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ORIGINAL ARTICLE

Relationship between gestational obesity and adverse perinatal outcomes: a multicenter study

Relación entre obesidad gestacional y desenlaces perinatales adversos: Estudio multicéntrico

Andrea Patricia Vargas-Sanabria[a], Maria Azucena Niño Tovar[b], Ariana Liseth Acosta Rodriguez[c], Angie Lorena Acosta Rodriguez[d], Luis Alfonso Pérez[e]

[a]Residente tercer año de Pediatría. Universidad Industrial de Santander. Santander, Colombia
[b]Clínica Materno Infantil San Luis. Universidad Industrial de Santander. Santander, Colombia
[c]Universidad Industrial de Santander. Santander, Colombia
[d]Universidad Cooperativa de Colombia. Magdalena, Colombia.
[e]Hospital Universitario de Santander. Universidad Industrial de Santander. Santander, Colombia

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What do we know about the subject matter of this study?

Obese pregnant women present a chronic proinflammatory state caused by the process of lipoinflammation associated with adverse perinatal outcomes that have been studied worldwide, finding statistically significant associations between the risk factor and these outcomes.

What does this study contribute to what is already known?

It provides an overview of the behavior of obese pregnant women in Northeastern Colombia and shows a statistically significant association between obesity as a risk factor and 3 adverse perinatal outcomes, even in pregnant women who did not have other comorbidities such as diabetes or hypertension.

Abstract

To identify the association between maternal obesity and perinatal adverse outcomes in a population from the Colombian northeast. **Patients and Method:** Multicenter, prospective, transverse study with patients who consulted and completed their pregnancy at the *Clinica Materno Infantil San Luis* and *Hospital Universitario de Santander*, between January 2019 and March 2020. The nutritional status of the patients was classified according to the Rosso-Mardones curve and obese and normal-weight pregnant women were included. The main outcome was prematurity, and the secondary ones were intrauterine growth restriction, large for gestational age, and early neonatal hypoglycemia. The analysis was made in subgroups of pregnant women without comorbidities. The strength of association was estimated through binomial regression (RR), and a confidence interval of 95%, adjusted by

Keywords:
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Correspondence:
Andrea Patricia Vargas
andree.vs@hotmail.com

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maternal age as a confounding variable according to a counterfactual model. A p- < 0.05 value was considered statistically significant. **Results:** 283 obese pregnant women and 276 normal body mass index pregnant women were included. There was a significant association between maternal obesity and prematurity (RR 2.5; CI95% 1.4-4.2), early neonatal hypoglycemia (RR 7.1; CI95% 2.1-23.7), and large for gestational age (RR 6.6; CI95% 3,3-13,1). These findings were similar in pregnant women without maternal hypertension or diabetes. **Conclusion:** Maternal obesity is associated with prematurity, large for gestational age, and early neonatal hypoglycemia; even in patients without maternal hypertension and diabetes.

Introduction

The World Health Organization (WHO) defines obesity as a Body Mass Index (BMI) or Quetelet index ≥ 30 kg/m^2 of body surface area[1]. This definition is maintained to determine pregestational or gestational obesity until the 10th week of pregnancy, so from this moment on, it is considered that weight gain depends not only on adipose tissue but also on gestational growth[2]. Therefore, from the 10th week of gestation, the nutritional status should be evaluated using one of the 3 methods proposed and validated worldwide, namely Rosso and Mardones, Atalah et al or Calvo et al[2]. In Latin America, the Rosso and Mardones method is the oldest and, compared with the other methods, has become the gold standard for the diagnosis of obesity in pregnant women[2].

It is important to define the method for the diagnosis and follow-up of nutritional status in pregnant women because maternal obesity is a nutritional pandemic whose prevalence has increased in recent years. By 2011, the United Kingdom, the United States, and Canada had doubled the 10% of obesity prevalence in women of childbearing age of 1990[3].

In Colombia, statistics do not differ from those worldwide. The 2015 national nutritional status survey revealed that obesity was more prevalent in women of childbearing age (22.4%) than in men (14.4%) and that they were less physically active (42.7%) compared with men (61.1%)[4]. The average BMI of Colombian women of childbearing age is 24.5 kg/m^2 [5]; however, the 2010 national nutritional status survey showed that out of 1927 pregnant women surveyed, 9.8% were obese and this condition was higher in mothers between 25 and 49 years of age[6].

