outcomes as gestational diabetes, macrosomia, obesity, and hypertension further in life. Dysregulation of adipokine, AT dysfunction, and an imbalance in the prooxidant-antioxidant systems are critical features in altered AT accumulation. This study was aimed to investigate the association between adipokines and oxidative stress markers in pregnant women and the influence of the GWG on this association. ***Methods:*** Maternal blood samples were obtained in the third trimester of pregnancy (n = 74) and serum adipokines (adiponectin, leptin, and resistin), oxidative damage markers: 8-oxo-2′-deoxyguanosine (8-oxodG), lipohydroperoxides (LOOH), malondialdehyde (MDA), and carbonylated proteins (CP), and glucose a metabolic marker were measured. ***Results:*** Women with EGWG had low adiponectin levels than women with adequate weight gain (AWG) or insufficient weight gain (IWG). Multiple linear regression models revealed a positive association between adiponectin and 8-oxodG in women with AWG (B = 1.09, 95% CI: 164–222, p = 0.027) and IWG (B = 0.860, 95% CI: 0.199–1.52, p = 0.013) but not in women with EGWG. In women with EGWG, leptin was positively associated with LOOH (p = 0.018), MDA (p = 0.005), and CP (p = 0.010) oxidative markers. ***Conclusion:*** Our findings sug-

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gest that concurrent mechanisms regulate adipokine production and oxidative stress in pregnant women and that this regulation is influenced by GWG, probably due to an excessive AT accumulation.

Introduction

Pregnancy involves deep anatomical, physiological, and biochemical adaptations that are important to provide proper fetal nutrition [1–3]. These maternal changes begin after conception and affect different organs, the immune system, and diverse metabolic pathways [4]. Gestational weight gain (GWG) is a critical process to support adequate fetal growth and development and is defined as the amount of weight gained during pregnancy, which is composed by the fetus, placenta, uterus, amniotic fluid, and the increase in the maternal breast tissue, blood volume, and adipose tissue (AT) [5–7]. GWG varies greatly depending on factors such as prepregnancy weight and the body mass index (BMI) [8, 9].

An excessive GWG (EGWG) increases the risk of maternal and neonatal adverse outcomes such as preeclampsia, gestational diabetes, preterm labor, and fetal macrosomia [10–13]. In addition to increasing the immediate risk of gestational complications, it has been demonstrated that EGWG is associated with postpartum weight retention, with short- and long-term metabolic consequences for the mother [5–7]. The EGWG also generates an adverse intrauterine environment that affects fetal growth and is associated with increased rates of obesity and other cardiometabolic diseases in the offspring [7, 13, 14], playing a key role in the metabolic programming of chronic diseases [15, 16]. EGWG may be a sign of higher AT accretion during pregnancy [6, 7, 13–16]. An excessive fat mass gain appears to be playing a key role in the metabolic programming of chronic diseases [15, 16].

Excessive AT accumulation is characterized by dysregulation of adipokine release, including leptin, adiponectin, and resistin; particularly, excess of visceral AT (VAT) appears to play a more significant pathogenic role in the development of chronic metabolic diseases in adults [17–20]. On the other hand, excessive AT generates an imbalance between the prooxidative – and antioxidative systems that usually results in a reactive oxygen species (ROS) increase [18, 21, 22]. While low ROS levels are essential to maintain diverse physiological functions, excessive ROS production alters different cellular components such as proteins, lipids, and DNA, generating oxidized biomolecules that function as biomarkers of oxidative damage. Elevation of malondialdehyde (MDA), carbonylated proteins (CP), and oxidized base 8-oxo-2′-deoxyguanosine (8-oxodG) as indicators of lipid peroxidation, protein, and DNA oxidation, respectively carries deleterious effects on cells [18, 21–25].

Both adipokine dysregulation and oxidative stress damage are focal points in inflammation and metabolic dysfunction and have been related to pregnancy complications and fetal programming, turning them into potential biomarkers of adverse perinatal outcomes. In this context, we have previously demonstrated a close relationship between these metabolic markers with the pregestational maternal weight status and maternal age [26].

