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No effect of a low dose of omega-3 on the lipid profile of pregnant women with obesity: a randomized trial

Nenhum efeito de uma dose baixa de ômega-3 no perfil lipídico de gestantes obesas: um ensaio clínico randomizado

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ABSTRACT

Objective: Evaluate the lipid profile, fasting blood glucose, Body Mass Index (BMI) and weight gain of pregnant women with obesity and the effect of a low dose (1,1 g/day) of omega-3 on these parameters. **Methods:** A randomized clinical trial was performed from May 1st, 2019 to October 31th, 2022 with pregnant women diagnosed with obesity by arrival BMI ≥ 30.0 kg/m^2. The participants were randomized into two groups: omega-3 and control. All pregnant women received standard prenatal follow-up and the same diet and physical exercise instructions. Laboratory tests were performed at three different times: first moment with gestational age (GA 12-20 weeks), second (GA 24-28 weeks) and third (GA 32-34 weeks) measuring maternal serum levels of glucose, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides (TG) as well as weight gain and BMI were monitored. **Results:** A total of 172 pregnant women with obesity were evaluated. Of these, 87 (50.6%) composed the control group and 85 (49.4%) the omega-3 group. There was no difference of lipid profile, fasting blood glucose, BMI and weight gain values between groups during the 1st, 2nd and 3rd evaluation moments. **Conclusion:** Low dose (1,1 g/day) of omega-3 showed no effect on the lipid profile, fasting blood glucose, BMI and weight gain in pregnant women with obesity in omega-3 group during the evaluation moments.

Keywords: Pregnancy; Triglycerides; Omega-3; Obesity; Glucose

RESUMO

Objetivo: Avaliar o perfil lipídico, glicemia de jejum, Índice de Massa Corporal (IMC) e ganho de peso de gestantes obesas e o efeito de uma dose baixa (1,1 g/dia) de ômega-3 sobre esses parâmetros. **Métodos:** Foi realizado um ensaio clínico randomizado de 1º de maio de 2019 a 31 de outubro de 2022 com gestantes diagnosticadas com obesidade através do IMC de chegada ≥ 30,0 kg/m^2. As participantes foram randomizadas em dois grupos: ômega-3 e controle. Todas as gestantes receberam acompanhamento pré-natal padrão e as mesmas orientações de dieta e exercícios físicos. Os exames laboratoriais foram realizados em três momentos distintos: primeiro momento com idade gestacional (IG 12-20 semanas), segundo (IG 24-28 semanas) e terceiro (IG 32-34 semanas) medindo os níveis séricos maternos de glicose, colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos (TG), assim como o ganho de peso e o IMC foram monitorados. **Resultados:** Foram avaliadas 172 gestantes com obesidade. Dessas, 87 (50,6%) compuseram o grupo controle e 85 (49,4%) o grupo ômega-3. Não houve diferença de perfil lipídico, glicemia de jejum, IMC e valores de ganho de peso entre os grupos durante o 1º, 2º e 3º momentos de avaliação. **Conclusão:** Baixa dose (1,1 g/dia) de ômega-3 não apresentou efeito sobre o perfil lipídico, glicemia de jejum, IMC e ganho de peso em gestantes obesas do grupo ômega-3 durante os momentos de avaliação.

Palavras-chave: Gestação; Triglicerídeos; Ômega-3; Obesidade; Glicose.

INTRODUÇÃO

Obesity is one of the great epidemics of this millennium, being considered a public health problem by the World Health Organization (WHO) (BRASIL, 2010). It is a chronic disease with multiple systemic complications, some of which result in severe organ and tissue deficiency, thus triggering other pathologies such as hypertension, diabetes, cardiovascular disease and cancer (CESARE, 2016; MAFORT et al., 2016).

In Brazil, cases of obesity have been growing in recent decades. In 1975 there were 1.9 million obese women, in 2014 it increased to 18 million (CESARE, 2016). The number of women affected by this public health problem increases in large proportion, especially in women of reproductive age (KAMPMANN et al., 2015). Maternal obesity during pregnancy is associated with the development of Gestational Diabetes Mellitus (GDM), the occurrence of hypertensive diseases, cardiovascular complications, thromboembolic events, cesarean sections and surgical complications during childbirth (VERNINI et al., 2016).