Obesity in pregnant women is associated with different high-risk conditions such as diabetes mellitus, miscarriage, hypertensive disorders, nonalcoholic liver disease, cesarean delivery, metabolic syndrome, and thromboembolism[7]. Likewise, the fetus born to an obese mother is at higher risk of preterm birth, respiratory distress syndrome, transient neonatal hypoglycemia, low birth weight, IUGR, large for gestational age, fetal macrosomia, congenital malformations, and even perinatal mortality[8-10].

One of the theories that explain the presence of adverse perinatal outcomes is lipoinflammation. Previously, adipose tissue was known as an energy storage organ; however, the study of adipocytes has identified their capacity to produce numerous immunomodulatory factors (leptin, TNF-α, IL-1β, and IL-6), which play a very important role in regulating endocrine and immune homeostasis[11].

In obese individuals, adipocytes hypertrophy, exhibit intracellular stress, do not function properly and their immune function is dysregulated causing a chronic proinflammatory state called lipoinflammation. This presents an excessive increase in leptin levels, leading to a resistance to its anorexigenic effect at the hypothalamic level, in addition to promoting the proinflammatory Th1 response in immune cells.

Additionally, proinflammatory factors can circulate in the bloodstream and increase platelet and fibrinogen activity causing endothelial injury and malperfusion which, associated with the increase of IL-6 and C-reactive protein production, eventually lead to apoptosis through the complement system activation[11,12].

The proinflammatory state appears mostly in adipocyte-dependent tissues in the process of hyperplasia and sudden hypertrophy since preadipocytes have a high production and storage capacity of inflammatory factors in vesicles compared with mature adipocytes, which could explain the increased risk in patients with rapid weight gain[11-13].

Endothelial injury and malperfusion derived from this inflammation not only affect the adipose tissue of pregnant women or those of childbearing age, but also other organs of the female reproductive system, affecting perfusion, implantation, placentation, and development of the fetus and placenta, leading to adverse perinatal outcomes[13-15].

Worldwide, there is a growing interest in the study of the relationship between gestational obesity and adverse perinatal outcomes. In Colombia, despite the considerable increase of this pathology in women of childbearing age and pregnant women, there are no studies that relate this type of findings, therefore, since obesity is a modifiable risk factor, it is essential to promote this type of study that allow health professionals to know the implications of obesity on maternal and fetal health in order to promote preconception and prenatal counseling, as well as the early and timely identification of women at risk[16].

The main objective of the study is to identify the association of gestational obesity with prematurity, which is a relevant public health problem, neonatal mortality, and long-term morbidity[17,18]. The secondary goals are to identify the association of gestational obesity with adverse perinatal outcomes, large for gestational age newborn, transient neonatal hypoglycemia, and intrauterine growth restriction (IUGR).

Patients and Method

Cross-sectional multicenter study with prospective collection of data obtained from the medical records of mothers who visited at any gestational age and for any reason the delivery room service of the *Clínica Materno Infantil San Luis* (CMISL) and the *Hospital Universitario de Santander* (HUS), between January 2019 and March 2020 and who additionally gave birth in these institutions which have available the medical records of their newborns. In both institutions, there were unified and standardized protocols for weighing and measuring pregnant women and instruments that were continuously adjusted during the data collection process.

The study was conducted with the approval of the ethics committee of the CMISL, the HUS, and the *Universidad Industrial de Santander* (CEINCI). The objectives and methodology of the study were explained to all the pregnant women, who gave their written informed consent, including assent in the case of pregnant minors.

We selected pregnant women with singleton pregnancies, who were measured, weighed, and classified according to the Rosso-Mardones curve[19]. Those with obese or normal nutritional status were included, and patients with overweight or malnutrition were not considered. We excluded those pregnant women who had indications for termination of pregnancy due to trauma, legal or illegal voluntary interruption of pregnancy according to Colombian law, non-viable births under 20 weeks of gestation, pregnant women with chorioamnionitis, incompetent cervix, previous chronic use of corticosteroids during pregnancy, or whose child presented malformations incompatible with life at birth. Medical records with incomplete data and extra-institutional births were also excluded.

