

Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
 Open Access Macedonian Journal of Medical Sciences. 2020 Nov 05; 8(B):1124-1130.
<https://doi.org/10.3889/oamjms.2020.5494>
 eISSN: 1857-9655
 Category: B - Clinical Sciences
 Section: Gynecology and Obstetrics



Probiotics May Improve Serum Folate Availability in Pregnant Women: A Pilot Study

Andrea Ballini^{1,2}, Luca Signorini³, Alessio Danilo Inchingolo⁴, Rajiv Saini^{4,5}, Antonio Gnoni⁶, Salvatore Scacco⁶, Stefania Cantore⁴, Gianna Dipalma⁴, Francesco Inchingolo⁴, Luigi Santacroce^{5,7*}

¹Department of Biosciences, Biotechnologies and Biopharmaceutics, Campus Universitario "Ernesto Quagliariello", University of Bari "Aldo Moro", Bari, Italy; ²Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy; ³Departmental Faculty of Medicine and Surgery, Unicamillus University, Rome, Italy; ⁴Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy; ⁵Department of Ionian, School of Medicine, University of Bari "Aldo Moro", Bari, Italy; ⁶Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, Bari, Italy; ⁷Department of Clinical Disciplines, School of Technical Medical Sciences, "A. Xhuvani" University, Elbasan, Albania

Abstract

BACKGROUND: Probiotics are living microorganisms that confer a health benefit when administered in adequate amounts. There is evidence in the current literature about the importance of probiotic use in pregnancy. The early supplementation of probiotics in the perinatal and postnatal periods seems to have a positive impact on the overall mother's health and future health of infants.

AIM: Our pilot study aimed to test the ability of specific probiotics strains in combination with the kiwi-unique enzyme actinidin to improve the availability of folic acid in 20 pregnant women.

METHODS: We investigate 20 pregnant women in early (4–10 weeks) (6 patients), intermedium (11–20 weeks) (6 patients), and late (21–30 weeks) (8 patients) pregnancy.

RESULTS: Our findings show that the tested formula promotes increased concentration of serum folate in women's blood and contributes to the control of blood sugar and body weight, regardless of the gestational period (early, intermediate or late).

CONCLUSIONS: Our data support the main results reported in the scientific literature about the importance of probiotics intake in pregnancy.

Edited by: Slavica Hristomanova-Mitkovska

Citation: Ballini A, Signorini L, Inchingolo AD, Saini R, Gnoni A, Scacco S, Cantore S, Dipalma G, Inchingolo F, Santacroce L. Probiotics May Improve Serum Folate Availability in Pregnant Women: A Pilot Study. Open Access Maced J Med Sci. 2020 Nov 05; 8(B):1-7. <https://doi.org/10.3889/oamjms.2020.5494>

Keywords: Probiotics; Folate; Folic acid; Glycemia; Weight; Pregnancy

***Correspondence:** Luigi Santacroce, Department of Ionian, Microbiology and Virology Lab, University Hospital of Bari, 70124 Bari, Italy. E-mail: luigi.santacroce@uniba.it

Received: 01-Oct-2020

Revised: 18-Oct-2020

Accepted: 26-Oct-2020

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interest exists

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Introduction

Breast milk is known to be the best form of nutrition for newborns, especially for those born preterm. Variation in the composition of fatty acids in infant feeding can influence the microbial composition of the gut. The use of prebiotics and probiotics to stimulate gut microbial composition is increasingly compelling evidence [1].

The prevalence of allergies in newborns is about 10%, but it can reach 20–30% in those with a first-degree allergic relative [2], [3]. Prebiotics promote particular changes in the gastrointestinal microflora, regard composition and activity [4]. They influence immune response, and their supplementation has been proposed as a way to prevent allergic diseases but also of a different nature, as in the case of oncological diseases [2], [3], [4]. Preterm birth is the main cause of death in newborns; moreover, it represents a risk factor

for adverse health outcomes: Nutritional approaches are a promising solution; among them, the use of zinc-folic acid, combined iron-folate, and probiotics [5].

Numerous studies in the literature confirm that the nutrition of women in pregnancy and especially during breastfeeding influences the growth, development, and health of the baby in intrauterine and extrauterine life [6]. According to the latest data, poor nutrition during pregnancy can lead to spontaneous abortion or to a premature birth [7].

