Project summary

Epidemiological and clinical studies show the pregnancy period as a 'window of opportunity' in terms of public health. Although there is a lot of evidence in the literature on the effect of probiotic supplementation on healthy pregnant women, there is a lack of evidence in individuals with gestational diabetes. Medical nutrition therapy is crucial for the increasing prevalence of gestational diabetes.One way to do that is by following the Mediterranean Diet, which has been shown to improve things like reducing inflammation, making insulin work better, controlling blood sugar, and managing weight during pregnancy.In this study with an allocation ratio of 1:1, the participants were divided into two groups: Control group, receiving standard diet compatible with Mediterranean diet (MD) and probiotic supplementation group receiving both the standard diet compatible with MD and probiotic supplementation (Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum and Enterococcus faecium). The participants' sociodemographic data, medical history, pregnancy data, adherence to the Mediterranean diet at 24 and 36 weeks of pregnancy were recorded. Edinburgh Postnatal Depression Scale (EPDS), Pregnancy-Related Anxiety Scale (PrAS), Maternal Antenatal Attachment Scale (MAAS) scales were used. Additionally, sleep problems, stressful events, and sedentary physical activity were added as exclusion criteria to optimize the impact of potential problems on depression. Depression (8.24±2.72; 8.56±2.75) and anxiety scores and weight gain during pregnancy (12.80±2.97; 12.07±2.41) in the group receiving probiotic supplements at the 36th week of pregnancy. p: 0.020) was lower than the control group.Mediterranean diet score was higher in the probiotic supplementation group(32.41±5.07), then control group(29.55±5.13) at week 36 (p: 0.004). Multiple regression analysis was performed to examine the prediction of depression risk based on the scores obtained from the Med-diet (Mediterranean diet) scale. Accordingly, EPDS (β =-.57, p=.001), PrAS (β =-.32, p=.004), and MAAS (β=.78, p=.003) significantly predicted the Med-diet score. A one-unit improvement in the Med-diet score resulted in a decrease of 0.57 units in depression, a decrease of 0.3 units in anxiety and an increase of 0.78 units in maternal attachment in both groups. There is a need for evidence obtained from randomized controlled trials conducted with larger samples to determine effects of probitic supplementation on maternal and fetal longterm mental health.

General İnformation

Probiotic supplementation for maternal depression (ISRCTN96215615, 02/02/2024)

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Rationale & background information

Probiotics were found to have an effect on the immune system, brain development and behavior along with changes in the gut microbiota. The use of probiotics for the treatment of depression and anxiety was first suggested in 1910 [1], and was reviewed in 2015 [2]. The effect of probiotics on mental health has been investigated in various groups [3,4], including the pregnancy period [5]. Probiotics exhibit antidepressant properties in the absence of other therapeutic options.Thus, microbiota-based interventions with probiotics may possess greater therapeutic potential for depression treatment, which can be used as an adjunct to current approaches. However, it is important to note that these benefits are strain-specific. We selected some strains that have already played an effective role in the treatment of depression to illustrate the specific mechanism of its action, clarify its dosage, periodicity, and other key information in the current treatment regimen.