A non-probability sampling of consecutive cases of all pregnant women who met the inclusion criteria was performed. The sample size was calculated using 2.71 OR for obese pregnant women according to preterm births (primary outcome) identified in the literature of a Swedish cohort by Cnattingius et al[14] with OpenEpi software. A sample size of 498 patients was determined, 249 obese pregnant women and 249 pregnant women with normal nutritional status, with 80% power and 95% significance level. A 10% of possible losses was considered.

The data collected from the medical records were maternal characteristics (sociodemographic variables, nutritional status, number of pregnancies, and history of preterm delivery, hypertensive disorders or diabetes), perinatal (route of birth and premature rupture of membranes), and neonatal ones (gestational age at birth, anthropometric parameters, sex, and presence of transient neonatal hypoglycemia).

Preterm birth was considered the main outcome. Gestational age was calculated according to the most reliable data found in the medical records in the following order: 1st-trimester ultrasound, date of last reliable menstrual period, and neonatal physical examination. Preterm birth was classified according to gestational age based on the classification proposed by the WHO[21].

Secondary outcomes were IUGR, large-for-gestational-age newborn, and transient neonatal hypoglycemia. IUGR was defined as 1) fetal growth below the 10th percentile for gestational age, associated with signs of fetal compromise (fetal-placental circulation abnormalities identified by Doppler ultrasound); 2) weight below the 3rd percentile for gestational age; and 3) deviation of the growth pattern with flattening of the growth curve out of the lane and deceleration of growth regardless of being above the 10th percentile[22].

A large-for-gestational-age newborn was defined as birth weight above the 90th percentile according to the Fenton curve[23]. Transient neonatal hypoglycemia was defined as blood sugar levels < 50 mg/dL in the first 48 hours or < 60 mg/dL from 48-72 hours[24].

The variables were recorded in a Google Drive survey, that allowed organizing the data in an Excel spreadsheet. Each variable was recorded by two different researchers, then they compared concordance and, in case of discordance, the record of variables by a third researcher was requested.

For the statistical analysis, categorical, nominal, and ordinal variables were presented as proportions and number of cases; and the continuous ones as median and interquartile range (IQR) since they did not have a normal distribution according to the Shapiro Wilk test. The group of obese pregnant women was compared with those of overall normal nutritional status, and additional analysis of pregnant women without comorbidities such as pregnancy-associated hypertensive disorder or diabetes was performed using the $\chi 2$ or Fisher's test for qualitative variables and the Wilcoxon test for the quantitative ones.

Any difference where the test performed showed a $p < 0.05$ was considered significant. The strength of association between being obese and the risk of presenting perinatal outcomes was estimated by binomial regression, which estimates the relative risk (RR) and the 95% confidence interval (95%CI). Analyses were adjusted for maternal age as a confounding variable identified by acyclic graphs and supported by findings in the literature that report that advanced maternal age is related to higher rates of obesity and higher proportions of preterm births[25-26]. We did not adjust for the socioeconomic stratum because we did not have complete information on this variable in all the pregnant women, and no interaction variables were identified. All analyses were performed with Stata software 16.1 (College Station, Texas, USA, 2019).

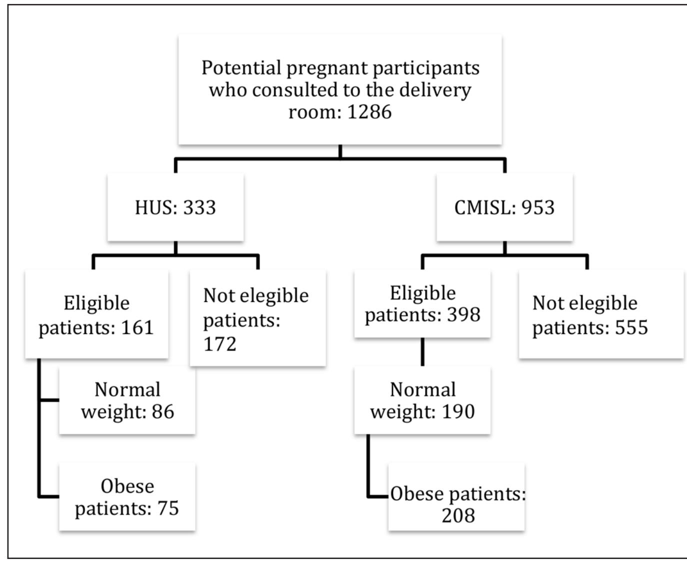

Figure 1. Selection and distribution of pregnant women with a single pregnancy who consulted to the delivery room service of the Hospital Universitario de Santander and Clinica Materno Infantil San Luis between January 2019 and March 2020 at any gestational age. CMISL: Clínica Materno Infantil San Luis, HUS: Hospital Universitario de Santander.