The maternal diet, in the prenatal period, is of great importance, as it determines the type of fatty acid that will accumulate in the fetal tissue (GONZÁLES, 2002). The transport of essential fatty acids (EFA), such as omega-3 (ω-3), takes place through the placenta, being deposited in the brain and retina of the conceptus (GAETE; ATALAH; ARAYA, 2002). The ω-3 fatty acids are so named because they have their first double bond on carbon 3 from the methyl radical of the fatty acid, and are found in large quantities in the oils of marine fish, such as sardines, salmon, tuna, herring, anchovies, algae seaweeds and in the oils and seeds of some vegetables, such as linseed (VALENZUELA; NIETO, 2001). The most researched and that have greater health

benefits are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present mainly in fish oils (HORNSTRA, 2002).

Considering the fetus does not have the ability to synthesize long-chain polyunsaturated fatty acids (LC-PUFA) through its precursors, such as ω-3, and this need being met only by the placenta (HOFFMAN et al, 2003), this study aims to contribute to the development of new prevention strategies for maternal-fetal outcomes related to obesity, as well as to provide a great impact on the standard of care in the clinical practice of obese pregnant women, and consequently in promoting the life quality of them.

METHODS

This manuscript derives from a specific objective of the study entitled "Effect of Omega-3 in Obese Pregnant Women on Unfavorable Gestational Outcomes", which began only after the approval of the Univille Research Ethics Committee (REC), according to the Presentation Certificate for Ethical Appreciation (PCEA) - 08488919.0.0000.5366. This study is registered in the Brazilian Clinical Trials Registry (ReBEC), with the code RBR-8nxwps and identification number: U1111-1249-9727. This report followed the recommendations of the Consolidated Standards Reporting Trial (CONSORT) and the requirements of Council Resolution 466/12 of the National Health Department of the Brazilian Ministry of Health, which regulates research involving human beings. The informed consent was obtained for all subjects (SCHULZ; ALTMAN; MOHER, 2010).

This is a randomized clinical trial with a low dose of omega-3 in pregnant women with obesity, which were diagnosed by the arrival BMI $\geq$ 30.0 kg/m^2, according to the IOM, and randomized into two groups: omega-3 and control. Omega-3 was used in the 1,1 g/day dose (13,6% of DHA and 24,9% of EPA), before breakfast.

Data collection was performed at High-Risk Care Service of Darcy Vargas Maternity (MDV), located in the city of Joinville, state of Santa Catarina, Brazil. Sample size was defined for convenience, covering all pregnant women followed-up at the service from May 1st, 2019 to October 31th, 2022 who met the inclusion criteria.

The inclusion criteria were pregnant women with obesity aged 18 years or older, single pregnancy, negative screening for GDM in early pregnancy and gestational age (GA) less than 20 weeks and more than 12 weeks. If pregnant women developed gestational diabetes during the study, they were maintained. In addition, pregnant women shall not present any pathology that would interfere with glucose metabolism, hypersensitivity to omega-3 or major drug allergy, history or presence of liver, renal or gastrointestinal disease, or other condition that interferes with absorption, distribution, excretion, or in the metabolism of the drug. The exclusion criteria were failure to perform any of the research follow-up exams and delivery performed at another service.

All the pregnant women with obesity, at the moment of their arrival, received the same individualized follow-up by MDV multiprofessional team, including nutritionist, physiotherapists and psychologists. Then, all the patients were approached individually by the research team. After this, they started with the medical consultations at High-Risk Care Service and received the same prenatal follow-up according to the basic routine recommended by the Brazilian Ministry of Health.

The dietary guidance given individualized by the nutritionist consisted of small reductions in caloric intake of 24 Kcal/kg/day, the diet being fractionated in five to six meals per day, with daily caloric composition including 40-50% complex carbohydrates with fiber, 20% protein and 30-40% unsaturated fats. The daily calorie distribution was 10-20% at breakfast, 20-30% at lunch, 20-30% at dinner and up to 30% at snacks, including a snack at bedtime to avoid nighttime hypoglycemia. Sequentially, the instructions given by physiotherapists were to take 10 to 30 minutes of regular walking a day, totaling 150 minutes per week, as recommended by The American College of Obstetricians and Gynecologists.