Considering the above, we hypothesized that GWG might lead to alterations in adipokine levels and oxidative damage. Therefore, this research was aimed to evaluate the association between serum adipokines and oxidative stress markers in women in the third trimester of pregnancy and the influence of the GWG status on this association.

Methods

Research Design and Study Population

This cross-sectional study was performed at the Instituto Nacional de Perinatologia in Mexico City and is a secondary analysis from the OBESO (epigenetic and biochemical origin of obesity) perinatal cohort. The project was approved by the Institutional Review Board (protocol number: 3300-11402-01-575-17). Participation was voluntary, and all women who agreed to participate signed the informed consent form. The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

For this analysis, we studied pregnant women in the third trimester of pregnancy, recruited between January 2018 and January 2019. Gestational age was calculated according to the fetal ultrasound performed in the first trimester of pregnancy. The sample was selected by convenience, according to the pregestational BMI (p-BMI [kg/m^2]) (p-BMI = 18.5–24.9 as normal weight, p-BMI ≥25 as overweight, and p-BMI ≥30 as obesity), following the WHO guidelines [27]. All women meet the following inclusion criteria: adult women and singleton pregnancy; exclusion criteria included: multiple pregnancy, comorbidities (diabetes mellitus, renal or hepatic diseases, congenital malformations, autoimmune diseases, or uncontrolled thyroid disease), and taking any medication that may affect endocrine metabolism (insulin, metformin, and/or corticosteroids).

Anthropometric and Biochemical Parameters

Pregestational weight (kg) was self-reported, and height (cm) was measured with a stadiometer (SECA 220, Hamburg, Germany) by trained personnel. Pregestational weight and height were used to calculate p-BMI. GWG was calculated in the last clinical

Table 1. Maternal characteristics, metabolic parameters, adipokine, and oxidative damage markers concentration according to the gestational weight gain (GWG) status

Variable	GWG status		
	insufficient (n = 28)	adequate (n = 20)	excessive (n = 26)
Age, years	30.2±1.61	31.1±1.73	29.8±1.69
p-BMI, kg/m^2	27.3±1.22	27.6±1.26	28.8±1.18
p-BMI status, n (%)			
Normal	12 (42.9)	9 (45.0)	6 (23.1)
Overweight or obese	16 (57.1)	11 (55.0)	20 (76.9)
GWG, kg	5.38±0.64	9.21±0.73[a]	14.8±0.68[b, c]
GA at sampling, weeks	35.0±0.62	34.6±0.77	35.6±0.56
Fasting glucose, mg/dL	82.0±2.36	84.6±3.72	83.2±2.62
Adiponectin, µg/mL	14.8±2.04	15.0±2.56	7.69±1.21[b, c]
Leptin, ng/mL	23.2±3.29	36.0±7.22	39.4±8.78
Resistin, ng/mL	20.2±1.76	21.1±2.83	19.9±2.15
LOOH, pmol I_3/mg dry weight	28.4±1.97	25.1±1.63	28.8±2.53
MDA, pmol MDA/mg dry weight	156±14.9	136±15.9	156±14.6
CP, nmol CP/mg protein	12.3±0.78	12.3±0.93	12.3±0.84
8-oxodG, ng/mL	195±4.52	200±5.28	186±4.50

Values represent mean±SEM. One-way ANOVA with the minimum significant difference post hoc test. [a] $p < 0.05$ adequate versus insufficient. [b] $p < 0.05$ excessive versus adequate. [c] $p < 0.05$ excessive versus insufficient. p-BMI, pregestational body mass index; GA, gestational age; LOOH, lipohydroperoxides; MDA, malondialdehyde; CP, carbonylated proteins; 8-oxodG, 8-oxo-2′-deoxyguanosine.

visit at the third trimester and women were categorized according to IOM 2009 guidelines [28] as adequate weight gain (AWG), insufficient weight gain (IWG), and excessive weight gain (EWG) for their specific gestational age.

Samples

Fasting maternal venous blood samples were drawn in Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ, USA) and centrifuged at 4°C for 15 min at 1,000 *g*. Serum samples were stored at −70°C until the assays were performed.