Results

1286 patients were admitted to the institutions. 727 were excluded, 248 (34.1%) due to extra-institutional birth, 36 (5.0%) due to multiple pregnancy, 247 (33.9%) due to overweight, and 196 (27.0%) due to low maternal weight. The eligible patients were 559, of which 161 (28.8%) belonged to the HUS and 398 (71.2%) to the CMISL, this distribution was randomized. There were 283 obese pregnant women and 276 normal-weight pregnant women (Figure 1).

The median gestational age at the first consultation of pregnant women with normal nutritional status was 31.4 (IQR: 30.3-32.4) and the median gestational age of obese women was 30.4 (IQR: 29-32).

Regarding the socio-economic aspect, the HUS cares for a population mainly from strata 1, 2, and 3 with affiliation to the subsidized regime and the CMISL cares for a population from strata 4, 5, and 6 with affiliation to the contributory regime. Despite randomly obtaining a higher proportion of patients from the CMISL, the proportion of obese patients in the CMISL (21.8%) was similar to that found in the HUS (22.5%). There was no statistically significant difference in this distribution ($p = 0.4$).

Most of the patients, regardless of their nutritional status, were from urban areas (Table 1). There were no differences between the groups related to origin, maternal age, number of previous pregnancies, and previous preterm delivery.

The bivariate analysis stratified by nutritional status showed that obese mothers had a higher prevalence of gestational diabetes, hypertensive disorder, and premature rupture of membranes, but not in cesarean section as a delivery route, nor pregestational diabetes. In obese pregnant women, chronic hypertension and preeclampsia predominated as hypertensive disorders associated with pregnancy, and in pregnant women with normal nutritional status, preeclampsia predominated (Table 2).

Table 3 shows the RR estimates adjusted for maternal age identified as a confounding variable[4]. Obese pregnant women had 2.5 times the risk of having a preterm birth; there were no differences between the degree of prematurity in the children of both groups of patients. In addition, these patients had 7.1 times the risk of their children having transient neonatal hypoglycemia, and 6.6 times the risk of their children being large for gestational age.

It was found that 3.5% of the child of obese pregnant women were classified as IUGR versus the 1.8% that occurred in the child of pregnant women with normal nutritional status, however, this difference was not statistically significant and may be related to a sample size that was smaller than necessary to make this phenomenon evident.

When the analysis of the pregnant women who did not have a diagnosis of diabetes or any type of hypertensive disorder was performed, it was observed that there was still an increased risk of preterm birth, hypoglycemia, and large-for-gestational-age newborns in children of obese pregnant women compared with those with normal nutritional status (Table 3). There was also a higher percentage of IUGR in obese pregnant women (4.3%) compared with pregnant women

Table 1. Sociodemographic variables and maternal history of pregnant women with normal nutritional status and obese pregnant women at the Hospital Universitario de Santander and Clinica Materno Infantil San Luis between January 2019 and March 2020

Variable; n and (%)	Nutritional status of the pregnant woman		
	Normal (n = 276)	Obese patients (n = 283)	p
Urban origin	232 (84.0)	242 (85.5)	0.60
Maternal Age			0.06
≤ 20 age	29 (10.5)	45 (15.9)	
21-34 age	215 (77.8)	192 (67.8)	
≥ 35 age	32 (11.5)	46 (16.2)	
Number of pregnancies			0.19
Igual a 1	104 (37.6)	89 (31.4)	
Igual a 2	110 (39.8)	115 (40.6)	
Igual a 3 o más	62 (22.4)	79 (27.9)	
Previous preterm delivery	7 (4.0)	14 (7.1)	0.18

with normal nutritional status (1.2%). This difference was also not statistically significant.