The first evidence of the importance of probiotic use in pregnancy was found on blood glucose values. Laitinen *et al.* [7] compared three intervention groups in a Finnish population of 256 pregnant women. The different groups followed three different models of nutrition: The first group followed a specific diet with probiotics, a second group a diet with a placebo effect, and a third and last control group followed a single and unique placebo diet. Women received the probiotic supplementation, containing *Lactobacillus* and *Bifidobacterium*, from the

early period to the postpartum period: In the test group, the normal diet supplemented with the use of probiotics had significantly reduced blood sugar values in the third trimester and consequently showed an improvement in insulin sensitivity [8]. Similarly, probiotics appear to show antioxidant properties as an iron-reducing activity in pregnant women [9].

The use of probiotics helps to maintain intestinal eubiosis and to control metabolic and immune changes, including the prevention of pathological situations both for the mother and the infant [10].

Our pilot study aimed to assess the benefits of the ability of specific probiotics strains in combined formula with the kiwi-unique enzyme actinidin to improve the availability of folic acid in pregnant women.

Materials and Methods

Participants

The Institutional Ethics Committee of the Faculty of Technical Medical Sciences of Elbasan "ALEKSANDËR XHUVANI" has approved the application to conduct the clinical trial in the Faculty. Title of the Protocol: Probiotics efficacy and safety in humans. Protocol identification: INTL_ALITCOOP/Probiotics/INRES2019_w/a/c.

The study was carried out according to the Helsinki declaration and informed written consent was obtained from all the subjects.

Folate and folic acid intakes of 20 pregnant women were assessed in early (4–10 weeks) (6 patients), intermedium (11–20 weeks) (6 patients), and late (21–30 weeks) (8 patients) pregnancy. Blood concentrations of folate and unmetabolized folic acid were measured with the use of immunoassays and liquid chromatography-mass spectrometry, respectively, in maternal samples in early, intermedium, and late pregnancy. Participants did not take antibiotics for ≥ 3 months before participating in the study. Furthermore, participants did not take drugs or food supplements (e.g., folate-rich foods) that could influence the dependent variables; a health history questionnaire was provided from investigators. Prebiotic/probiotic foods (e.g., yogurt) have not been included in their diet. Participants were able to consume 450 g/day (~16 fl. oz./day) of black coffee with caffeine or unsweetened black tea if used to consuming them regularly.

Targeted probiotic strains (TPS) specifically chosen for the support they can provide to pregnant and breastfeeding moms such as encouraging nutrient absorption, supporting the production of natural (non-synthetic) folate, and breastfeeding and immune system support: *Bifidobacterium infantis*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus*

fermentum, *Lactobacillus reuteri*, and *Lactobacillus acidophilus* in combination with the kiwi-unique enzyme actinidin (Kiwifruit Powder). The formula containing 5 Billion colony forming units† (CFUs) per BIO-tract® tablet, which is equivalent to 75 Billion CFU of probiotic veggie capsules. Moreover, the Kiwifruit Powder is a whole food that helps patients' probiotics colonize and naturally supports regularity, a common concern during pregnancy.

Experimental design

The tested formula (PRO-MOM Hyperbiotics, USA) contains six TPS specifically chosen for the support they can provide to pregnant and breastfeeding moms such as encouraging nutrient absorption, supporting the production of natural (non-synthetic) folate, and breastfeeding and immune system support: *B. infantis*, *L. rhamnosus*, *L. plantarum*, *L. fermentum*, *L. reuteri*, and *L. acidophilus* in combination with the kiwi-unique enzyme actinidin (Kiwifruit Powder). The formula containing 5 Billion CFUs† per BIO-tract® tablet, which is equivalent to 75 Billion CFU of probiotic veggie capsules. Moreover, the Kiwifruit Powder is a whole food that helps patients' probiotics colonize and naturally supports regularity, a common concern during pregnancy.

A randomized, double-blind, and placebo-controlled parallel-group investigation was applied for this study. After completing baseline measures, the participants were divided by age and month of pregnancy and randomized into one of two groups: integration with PRO-MOM Hyperbiotics, USA (1 tablet per day) (test group) or without probiotic administration (placebo group). Measurements of key outcome variables (body weight) were performed at baseline (T0) and after the 8-week treatment period (T1) within each of the three groups (early, intermediate, and late – pregnancy). All measurements were taken between 7:00 am and 11:00 am. Blood was collected at baseline and after 8 weeks of treatment for glycemic control and serum folate status.