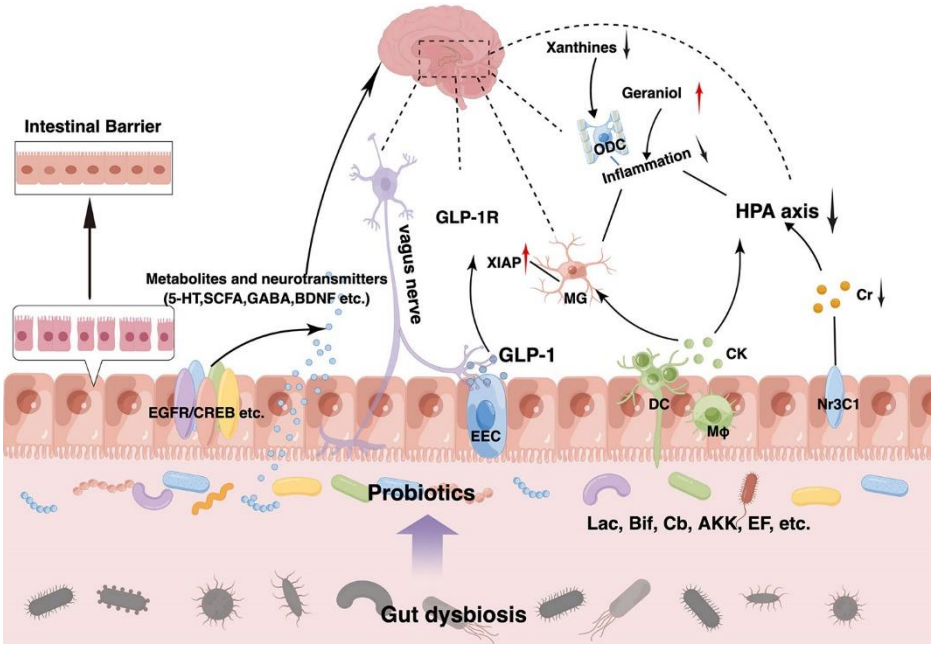

Figure.Therapeutic effects of probiotics on depression and its comorbidities. Probiotics exert antidepressant effects at multiple targets. Supplementation of probiotics can increase beneficial microorganisms and reduce harmful ones to achieve new gut eubiosis. Meanwhile, they can produce beneficial substances such as 5-hydroxytryptamine (5-HT), short-chain fatty acids (SCFAs) and brain-derived neurotrophic factor (BDNF) and so on by themselves or indirectly through upregulation of beneficial microbiota, which can act on various receptors on the intestinal epithelium such as EGFR, CREB, Nr3C1, etc. Moreover, probiotics can enhance intestinal barrier function in a variety of ways, such as upregulating mucus production by goblet cells, enhancing zonula occludens-1 (ZO-1), occludin, and claudin-1 expression, and reducing inflammation. Probiotics can also regulate brain function and improve neurological function through the vagus nerve, glucagon-like peptide-1 (GLP-1) pathway, etc. And it can activate the immune system to produce anti-inflammatory factors, alleviating circulatory inflammation and neuroinflammation while downregulating the hyperactive microglia and hypothalamus-pituitary-adrenal (HPA) axis. Similarly, decreased xanthines levels and elevated geraniol levels can also reduce inflammation.

Objectives, hypothesis and research questions

Our research questions are

1. Does probiotic supplementation affect anxiety, depression and attachment in gestational diabetes?
2. Does compliance with the Mediterranean diet make a difference in gestational diabetes?
3. Does probiotic supplementation affect compliance with the Mediterranean diet in gestational diabetes?

Our hypothesis is

1. Probiotic supplementation affects anxiety, depression and maternal attachment in gestational diabetes.
2. Probiotic supplementation increases compliance with the Mediterranean diet in gestational diabetes.

Aims

1. To investigate the effect of probiotic supplementation on anxiety, depression and maternal attachment in individuals with gestational diabetes.
2. To investigate the effect of probiotic supplements on compliance with the Mediterranean diet in individuals with gestational diabetes.
3. To contribute to the literature by looking at its effect on individuals with gestational diabetes (There are studies on the effects of probiotic supplements on various groups. However, there are no studies on its effect on depression, anxiety and attachment in gestational diabetes..

Study design

This is a single-center randomized controlled trial (parallel groups) designed to investigate the effect of probiotic supplementation on maternal anxiety, depression and antenatal attachment in women with GDM.

With an allocation ratio of 1:1, the participants were divided into two groups: Control group, receiving standard diet compatible with Mediterranean diet (MD), and probiotic supplementation group receiving both the standard diet compatible with MD and probiotic supplementation. The randomization was designed using double-blind randomization. The distribution of the participants was determined by an individual outside the study(Table1).

The participants received intervention as per their groups. The pregnant women were enrolled at 24 weeks of gestation and followed up until the 36th week. The first assessment was conducted at the 24th week of pregnancy. The Mediterranean diet adherence at the 24th week of pregnancy, depression, anxiety and antenatal attachment scales were administered. At the 36th week of pregnancy, the Mediterranean diet adherence, depression, anxiety, and antenatal attachment scales were re-administered. The data obtained from the participants were compared between the groups and between the 24th and 36th weeks of pregnancy.

Diagnosis of gestational diabetes mellitus

Women aged 20-35 years and diagnosed with gestational diabetes as per the International Association of the Diabetes and Pregnancy Study Groups (ADPSG) criteria and an oral glucose tolerance test were included in the study [6].