Table 4 describes the causes of preterm birth. There was no difference between the two groups for the possible causes (p = 0.6), and the premature labor not associated with infection was the most frequent in both groups (72.2% vs. 71.1%).

Discussion

This study found an association between gestational obesity and the primary outcome preterm birth (RR 2.5, 95%CI 1.4-4.2), as well as transient neonatal hypoglycemia (RR 7.19, 95%CI 2.17-23.79) and large-for-gestational-age newborn (RR 6.6, 95%CI 3.3-13.1) as 2 of the 3 secondary outcomes. In addition, the prevalence of IUGR in obese pregnant women was higher than in pregnant women with normal nutritional status (3.53% vs. 1.81%), however, the sample size did not allow us to show that this was statistically significant.

Another prospective cohort study of more than 80,000 Norwegian pregnant women in which preconception nutritional status was analyzed by BMI or Quetelet index, showed that the risk of preterm birth was higher in mothers with preconception obesity (OR 2; 95% CI 1.4-2.7)[27]. These results are similar to those obtained in a cohort of more than 60,000 Danish women which showed that pregestational obese women according to BMI or Quetelet's index, had a 1.5 risk ratio for spontaneous preterm birth with premature rupture of membranes compared with mothers with normal nutritional status[28].

In a Swedish cohort study[20] that included 1,857,822 pregnant women and their children, an OR of 2.71 was observed for the association between gestational obesity diagnosed according to the Quetelet index at the first prenatal visit before week 12 and preterm delivery, similar to that observed in our study. In a meta-analysis[29] on pregestational BMI and preterm delivery that included 39 studies (3 case-control studies and 36 cohort studies) with 1,788,633 pregnant women with preconception obesity and their child, it was observed that the association between these two variables was not statistically significant, but when analyzing by subgroups, patients with grade II and III preconception obesity are at higher risk of having preterm deliveries (OR 1.3; 95% CI: 1.1- 1.5 and OR 1.8; 95% CI 1.6-1.07, respectively).

Table 2. Variables of maternal morbidity and way of birth in pregnant women with normal nutritional status and obese pregnant women at the Hospital Universitario de Santander and Clínica Materno Infantil San Luis between January 2019 and March 2020

Variable; n and (%)	Nutritional status of the pregnant woman		p
	Normal (n = 276)	Obese patients (n = 283)	
Gestational diabetes	14 (5.07)	40 (14.1)	< 0.001
Pregestational diabetes	2 (0.7)	4 (1.4)	0.35
Hypertensive disorder associated with pregnancy	19 (6.8)	68 (24.0)	< 0.001
• Preeclampsia	10 (3.6)	27 (9.5)	
• Eclampsia	2 (0.7)	7 (2.4)	
• Chronic hypertension	4 (1.4)	29 (10.2)	
• Gestational hypertension	3 (1.0)	5 (1.7)	
• Without hypertensive disorder	257 (93.1)	215 (75.9)	
Premature rupture of membranes	6 (2.1)	20 (7.0)	0.006
Caesarean section	143 (51.8)	160 (56.5)	0.15

Table 3. Perinatal outcomes of pregnant women with normal nutritional status and obese pregnant women at the Hospital Universitario de Santander and Clínica Materno Infantil San Luis between January 2019 and March 2020, analysis adjusted for confounding variable and analysis by subgroup of pregnant women without comorbidities

Perinatal outcomes

Variable; n and (%)	Nutritional status of the pregnant woman: Normal (n = 276)	Obese (n = 283)	RR (IC 95%)	RRa* (IC 95%)	*p*
General preterm (< 37 weeks)	18 (6.5)	45 (15.9)	2.4 (1.4-4.1)	2.5 (1.4-4.2)	0.001
Late preterm (34-36.6 weeks)	15 (83.3)	40 (88.8)			0.41
Premature < 34 weeks	3 (16.6)	5 (11.2)			
Hypoglycemia	3 (1.0)	22 (7.7)	7.1(2.1-23.6)	7.1 (2.1-23.7)	0.001
Large for gestational age	9 (3.2)	62 (21.9)	6.7 (3.4-13.2)	6.6 (3.3-13.1)	< 0.001
IUGR	5 (1.8)	10 (3.5)	1.9 (0.6- 5.6)	2.1 (0.7-6.1)	0.159