Statistical analysis

Outcome measures were analyzed with a t-test for paired samples for pre-post differences with time as the factor using (Statistical Package for the Social Sciences for Windows, Version 11.5, Chicago, Ill) software to detect significant differences between pre-test and post-test scores.

Results

Furthermore, on the first visit, the participants were instructed on the objectives and methods of

clinical trials. Subjects who agreed to participate in the study, after having signed the informed consent, were randomly included and divided into two groups: A test group using probiotics, instead, the other group of a placebo, without probiotics.

Twenty people were enrolled as follows:

- a. Placebo group: 3 early, 3 intermedium, and 4 late
- b. Test group: 3 early, 3 intermedium, and 4 late.

Folate values

Serum folate concentration was measured in the placebo group and test group at T0 and T1. Laboratory values were carefully analyzed and reported in Table 1.

Table 1: Blood concentration of folate in the placebo group and test group at T0 and T1.

Blood concentration of folate: Placebo group				Blood concentration of folate: Test group			
ID	Pregnancy period	T0 (ng/ml)	T1 (ng/ml)	ID	Pregnancy period	T0 (ng/ml)	T1 (ng/ml)
EA	Early	5.5	7.3	MM	Early	7	10
CB	Early	6	8.8	AC	Early	7.8	10.1
FG	Early	7.3	9	PA	Early	6.2	9.1
IM	Intermedium	9.9	11.5	FV	Intermedium	11.9	13.9
MT	Intermedium	11	12.9	ACC	Intermedium	10	12.7
RR	Intermedium	12.7	13.9	BG	Intermedium	11	14
SA	Late	16	18.1	KL	Late	17	19.8
FT	Late	15.3	16.8	VF	Late	18	21
MTO	Late	18	20	DC	Late	16.5	19.7
FP	Late	16.9	19.2	ST	Late	19	21.8

Moreover, serum folate values were evaluated at time T0 and T1 in placebo group and test group.

As shown in Figure 1a, the trend of serum folate values was evaluated at time T0 and T1 in the placebo group. The results showed an increasing trend of around 16% from baseline to T1, since during the gestation period, folate levels increase, linked to the supplements that pregnant women usually implement in their diet.

In Figure 1b, the trend of serum folate values was evaluated at time T0 and T1 in the test group. The results showed a variation of blood folate levels from T0 to T1 in the test group. It should be noted that the data present at time 0 increased by about 22% at T1, a

substantial increase compared to the conditions of the placebo.

In both groups, the T0 values are included in the standard ranges, which vary according to the gestation period: In the early period, folate values are slightly lower than in the intermediate and late one. Therefore, the resulting data show how prebiotic intake has been able to favor a greater increase in blood folate values.

Glycemia values

Blood glucose concentration was measured in the placebo group and test group at T0 and T1 and reported in Table 2.

Table 2: Glycemia in the placebo group and test group at T0 and T1

Glycemia: Placebo group				Glycemia: Test group			
ID	Pregnancy period	T0 (mg/d)	T1 (mg/dL)	ID	Pregnancy period	T0 (mg/dL)	T1 (mg/dL)
EA	Early	69	68.9	MM	Early	67	65.3
CB	Early	70	71	AC	Early	78	76
FG	Early	71	70	PA	Early	77.9	76
IM	Intermedium	67	66.8	FV	Intermedium	67.9	65.5
MT	Intermedium	65	66	ACC	Intermedium	81	79.1
RR	Intermedium	80	78.8	BG	Intermedium	79.9	77
SA	Late	79	78.5	KL	Late	83.4	82
FT	Late	76.4	77.7	VF	Late	73	72
MTO	Late	78	78	DC	Late	75.7	73
FP	Late	87.1	86.7	ST	Late	82.3	80.4

Glycemia values were also evaluated at time T0 and T1 in placebo group and test group.

As shown in Figure 2a, the glucose concentration (mg/dL) does not vary substantially from T0 to T1 in the placebo group: The two lines overlap in the graph. Moreover, the obtained values are all lower than 92 mg/dL, which underlines the good health condition of women enrolled in T0 that is also maintained at T1.