Intervention

The researcher planned a medical nutrition therapy (MNT) according to GDM, accordance with the Mediterranean diet Enegry requirements were calculated using equations that estimate resting energy expenditure by multiplying the pre-pregnancy weight and height with the physical activity level, as determined by Henry's equations [7]. Because all participants were in the third trimester, 537 kcal was added. The estimated energy requirement was reduced by 30% if the participant was overweight (prepregnancy BMI >25 kg/m2) or achieved the optimal gestational weight gain as recommended by the Institute of Medicine (IOM) [8]. The macro-nutrient components were designed to align with current clinical practices for gestational diabetes. Despite the limited evidence for diet modification in GDM, many centers recommend

a slight reduction in carbohydrates and a slight increase in protein for satiety [9]. In this study, the planned intervention included 40% carbohydrates and 25% protein. The higher protein intake at these levels was considered to be in relation with the reduced birth weight [10]. Carbohydrate sources were obtained from low glycemic index food, following the guidelines of the National Institute for Health and Care Excellence (NICE) [11].

The group receiving probiotic supplementation was given products containing Lactobacillus acidophilus (4.3×108 cfu/sachet), Lactobacillus rhamnosus (4.3×108 cfu/sachet), Bifidobacterium bifidum (4.3×108 cfu/sachet), Bifidobacterium longum (4.3×108 cfu/sachet), and Enterococcus faecium (8.2×108 cfu/sachet), as well as prebiotics (fructo-oligosaccharides (FOS) 625 mg, lactulose 400 mg) and vitamins A (6 mg), B1 (1.8 mg), B2 (1.6 mg), B6 (2.4 mg), E (30 mg), and C (75 mg) (NBL Probiotic Gold®, Nobel Pharmaceuticals, Turkey). Each participant receiving probiotics was given 84 capsule (one per day for 12 weeks in total). The researcher instructed all participants to take the probiotics orally on an empty stomach with 100 ml of water and to store them in their original packaging at room temperature (with an aim to equalize the effect of probiotics). The participants were requested to refrain from taking any other probiotics throughout the entire trial period. Additionally, participants were instructed to maintain their current dietary and exercise habits and to avoid consuming yogurt or similar nutritional supplements during the study (they were reminded of this and confirmed at each subsequent visit). Care was taken to ensure that other pharmaceutical drugs remained unchanged throughout the study. [12]. Compliance with probiotic intake was evaluated as an additional outcome.

Diet assessment and adherence to the Mediterranean diet

The impact of the Mediterranean diet on maternal mental health was examined. To assess dietary habits, a food frequency questionnaire and a three-day food record were used[13]. Adherence to the Mediterranean diet was examined in the diet assessments. The MedDiet scoring system was used as the assessment tool. This includes the consumption of unrefined grains (whole bread, pasta, rice, other grains, biscuits, etc.), fruits, vegetables, legumes, potatoes, fish, meat and meat products, poultry, whole fat dairy products (such as cheese, yogurt and milk), olive oil and alcohol intake. The scoring ranges from 0 to 55; however, alcohol consumption was not taken into consideration because it is contraindicated in pregnant women. Therefore, the total score range in this study is from 0 to 50. Higher values of this diet score indicate greater adherence to the Mediterranean diet.

Edinburgh Postnatal Depression Scale

Depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS), an approved tool for screening antenatal and postnatal depressive symptoms [14]. The 10 item EPDS is the most commonly used depression screening tool in perinatal care; cut-off values of 10 or higher and 13 or higher are most often used to identify women who might have depression [15].

Pregnancy-Related Anxiety Scale

Brunton et al. developed the Pregnancy-Related Anxiety Scale (PrAS), a 33-item Likert-type scale in 2018 [16]. Its Turkish validity and reliability study was conducted in 2020 [17].

Maternal Antenatal Attachment Scale

The approved Maternal Antenatal Attachment Scale (MAAS) evaluated the participant's relationship with the fetus. The MAAS consists of 5 items rated on a 19-point Likert scale. An increase in the total score obtained from the scale indicates an increase in maternal attachment[18]. The total scores range from 19 to 95, with higher scores indicating a more adaptive maternal-fetal attachment style. The reliability and validity of the MAAS have previously been structured [19].

Statistical Analysis

The suitability of variables to normal distribution was examined through visual methods (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The mean (x) and standard deviation (SD) were used for the analysis of continuous data. To describe categorical variables, the frequency (n) and percentage (%) values were used. Fisher's exact test and Chi-square test were used to evaluate the relationship between categorical variables. Independent t-test was used to compare the mean scores of two independent groups. Paired t-test was used to compare repeated measurements of the groups at 24 and 36 weeks. Pearson's test was used to assess the correlation with every scale outcome. The statistical significance level was set at $p<0.05$. Statistical analyses were performed using the MedCalc software and www.e-picos.com.