After this, during the researcher's approach, the study was explained to the patients and those who fulfilled the inclusion criteria and accepted voluntarily to participate were assessed through a questionnaire on maternal baseline characteristics. The collected variables were name, age, race, marital status, education status, GA, weight at arrival and height. The diagnosis of obesity was checked by measuring the arrival weight and height through the Welmy® anthropometric balance using the BMI formula [weight (kg) / height (m^2)]. Once included in the study, the randomization was made with a simple draw, in which the women had to choose a role with the word "control" or "omega-3" having equal chances of being allocated to each of the groups. At this same time of arrival, recruitment and allocation, laboratory tests of the lipid profile and fasting blood glucose were requested and a return with the results was scheduled with GA still less than 20 weeks.

During the prenatal follow-up at High-Risk Care Service of MDV the patients had 3 more different moments of meeting with the research team in which they were weighed again and laboratory tests were performed to measure maternal serum levels of lipid profile and fasting blood glucose. The moments were: first (GA 12-20 weeks), second (GA 24-28 weeks) and third (GA 32-34 weeks). The parameters measured were Glucose (GLU); total cholesterol (TC); low density lipoprotein (LDL); high density lipoprotein (HDL); and triglycerides (TG).

To perform this lipid profile and fasting blood glucose analysis, the ADVIA 1800 Siemens® biochemical analysis equipment was used, through the enzymatic/colorimetric method, using the reagents Direct HDL Cholesterol (D-HDL), Cholesterol_2 (CHOL_2), Triglycerides_2 (TRIG_2) and Glucose_2 (GLU_2). From the values of CT, TG and HDL measured, the LDL value was determined using the method suggested by Martin et al (2013).

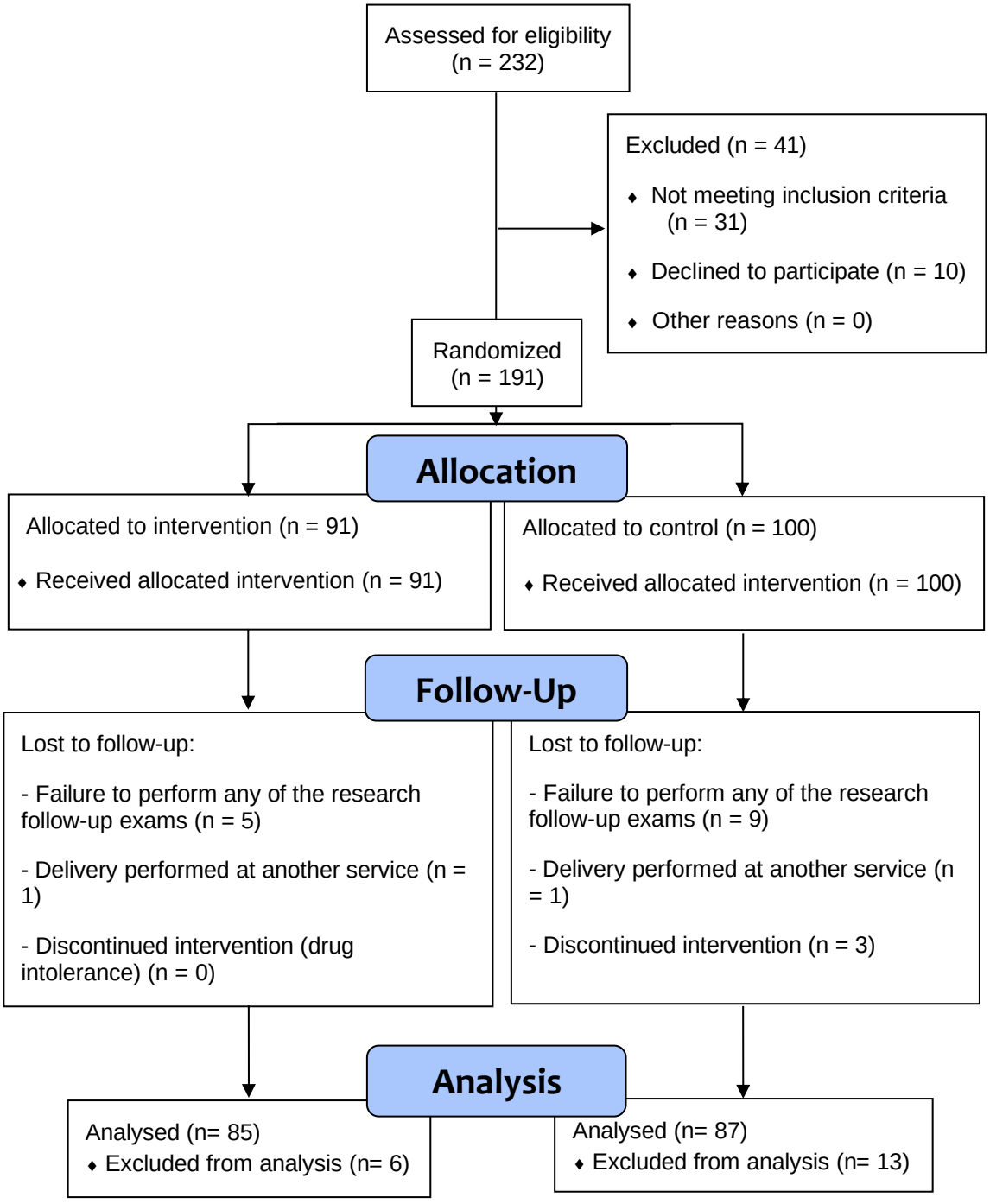
The adherence to diet, physical activity guidance and treatment with omega-3 were checked in each of the moments with the research team through a direct question to the patient. In addition, the medical team of the High-Risk Care Service of MDV that performed the prenatal care of patients was also instructed to question adherence in each of the monthly consultations and write the answer on the patient's electronic medical record. In a final moment, the information collected at each medical consultation was crossed with that collected at each of the moments with the research team in order to obtain the highest degree of reliability possible. Only patients who performed all the proposed interventions for their group in the way they were instructed were considered as adherent.