As shown in Figure 2b, the glucose concentration (mg/dL) slightly varies from baseline to T1 in the test group after taking the probiotics: T1 values are 2.5% lower than T0, which allows us to say that taking probiotics could help to control blood

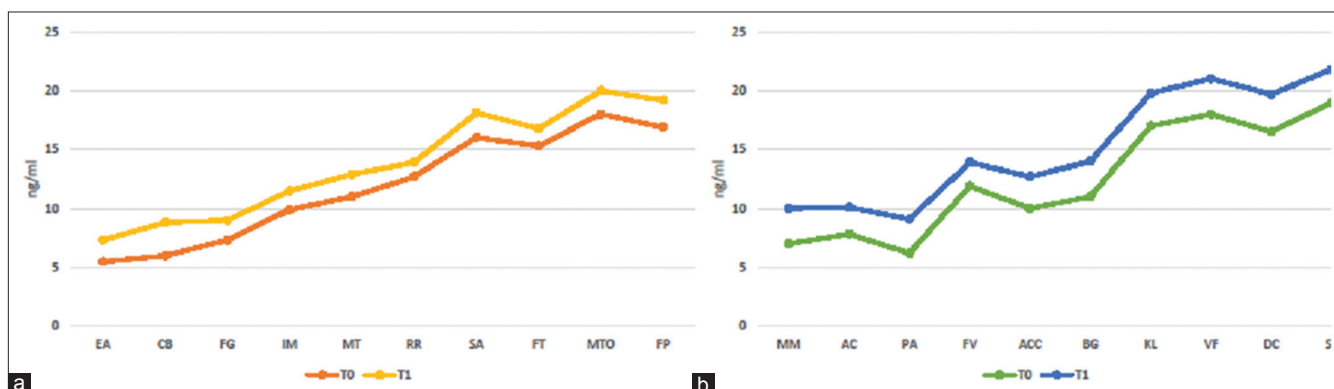


Figure 1: Serum folate concentration (ng/ml) at time T0 and T1 in placebo group and test group: (a) This graph shows the trend of serum folate values at time T0 and T1 in the placebo group. There is an increasing trend from baseline T0 to T1 of around 16%; (b) the graph shows how blood folate levels vary from T0 to T1 in the test group. It should be noted that T0 values increase by about 22% at T1 that is a substantial increase if compared to the placebo one. The results show that the probiotic intake promotes the increase of folate values in the blood

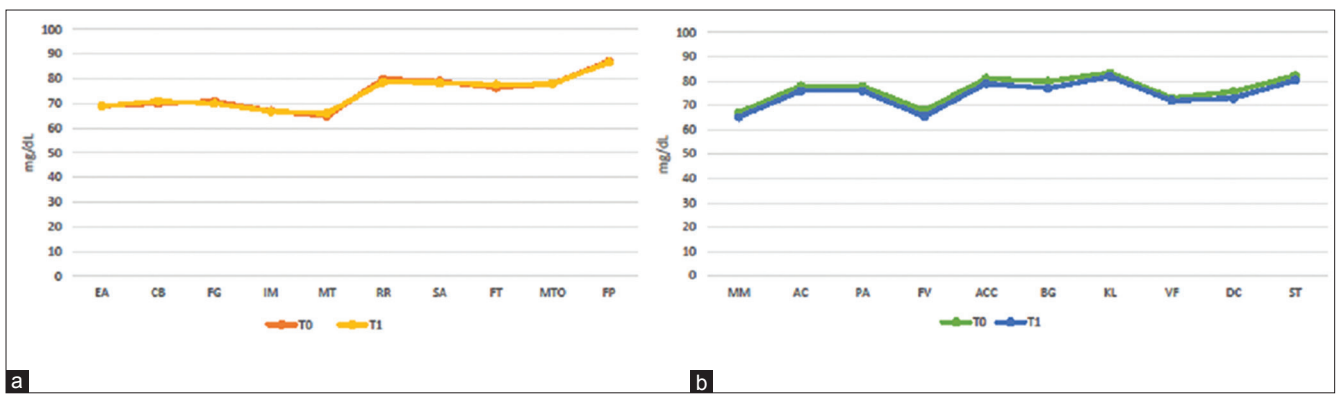


Figure 2: Blood glucose concentration (mg/dL) at time T0 and T1 in placebo group and test group: (a) The graph shows the glucose values in T0 and T1 in the placebo group: The two lines overlap and the trend of the graph is linear as there are no differences in the values; (b) the graph shows the glucose values in T0 and T1 in the test group: Glycemia varies from baseline to T1, reducing of 2.5% that is a great result to say that taking probiotics could help to control glycemia

glucose concentration; moreover, it could be a way to prevent gestational diabetes.