Perinatal outcomes in pregnant women without diabetes or hypertensive disorder

Variable; n and (%)	Nutritional status of the pregnant woman: Normal (n = 243)	Obese (n = 184)	RR (IC 95%)	RRa (IC 95%)	*p*
Preterm (< 37 weeks)	13 (5.3)	24 (13)	2.4 (1.2-4.6)	2.4 (1.2-4.6)	0.001
Hypoglycemia	2 (0.8)	10 (5.4)	6.6 (1.4-29.7)	6.6 (1.4-30.1)	0.001
Large for gestational age	8 (3.2)	32 (17.3)	5.2 (2.4 -11.1)	5.2 (2.4 -11.1)	< 0.001
IUGR	3 (1.2)	8 (4.3)	3.5 (0.9-13.0)	3.5 (0.9-13.3)	0.12

RRa: Relative risk adjusted for maternal age, defined as a confounding variable. IUGR: Intrauterine growth restriction

This study analyzed gestational obesity using the Rosso-Mardones curve in a general category, finding that obese pregnant women are at 2.5 times higher risk of preterm delivery than pregnant women with normal nutritional status. It was considered that these results may be related to the theory that the proinflammatory state is greater in pregnant women who quickly gain weight than in those who are chronically obese with mature adipocytes[11].

The literature considers that a sequence of events within the context of metabolic imprinting, including gestational diabetes and hypertensive disorders associated with pregnancy, is necessary for obese pregnant women to present more frequently with adverse outcomes such as preterm delivery, however, in this study, it was shown that this sequence of events was not necessary to find statistically significant associations between obesity and adverse neonatal outcomes (Table 3)[30,31]. This supports the lipoinflammation theory in which hyperplasia and dysregulation in adipose tissue can cause endothelial injury and malperfusion, favoring the appearance of unfavorable outcomes, even without activation of the metabolic syndrome pathway and other comorbidities[11,15].

Table 4. Causes of preterm birth in pregnant women with normal nutritional status and obese pregnant women at the Hospital Universitario de Santander and Clínica Materno Infantil San Luis between January 2019 and March 2020

Preterm birth cause; n and (%)	Nutritional status of the pregnant woman: Normal (n = 18)	Obese patients (n = 45)
PL without infection	13 (72,2)	32 (71,1)
Preeclampsia	3 (16,6)	8 (17,7)
PROM + oligohydramnios	0	2 (4,4)
IUGR	1 (5,5)	1 (2,2)
Placenta Accreta	0	1 (2,2)
Intrahepatic cholestasis	0	1 (2,2)
Maternal cholecystitis	1 (5,5)	0

PL: Preterm Labor. PROM: Premature rupture of membranes. IUGR: Intrauterine growth restriction

The precise moment at which pregnant women became obese is not known since, in Colombia, there are no unified prenatal checkups records that allow identifying this information. In other countries, there are standardized databases that store the most relevant information on pregnancies, which makes it possible to identify preconception nutritional states and to follow up anthropometric parameters throughout the pregnancy, regardless of whether the mother visited different health institutions[20]. It is essential to prioritize the establishment of similar systems that allow this type of analysis in this country.

Among the strengths of this study is that it is a prolective cohort study and the sample size allowed us to find significant associations for three of the four outcomes studied. Another great strength is that it was carried out in two highly complex institutions that care for pregnant women in Northeastern Colombia, where there were unified protocols for weighing and measuring patients with the same measuring instruments that were adjusted and supervised throughout the collection of the sample. Additionally, we found that both the population of obese pregnant women and those with normal nutritional status presented comparable sociodemographic variables.

This study sets an important precedent that broadens the analysis of the behavior of obese pregnant women in Northeastern Colombia; in addition, it allowed finding associations that agree with the pathophysiology and the theory of lipoinflammation as triggers of chronic proinflammatory states and malperfusion during gestation, which had been difficult to demonstrate in other studies.

We suggest future lines of research through experimental designs to determine the causality between the maternal inflammatory status of obese mothers and the occurrence of preterm delivery, to finally approach therapeutic targets to decrease fat-induced inflammation and its adverse outcomes, combined with the promotion of solid and well-structured programs for the prevention of obesity and excessive weight gain in pregnancy.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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