Biochemical Analysis

Fasting serum glucose concentrations were measured by enzymatic colorimetric methods using an automated analyzer (ISE Echo Lory 2000) and commercial kits (DiaSys Diagnostic Systems GmbH, Germany).

Adipokines

ELISA commercial kits to measure serum adiponectin (DY1065), leptin (DY398), and resistin (DY1359) (R&D Systems Inc., Minneapolis, MN, USA) were used according to the manufacturer's instructions and read at 450 nm in a Synergy HT plate reader (BioTek, Winooski, VT, USA).

Oxidative Stress Markers

Serum 8-oxodG was measured to evaluate DNA oxidative damage using a commercial ELISA kit (4380-096-K) (TREVIGEN, Gaithersburg, MD, USA). Oxidative lipid damage was assessed by quantifying lipohydroperoxides (LOOH) [29] and MDA [30], as previously reported. Protein oxidative damage was evaluated by measuring the carbonyl group content [31].

Statistical Analysis

Descriptive statistics were used for data distribution and frequencies, and one-way ANOVA with the minimum significant difference post hoc test was used to analyze differences by GWG categories (AWG, IWG, or EWG). Data were expressed as mean ± SEM, and p values <0.05 were considered statistically significant. Spearman correlations were performed to study the correlation between adipokines and oxidative damage markers. Multiple linear regression models were done to investigate associations between adipokines and oxidative damage markers. Models were stratified by GWG categories. Statistics were performed using SPSS software (version 22, SPSS Statistics/IBM Corp., Armonk, NY, USA).

Results

Seventy-four women in the third trimester of pregnancy were studied. The mean age was 30.3 ± 0.96 years old, and the mean gestational age was 35.2 ± 0.37 weeks of gestation. Before pregnancy, 71.1% (n = 47) of women were overweight or had obesity. According to GWG, 37.8% (n = 28) had IWG and 35.2% (n = 26) had EWG. Maternal anthropometric and metabolic parameters, ad-

Table 2. Effect of adipokines on LOOH levels in pregnant women according to gestational weight gain

	B	95% CI	*p* value	R^2/(R^2 adjusted)
AWG				
Constant	32.3	21.5–43.1	**<0.0001**	0.147 (–0.13)
Adiponectin	–0.169	–0.496 to 0.157	0.288	
Leptin	–0.028	–0.147 to 0.092	0.631	
Resistin	–0.171	–0.461 to 0.119	0.229	
IWG				
Constant	42.5	31.5–53.5	**<0.0001**	0.274 (0.179)
Adiponectin	–0.293	–0.646 to 0.059	0.099	
Leptin	–0.167	–0.393 to 0.058	0.139	
Resistin	–0.270	–0.674 to 0.134	0.180	
EWG				
Constant	33.0	20.3–45.7	**<0.0001**	0.438 (0.349)
Adiponectin	–0.220	–1.04 to 0.602	0.471	
Leptin	0.145	0.036–0.254	**0.012**	
Resistin	–0.423	–0.841 to –0.006	**0.047**	

Models included 74 pregnant women; adequate weight gain (AWG) ($n = 20$), insufficient weight gain (IWG) ($n = 28$), and excessive weight gain (EWG) ($n = 26$). LOOH, lipohydroperoxides.

Table 3. Effect of adipokines on MDA levels in pregnant women according to gestational weight gain

	B	95% CI	*p* value	R^2/(R^2 adjusted)
AWG				
Constant	102	2.48–202	**0.045**	0.233 (0.090)
Adiponectin	1.85	–1.16 to 4.86	0.211	
Leptin	0.836	–0.264 to 1.94	0.127	
Resistin	–1.15	–3.83 to 1.52	0.375	
IWG				
Constant	257	176–339	**<0.0001**	0.302 (0.211)
Adiponectin	–1.10	–3.73 to 1.53	0.398	
Leptin	–2.15	–3.83 to –0.466	**0.015**	
Resistin	–1.60	–4.61 to 1.41	0.283	
EWG				
Constant	164	94.0–235	**<0.0001**	0.435 (0.350)
Adiponectin	0.996	–3.65 to 5.64	0.659	
Leptin	0.956	0.345–1.57	**0.004**	
Resistin	–2.42	–4.80 to 0.044	**0.046**	