For statistical, an intention-to-treat analysis was performed including all patients who were randomized and had received the low dose of 1.1 g/day omega-3. The information obtained was analyzed through the software Statistical Package for Social Science (SPSS, IBM Corp., Armonk, NY, US), version 26. Quantitative variables were presented through means and standard deviations and qualitative ones through absolute and relative frequencies. The T-test was applied to compare means, Mann-Whitney U test for medians and Chi-square test for proportions. The distributions of the variables studied were determined from the Shapiro-Wilk test. In all analytical models, $p < 0.05$ was considered significant.

RESULTS

The Basic Health Units from public health system of Joinville referred 232 pregnant women with BMI $\geq$ 30.0 kg/m^2 to the High-Risk Care Service of MDV during the study period. Of these, a total of 172 fulfilled the inclusion criteria and were evaluated in the study. After randomization, we obtained 87 (50,58%) pregnant women in the control group and 85 (49,42%) in the omega-3 group, better described in Figure 1.

Figure 1: Flowchart of participants at each study stage.



Regarding the maternal characteristics, no significant difference in maternal age, race, marital status and schooling between groups was found, according to Table 1. The BMI at arrival median was 34.89 kg/m^2 in the control group whereas in the omega-3 group was 37.6 kg/m^2, which demonstrates that the groups had no difference in the degree of obesity in which they arrived. Consequently, the mean weight at arrival was also similar, showing a difference of 3.87 kg between the groups, without statistical significance. Similarly, the study patients arrived at the service with a mean GA around 19 weeks, which allowed the first moment to assess the

lipid profile and weight to be with GA before 20 weeks and, also, a long follow-up of pregnancy.

Table 1 also shows that, at the control group, 59 (67.8%) pregnant women adhered to the diet and physical exercise, and in the omega-3 group 66 (77.6%), which demonstrates a medium adherence. However, there was no significant difference between the groups.

Table 1: Maternal characteristics

	Global (N=172)	**Control (N=87)**	**Omega-3 (N=85)**	**p value**
Age (mean (SD))	28.9 (6.4)	28.9 (6.2)	29.0 (6.5)	0.968[a]
Race				
White	109 (63.4%)	52 (59.8%)	57 (67.1%)	0.424[b]
Black	12 (7%)	8 (9.2%)	4 (4.7%)	
Other	51 (29.6%)	27 (31%)	24 (28.2%)	
Marital status				
Single	39 (22.7%)	17 (19.5%)	22 (25.9%)	0.601[b]
Married	124 (72.1%)	65 (74.7%)	59 (69.4%)	
Other	9 (5.2%)	5 (5.8%)	4 (4.7%)	
Education				
< 8 years	42 (24.4%)	20 (23%)	22 (25,9%)	0.186[b]
Middle school	15 (8.8%)	6 (6.9%)	9 (10,6%)	
High school	90 (52.3%)	52 (59.8%)	38 (44,7%)	
College	25 (14.5%)	9 (10,3%)	16 (18,8%)	
BMI (median (IQR))				
Arrival	36.73 (6.53)	34.89 (6.19)	37.6 (6.91)	0.503[c]
Weight (mean (SD))				
Arrival	95.41 (15.91)	94.39 (14.64)	98.26 (18.50)	0.535[a]
GA (median (IQR))				
Arrival	19.3 (3.0)	19.5 (2.0)	18.0 (5.0)	0.165[c]
FBG (median (IQR))	82.0 (11.5)	79.5 (12.0)	84.0 (15.25)	0.374[c]
Adherence to diet and physical activity guidance	125 (72,7%)	59 (67,8%)	66 (77,6%)	0.148[b]