Weight values

Weight values were measured in the placebo group and test group at T0 and T1. Data were carefully analyzed and reported in Table 3.

Table 3: Weight in the placebo group at T0 and T1

Weight: Placebo group				Weight: Test group			
ID	Pregnancy period	T0 (kg)	T1 (kg)	ID	Pregnancy period	T0 (kg)	T1 (kg)
EA	Early	65	67	MM	Early	54	55.1
CB	Early	52	54.6	AC	Early	59	60.1
FG	Early	59.4	61.9	PA	Early	70	72
IM	Intermedium	51.5	53.7	FV	Intermedium	56	57.3
MT	Intermedium	56	59	ACC	Intermedium	67	68.4
RR	Intermedium	63.6	67	BG	Intermedium	65	66.9
SA	Late	53.9	55.8	KL	Late	53	55
FT	Late	61.6	64.2	VF	Late	56.8	58
MTO	Late	59	61.9	DC	Late	64.1	65.8
FP	Late	70	71.8	ST	Late	54.9	56

Weight values were evaluated at time T0 and T1 in placebo group and test group.

As shown in Figure 3a, weight values slightly vary from baseline to T1 in the placebo group: There is a normal weight gain of 4% from T0 to T1 due to the physiological increase during pregnancy.

As shown in Figure 3b, weight values slightly vary from baseline to T1 in the test group: There is an increase of 2.5% from T0 to T1, which is a minimum increase if compared to the placebo group. This result allows us to underline that the use of probiotics is also useful for weight monitoring, an important factor to safeguard fetus health.

Discussion

It is well known that imbalances in the intake of macronutrients and micronutrients during pregnancy can alter the growth and development of the fetus,

predisposing it to the risk of pathologies in recent and future times [10], [11]. According to a review conducted on Cochrane, from Haider and Bhutta, a diet, in pregnant women, enriched with micronutrients with iron and folic acid and with the external integration of prebiotics has resulted in a significant reduction of infants born with low weight but also a reduction equally significant number of infants born premature and/or dead [12]. This is about a 20% lower probability of women giving birth to children who will develop inflammations, atypical diseases compared to those women who do not include the use of probiotics in their diet [13]. On a practical plan, this corresponds to 44 cases of eczema per thousand children. To suggest, it is a study published by Kalliomäki *et al.* in 2007 [14].

A diet during the gestational period and in the 2 months following birth, therefore, during lactation, rich in *L. rhamnosus* and *Bifidobacterium lactis* brings beneficial effects on maternal health, fetal growth, and morbidity of the baby [15]. The same use of probiotics can guarantee, even in part, good bone regeneration and prevent mothers from any pathologies related to bone and dental loss [16], [17], [18]. In fact, in a clinical study involving 208 mother/child couples, particular benefits were found after probiotics intake: There was constant maintenance of body weight in pregnant women, and an increase in length and a reduction in the incidence of diarrhea in the newborn [17].

In a recent study, *L. plantarum* A41 and *L. fermentum* SRK414 showed high probiotic potential and a strong impact on the bone health of pregnant women by modulating the production of pro-inflammatory cytokines and markers related to bone metabolism [18]. In line with even more recent studies, the use of translational researches in regenerative medicine, as well as the use of pharmacological nanotechnologies alongside the consumption of probiotics, can improve bone health in pregnancy by guaranteeing the right supply of calcium and micronutrients [19], [20].

According to a study conducted in 2018 and published by the World Nutritional Journal, Vitamin B12