Models included 74 pregnant women; adequate weight gain (AWG) ($n = 20$), insufficient weight gain (IWG) ($n = 28$), and excessive weight gain (EWG) ($n = 26$). MDA, malondialdehyde.

ipokine levels, and oxidative damage markers according to GWG are summarized in Table 1. No differences were observed in maternal characteristics when stratified by GWG. Women with EWG had significantly lower concentrations of adiponectin than women with AWG ($p = 0.016$) and IWG ($p = 0.010$), showing a trend toward higher leptin levels ($p = 0.080$) than IWG. Also, women with EWG showed a trend of lower levels of 8-oxodG ($p = 0.059$) than AWG women. There were no differences in resistin, LOOH, MDA, and CP concentrations between EWG and AWG or IWG.

Spearman correlation analysis between adipokines and oxidative damage markers revealed a positive significant correlation between adiponectin and 8-oxodG concentration ($r = 0.401$; $p = 0.001$) and inverse significant correlations with LOOH ($r = –0.262$; $p = 0.027$) and CP ($r = –0.237$; $p = 0.046$). Resistin was inversely correlated with LOOH ($r = –0.303$; $p = 0.009$) and MDA ($r = –0.256$;

Table 4. Effect of adipokines on CP levels in pregnant women according to gestational weight gain

	B	95% CI	*p* value	R^2/(R^2 adjusted)
AWG				
Constant	12.4	6.32–18.4	**0.001**	0.166 (0.010)
Adiponectin	−0.006	−0.189 to 0.176	0.942	
Leptin	0.039	−0.028 to 0.106	0.234	
Resistin	−0.067	−0.229 to 0.095	0.393	
IWG				
Constant	16.4	11.6–21.1	**<0.0001**	0.172 (0.064)
Adiponectin	−0.071	−0.223 to 0.081	0.346	
Leptin	−0.076	−0.173 to 0.022	0.121	
Resistin	−0.063	−0.238 to 0.111	0.238	
EWG				
Constant	11.8	7.55–16.1	**<0.0001**	0.367 (0.267)
Adiponectin	−0.041	−0.318 to 0.236	0.761	
Leptin	0.053	0.016–0.089	**0.016**	
Resistin	−0.049	−0.189 to 0.092	0.475	

Models included 74 pregnant women; adequate weight gain (AWG) (*n* = 20), insufficient weight gain (IWG) (*n* = 28), and excessive weight gain (EWG) (*n* = 26). CP, carbonylated proteins.

Table 5. Effect of adipokines on 8-oxodG levels in pregnant women according to gestational weight gain

	B	95% CI	*p* value	R^2/(R^2 adjusted)
AWG				
Constant	193	164–222	**<0.0001**	0.365 (0.246)
Adiponectin	1.09	0.222–1.95	**0.027**	
Leptin	0.015	−0.301 to 0.330	0.922	
Resistin	−0.485	−1.25 to 0.281	0.198	
IWG				
Constant	164	141–187	**<0.0001**	0.404 (0.318)
Adiponectin	0.860	0.199–1.52	**0.013**	
Leptin	−0.097	−0.544 to 0.350	0.657	
Resistin	0.867	0.066–1.67	**0.035**	
EWG				
Constant	190	168–211	**<0.0001**	0.235 (0.121)
Adiponectin	1.04	−0.408 to 2.49	0.149	
Leptin	−0.142	−0.33 to 0.049	0.137	
Resistin	−0.121	−0.862 to 0.620	0.737	

Models included 74 pregnant women; adequate weight gain (AWG) (*n* = 20), insufficient weight gain (IWG) (*n* = 28), and excessive weight gain (EWG) women (*n* = 26). 8-oxodG, 8-oxo-2′-deoxyguanosine.

$p = 0.028$), as well as 8-oxodG with LOOH ($r = -0.343$; $p = 0.003$).