Methodology

Study Phases	First Visit(week 24)	Intermediate Visit (week 30)	Final Visit(week 36)
Signed informed consent	X		
Measuring adherence to the Mediterranean diet	X		X
Scoring of scales[a]	X		X
Analysis of potential problems[b]	X		
Beginning of dietary intervention	X		
Product distribution[c]	X		
Clinical assessment[d]	X	X	X
Diet reminders		X	
Product reminders		X	

To achieve Aim 1: 1.To investigate the effect of probiotic supplementation on anxiety, depression and maternal attachment in individuals with gestational diabetes.

Depression, anxiety and maternal attachment scales were administered to the participant separately at the beginning of the intervention (24th week of pregnancy) and at the end (36th week of pregnancy). It was analyzed whether there were differences in the control group and probiotic group.

To achieve Aim 2: 2.To investigate the effect of probiotic supplements on compliance with the Mediterranean diet in individuals with gestational diabetes

Compliance of the probiotic group and the control group with the Mediterranean diet at the 24th week of pregnancy was analyzed. Compliance with the Mediterranean diet was analyzed again at the 36th week of pregnancy. Differences between the two groups were analyzed.

Safety considerations

The following questions were asked during routine gynecological checks to ensure that the intervention applied during the study did not cause side effects on pregnant women**:**

'Do you have gastrointestinal complaints? (diarrhea, constipation, nausea, etc.)'

'Do you have any problems caused by the probiotics you use?'

In the study, potential risks that were thought to affect mental health parameters were taken under control;

Sleep state; Sleep was measured using the Pittsburgh Sleep Quality Index (PSQI). According to this, a total score of ≤ 5 indicates "good sleep quality", and a score > 5 indicates "poor sleep quality". Patients with low sleep quality were not included in the study [20].

Adverse events; Serious adverse events were recorded throughout the study. In the event of adverse events arising from the study, the related participants were excluded from the study by the physician[21-22].

Physical activity; The aim was to control the impact of physical activity status on both energy balance and mental health. The Pregnancy Physical Activity Questionnaire was administered at the beginning of the study (t1) and pregnant women with sedentary activity (1.5 METs) were not included[23]. Participants with METs values below this value were not included.

Dissemination of results and publication policy

Potential impact and scientific innovation of your proposal to our knowledge, this will be the first study aimed at elucidating the effect of probiotic supplementation on depression, anxiety, and attachment in individuals with gestational diabetes. The rationale behind this study resides in that the potential effects of probiotic on mood may be mediated by several variables potentially involved in gut-to-brain communication. Therefore, the potential impact of this

project will influence the current strategy for mental health, particularly in individuals with gestational diabetes, so that maximum benefit can be achieved from this intervention.The protocol should specify not only dissemination of results in the scientific media, but also improve mental health in individuals with gestational diabetes. It is planned to transfer the study data to the public and medical professionals through training and seminar programs.

Duration of the project

Patient recruitment: 4 months : October 2022- January 2023

Intervention and Monitoring: October 2022- June 2023

Collection of clinical and biochemical data: June-October 2023

Problems anticipated

1. In order to clearly observe the probiotic effect, major differences affecting mental health were taken under control.
2. For dietary compliance, participants were asked to photograph the meals and forward them to the researcher.

Project management

Designed the study;Fatma Bengü Kuyulu Bozdoğan

Conducted the study, analyzed the samples and conducted the statistical analysis:Fatma Bengü Kuyulu Bozdoğan, Seray Kabaran

Wrote the manuscript:Fatma Bengü Kuyulu Bozdoğan, Seray Kabaran, Aybala Tazeoğlu.

All authors contributed to the article and approved the submitted version.

Ethics

This is a randomized controlled trial that is approved by the Ethics Committee of Eastern Mediterranean University (approval date:04.10.2022, approval no: ETK00-2022-0273).

Informed consent forms

The first sign of love in human life comes from the deep bond between mother and baby.

The newborn is dependent on its parents to meet its needs until it becomes self-sufficient.

Therefore, the aim of this study is to make the mother's feelings towards her baby more clear and, accordingly, to help and support the mother in defining her feelings towards her baby. We want you to follow the nutritional and probiotic intervention presented to you in the study completely and completely.

Otherwise, we would like to inform you that we have to remove you from the study.

If you agree to participate in our study, please write your name, surname and today's date in the section below and sign.

Thank you for your interest.

I agree to fill out the relevant survey and scale for the purpose stated above.

DATE

NAME AND SURNAME

SIGNATURE

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