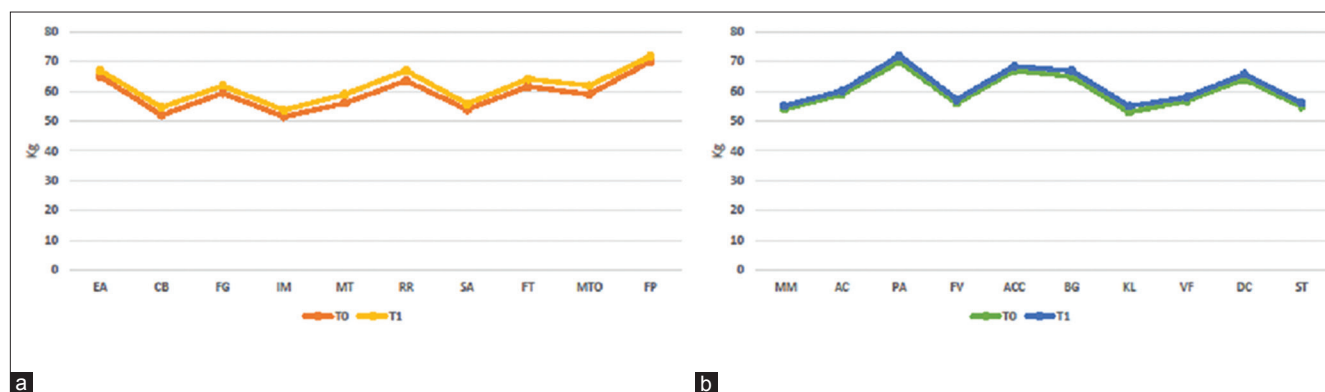


Figure 3: Weight values at time T0 and T1 in placebo group and test group: (a) The graph shows that there is a normal weight gain of 4% from T0 to T1 in placebo group, probably due to the physiological increase in pregnancy; (b) the graph shows the weight trend from T0 to T1 in pregnant women in the test group: Weight varies from baseline to T1, increasing of 2.5%. Compared to the placebo group, this result means that the use of probiotics can help in the weight monitoring of pregnant women

plays an important role in preventing congenital birth defects such as malformations to hydrocephalus and spina bifida [21].

In this randomized clinical study conducted on pregnant women, it has been shown how the intake, in the three gestational quarters, of probiotics increases the serum concentration of Vitamin B12. In particular, by integrating a normal probiotic containing *Bifidobacterium animalis* subsp. *lactis* (HNO19), blood levels of Vitamins B9 and B12 appear to increase in the 2nd and 3rd trimester. The consumption of pre and probiotics during the periconceptional period can be a useful strategy for improving maternal Vitamin B concentrations [22]. The British Journal of Nutrition has published the results of a randomized clinical trial according to which the problem of many pregnant women to develop gestational diabetes could be solved by the use of probiotics. The study was conducted on over 250 pregnant women and the results show a reduction in glucose concentration in women who have followed the diet supplemented with probiotics of approximately 20%. Glucose homeostasis guarantees optimal fetal growth with health implications before and after childbirth, both for mothers and newborns [7].

According to the results of a further study published in the Journal of Diabetes Investigation, in women with gestational diabetes, following a diet supplemented with probiotics for 4 weeks resulted in a reduction in fasting blood sugar and increased sensitivity to insulin. The study was conducted double-blind on 57 women between 24 and 28 weeks of gestation. The participants were divided into two groups; the first group was assigned a diet with probiotics containing bifidobacteria and lactobacilli, while the second group took placebo. Feeding with probiotics for 4 weeks, between the end of the second and the beginning of the third trimester of pregnancy, resulted in positive metabolic changes in favor of fasting blood sugar. In fact, there has been a drop in blood glucose value. Furthermore, these effects were not accompanied by significant differences in weight gain between the two

treatment groups. The authors have consequently shown how integration with probiotics has proven safe and well-tolerated by pregnant women. Kijmanawat *et al.*, therefore, deduced that for women with gestational diabetes, supplementation with probiotics at 24–28 weeks of pregnancy can be considered an additional treatment for glycemic control [23]. In more recent times, the use of pharmacological therapy with the advent of nanotechnologies can also further improve the health of women with gestational diabetes [24]. In recent years, there have been several studies that have focused on the beneficial effects of probiotics in different fields [25], [26], [27], [28], [29], [30], [31], [32], [33], [34].

Conclusions

Based on the resulting data, our clinical study indicates that the supplementing probiotics of PRO-MOM Hyperbiotics USA in the diet of pregnant women would bring numerous benefits to them, regardless of the gestational period (early, intermediate or late). In pregnant women enrolled in our study, taking probiotics favored the increased concentration of folate in the blood and contributed to the control of blood sugar and body weight. Our data confirmed and improved the main results reported in the scientific literature about the importance of probiotics intake in pregnancy.

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