Multiple linear regression models were performed to evaluate the association of adipokines and oxidative damage markers, according to GWG. In women with EWG, a significant positive association was observed between leptin and LOOH ($B = 0.145$; 95% CI = 0.036–0.254; $p = 0.012$) (Table 2), MDA ($B = 0.956$; 95% CI = 0.345–1.57; $p = 0.004$) (Table 3) and CP ($B = 0.053$; 95% CI = 0.016–0.089; $p = 0.016$) (Table 4), and a negative association was observed between resistin and LOOH ($B = -0.423$; 95% CI = −0.841 to −0.006; $p = 0.047$) (Table 2) and MDA ($B = -2.42$; 95% CI = −4.80 to 0.044; $p = 0.046$) (Table 3).

Women with IWG presented a negative association between leptin and MDA ($B = -2.15$; 95% CI = −3.83 to −0.466; $p = 0.015$) (Table 3). A positive association be-

tween adiponectin and 8-oxodG was observed in women with AWG (B = 1.09, 95% CI: 0.222–1.95, p = 0.027) and IWG (B = 0.860, 95% CI: 0.199–1.52, p = 0.013) but not in women with EWG. In women with IWG, a positive association was also observed between resistin and 8-oxodG (B = 0.867, 95% CI: 0.066–1.67, p = 0.035) (Table 5).

Discussion

In this study, we are providing novel evidence that adiponectin and 8-oxodG concentrations in women with AWG and IWG are positively correlated, while in women with EWG, this association is not observed. Adiponectin is secreted by adipocytes and it is involved in multiple functions as insulin sensitizing, stimulation of lipid metabolism, and glucose uptake, displaying anti-inflammatory properties, and correlating inversely with body weight and fat mass [19, 32–34]. During pregnancy, adiponectin concentration drops due to an increase in fat mass, and it has been negatively correlated with birth weight, suggesting that adiponectin may be involved in placental nutrient transport [35, 36].

Although no differences were found in 8-oxodG levels among the groups, this marker showed a trend to be lower in EWG than AWG women. 8-oxodG has been classically studied as the most common base modification produced in DNA by oxidative damage, as a separate molecule, 8-oxodG exhibits protective functions [37]. 8-oxodG inactivates Rac1 and Rac2 proteins, inhibiting Rac-linked functions such as ROS production, controlling oxidative stress damage [38]. Besides the antioxidant activity, 8-oxodG displays anti-inflammatory properties, reducing the transcription of pro-inflammatory cytokines as TNF-, IL-1β, IL-6, and IFN-γ [37, 38]. In an obese mice model, the administration of 8-oxodG induces elevation of serum adiponectin, improves hyperglycemia and lipid profile, and diminishes the concentration of the pro-inflammatory cytokines TNF-α and IL-6, ameliorating the hallmarks of metabolic syndrome, including insulin resistance [39]. Thus, the positive association between 8-oxodG and adiponectin in women with AWG and IWG could indicate an adequate inflammatory oxidative stress balance, which is disrupted in pregnant women with EWG. This is in accord with our findings that adiponectin concentrations are higher in AWG and IWG women than women with EWG, correlating negatively with LOOH and MDA concentrations. In light of these observations, our data suggest that EWG, as an indicator of excessive fat mass accretion, appears to be involved in downregulation of adiponectin and could be related to a decreased ability to regulate oxidative damage, promoting the development of insulin resistance, gestational diabetes, preeclampsia, and placental dysfunction [40–42].

Leptin is secreted by AT and placenta and participates in regulating food intake, energy homeostasis, insulin secretion, as well as transport of nutrients to the fetus, correlating with p-BMI and adiposity [32, 43, 44]. In our study, women with EWG showed a tendency to higher leptin levels than the AWG group (p = 0.087), which is probably related to abnormal accumulation of body fat. Accordingly, several studies have reported that high leptin levels in the 2nd and 3rd trimester of pregnancy correlate with EWG [35, 45–47]. In contrast, Patro-Małysza et al. [48] did not find differences in leptin concentration after delivery between AWG and EWG women.