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; GA, gestational age; FBG, fasting blood glucose.

Notes: [a]T test; [b]Chi-square; [c]Mann-Whitney U.

Evaluating the lipid profile, fasting blood glucose, BMI and weight gain, in the 1st, 2nd and 3rd evaluation moments and from 1st to 3rd moment, significant differences between groups were not found, according to Table 2 and 3, respectively.

Table 2: Difference of lipid profile, fasting blood glucose, BMI and weight values.

	Control (N=87)	Omega-3 (N=85)	p value
GA (<20 WEEKS)			
FBG (mean (SD))	79.5 (12.0)	84.0 (15.25)	0.374 [a]
TC (mean (SD))	200.72 (19.85)	192.44 (62.30)	0.709 [b]
HDL (mean (SD))	67.35 (12.32)	64.60 (10.41)	0.604 [b]
LDL (mean (SD))	106.70 (21.16)	115.31 (31.76)	0.521 [b]
TG (mean (SD))	154.55 (46.82)	178.10 (56.52)	0.340 [b]
GA (24-28 WEEKS)			
Weight (mean (SD))	100.43 (16.99)	105.36 (19.75)	0.557 [b]
BMI (mean (SD))	38.77 (5.53)	41.16 (6.43)	0.385 [b]
FBG (mean (SD))	83.33 (3.01)	87.14 (8.84)	0.338 [b]
TC (mean (SD))	212.5 (20.64)	209.67 (34.52)	0.866 [b]
HDL (mean (SD))	77.17 (16.34)	64.33 (6.59)	0.105 [b]
LDL (mean (SD))	99.50 (21.59)	114.0 (43.31)	0.509 [b]
TG (mean (SD))	203.17 (76.61)	189.0 (73.62)	0.751 [b]
GA (32-35 WEEKS)			
Weight (mean (SD))	102.1 (13.89)	109.33 (18.5)	0.490 [b]
BMI (median (IQR))	37.4 (11.16)	43.8 (11.46)	0.180 [a]
FBG (mean (SD))	78.00 (7.40)	87.8 (14.04)	0.251 [b]
TC (mean DIA(SD))	238.33 (38.80)	247.0 (7.07)	0.786 [b]
HDL (mean (SD))	74.0 (16.64)	61.5 (6.36)	0.402 [b]
LDL (mean (SD))	131.16 (36.77)	140.5 (13.43)	0.774 [b]
TG (mean (SD))	187.33 (93.28)	208.0 (25.46)	0.789 [b]

Abbreviations: GA, gestational age; TC, total cholesterol; IQR, interquartile range; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; BMI, body mass index; SD, standard deviation; FBG, fasting blood glucose.
Notes: [a]Mann-Whitney U; [b]T Test.

Table 3: Difference of lipid profile, fasting blood glucose, BMI and weight gain values from 1st to 3rd moment.

	Control (N=87)	Omega-3 (N=85)	p-value
GA (20-35 weeks)			
Weight Gain	7.71 (94.39-102.1)	11.07 (98.26-109.33)	0.122
BMI	2.51 (34.89-37.4)	6.2 (37.6-43.8)	0.201
FBG	1.5 (79.5-78)	3.8 (84.0-87.8)	0.462
TC	37.61 (200.72-238.33)	54.56 (192.44-247.0)	0.126
HDL	6.65 (67.35-74)	3.1 (64.60-61.5)	0.795
LDL	24.46 (106.70-131.16)	25.19 (115.31-140.5)	0.308
TG	32.78 (154.55-187.33)	29.9 (178.1-208.0)	0.308

Abbreviations: GA, gestational age; BMI, body mass index; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; FBG, fasting blood glucose.
Notes: [a]Mann-Whitney U; [b]Paired T Test.