Physiologically, pregnant women experience an increase in AT, mainly VAT [49]. During a persistent positive energy balance, VAT is increased due to adipocyte hypertrophy, leading to adipocyte dysfunction [50], and altered adipokine profiles, where adiponectin decreases and leptin concentration increases [51]. As far as we know, our study shows for the first time a positive association between leptin concentration and LOOH, MDA, and CP markers in pregnant women with EWG. Studies not associated with GWG or pregnancy have showed that high leptin levels induce ROS production, increasing lipid peroxidation, and protein carbonylation [40, 52, 53]. Interestingly, in our study, women with IWG showed a negative association between leptin and MDA concentrations, possibly related to VAT hypertrophy or less accumulation of this tissue.

Another interesting finding was the association between resistin and 8-oxodG in women with IWG that was not observed in AWG and EWG groups; as far as we know, no studies are reporting this association. Resistin is expressed in several tissues besides AT such as placenta and fetal membranes [54, 55]. The effect of GWG on resistin levels remains unknown; in our study, we did not find differences in resistin levels between the groups but we are demonstrating an inverse association with LOOH and MDA concentrations.

It has been demonstrated that oxidative stress may be related to resistin decrease; 3T3-L1 cells exposed to low levels of H_2O_2 for a long time showed impaired resistin expression [56]. Very few studies have reported associations between resistin and oxidative damage markers with discrepant results. In N2a cells used as an Alzheimer model disease, resistin exerts a protective effect against neurotox-

icity of amyloid-β peptides, through the regulation of ROS levels and mitochondrial function [57]; however, other study showed a negative correlation between serum resistin and oxidative damage in normal weight individuals [58]. On the other hand, resistin may lead to the overproduction of ROS, generating oxidative stress by mitochondrial damage [59]. The protective effect of several adipokines against oxidative damage occurs through the interaction with their receptor in the cell membrane, triggering the transduction of signals involved in antioxidant defense. In the case of resistin, its receptor or receptors involved in antioxidant function have not been fully identified, and further research is required to understand if resistin is involved in oxidative damage control during pregnancy.

Pregnancy carries oxidative stress with increasing circulating ROS due to maternal physiological changes, which is counteracted by the synthesis of antioxidants [60]. Oxidative stress is caused by an imbalance between prooxidants secretion and antioxidant capacity and is a crucial factor in the pathophysiology of various pregnancy complications (i.e., preeclampsia and gestational diabetes mellitus) [61]. In this work, we studied if GWG modifies the three levels of oxidative damage to biomolecules: lipids, proteins, and DNA. Our results did not show any differences in oxidative damage markers (LOOH, MDA, and CP) between the study groups and as far as we know there are no studies to compare our findings. Since pregestational obesity is known to be a factor of oxidative stress [26], ongoing work in our lab is focused on elucidating whether pregnancy complicated with obesity and EGWG could represent an increased risk of oxidative damage.

This study has some limitations that should be addressed. Given the inability to weigh women before pregnancy, we used self-reported p-BMI, which may introduce bias in the classification of GWG. The sample size is relatively small and women were highly selected; therefore, results may not apply to all pregnant women. Variability may be an issue even though it was decreased by selecting study groups based on the p-BMI status.

Conclusion

Our findings suggest that concurrent mechanisms regulate adipokine production and oxidative stress in pregnant women and that this regulation is influenced by the GWG status, probably due to an excessive fat mass accumulation. As recommended by the Institute of Medicine [28], future work should be focused on the mechanisms that underlie the effects of GWG on the mother-baby dyad, which may result in adverse metabolic consequences later in life.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The project was approved by the Institutional Review Board of Instituto Nacional de Perinatologia (protocol number: 3300-11402-01-575-17). Participation was voluntary, and all women who agreed to participate signed the informed consent form.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

G.E.-G., J.M.S.-P., and O.P.-P. designed the study; S. E.-S., O.P.-P., and J.M.S.-P. did statistical analysis; J.M.S.-P., A.M.-E., S.N.-S., M.S.-M., V.O.-C., and M.T.-D did methodology; G.E.-G., J.M.S.-P., S. E.-S., A.M.-E., E.R.-M., and O.P.-P. participated in data interpretation; J.M.S.-P. and D.M.-B. wrote the manuscript; and G.E.-G, O.P.-P., and E.R.-M did review the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data that support the findings of this study are available from the corresponding author (Guadalupe Estrada-Gutierrez) on reasonable request.

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