DISCUSSION

The development of obesity, especially in adults, is growing exponentially, becoming one of the great challenges for public health in this century, and a worrying factor is the large proportion of women who are obese at the beginning of the gestational period. (GONZÁLES, 2002; GAETE; ATALAH; ARAYA, 2002).

Research shows ω-3 is able to help the lipid profile control and contain inflammatory reactions. In addition, fish consumption and fish oil supplementation can reduce the incidence of premature birth and improve the baby's birth weight, with the content of long-chain polyunsaturated fatty acids (CL-PUFA) in the umbilical cord also correlates directly with the consumption of these fatty acids by the mother. (GONZÁLES, 2002; GAETE; ATALAH, 2003). However, in our study, no significant differences were observed in the lipid profile between the control and omega-3 groups.

At the beginning of the gestational period, increased levels of estrogen and progesterone cause hyperplasia of pancreatic cells, thereby enhancing an insulin response to glucose. (POULAKOS et al., 2015; MCCABE, 2017). But the purpose of this increase is to facilitate lipogenesis and glycogenesis, aiding in greater deposits of glycogen, triglycerides and proteins (MCCANCE, 2015).

Over time, and approaching the second half of pregnancy, the hormone Human Placental Lactogen (HPL), a polypeptide with structure and function similar to growth hormone, produces greater insulin secretion, thus stimulating lipolysis (ALFADHLI, 2015; KAMPMANN et al.,

2015). Due to these physiological changes, in the second trimester of pregnancy, hyperglycemic and counter-insulin factors begin to appear, rapidly increasing blood glucose and, as a consequence, the need for insulin supply, aiming to meet fetal nutritional intake (SILVA et al., 2014; 4; MCCABE, 2017).

In the third gestational trimester, the greatest change in blood glucose occurs due to the high use of glycogen (KAMPMANN et al., 2015; POULAKOS et al., 2015). Therefore, pregnant women with limited pancreatic insulin reserves develop gestational diabetes (MCCANCE, 2015). Several factors are related to the mechanisms of insulin resistance, such as age, obesity, lifestyle, family history, genetics and changes in cell receptors (ALFADHLI, 2015; SENAT; DERUELLE, 2016).

A study carried out with forty-four patients with type 2 diabetes divided into two groups (group A received 4 g/day of omega-3 in the form of gelatin capsules and group B received a placebo for 10 weeks), demonstrated that supplementation with ω-3 in type 2 diabetic patients improved insulin sensitivity, probably due to the decrease in the concentration of non-esterified fatty acids (NEFA) (DJAZAYERY et al, 2014). In our study, no significant differences in fasting blood glucose were observed with 1,1g of ômega-3, between the groups.

According to the IOM 2009 recommendations, ideal weight gain during pregnancy takes into account the patient's pre-conception BMI [19]. However, due to the paucity of data on short and long-term maternal and neonatal outcomes, the IOM recommendation for weight gain during the gestational period is 5 to 9 kg for all women with obesity. The guidelines for gestational weight gain aim to balance the risks of having large for gestational age (LGA) babies, small for gestational age (SGA) babies, preterm births and postpartum weight retention.

In our study, omega-3 use by pregnant women with BMI $\geq$ 30.0 kg/m^2 had no influence on the increase in BMI throughout the three moments, as well as on weight gain. Although both groups of pregnant women demonstrate a medium adherence to the diet and physical exercise, we observed no significant difference between the groups.

The present study had some limitations, such as: the lack of a placebo group and the conducting of the research in a single center.

CONCLUSION

During the first, second and third evaluation moments, control and omega-3 groups showed no significant difference on evaluated parameters.

Given the lack of studies in the literature about the subject and despite our study being one of the first randomized clinical trials that evaluated obese pregnant women with omega-3, our results suggest that low doses of omega-3 to the maintenance of weight gain, BMI, HDL, LDL and TG have no significant results. As well as fasting blood glucose.

The progressive trend of increasing prevalence of obesity among pregnant women is alarming and suggests the need for more efforts in public health intervention for the gestational obesity control (MAFFEIS; MORANDI, 2017). Obesity during pregnancy increases the risk of maternal and fetal complications, thus justifying specific treatment for these patients, before and during pregnancy (MISSION; MARSHALL; CAUGHEY, 2013). However, therapeutic options are limited and studies are needed to optimize prevention and treatment for obese pregnant women.

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