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GESTATIONAL DIABETES AND MICROBIOTA: ROLE OF PROBIOTIC INTERVENTION

A.R.
ARTIGO DE REVISÃO

DIABETES GESTACIONAL E O MICROBIOTA: O PAPEL DA INTERVENÇÃO COM PROBIÓTICOS

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Histórico do artigo:

Recebido a 30 de janeiro de 2018
Aceite a 18 de junho de 2018

ABSTRACT

The number of women with Gestational Diabetes is increasing over the years. The microbiota has been related to energy regulation, immune function and metabolic disorders, such as insulin resistance. It is essential to understand the changes in the gut, placental and vaginal microbiota during pregnancy and the impact this may have on mother and fetus health. Supplementation with probiotics appears to be an effective strategy in the prevention and treatment of Gestational Diabetes and weight gain. Studies shown that probiotic intake improves maternal glucose tolerance and insulin sensitivity. This review intends to shed some light on the influence of gut, placental and vaginal microbiota on Gestational Diabetes and the role of probiotics intervention.

KEYWORDS

Gestational Diabetes, Microbiota, Pregnancy, Probiotics

RESUMO

O número de mulheres com Diabetes Gestacional tem vindo a aumentar. A microbiota tem sido associada à regulação energética, função imunológica e doença metabólica, como a resistência à insulina. É essencial compreender quais as mudanças que ocorrem no microbioma do intestino, da placenta e da vagina durante a gravidez e qual o impacto que essas mudanças podem ter sobre a saúde da mãe e do feto. A suplementação com probióticos parece ser uma terapia eficaz na prevenção e tratamento da Diabetes Gestacional e do ganho de peso. Estudos demonstram que a ingestão de alimentos ricos em probióticos melhora a tolerância à glicose e a sensibilidade à insulina das grávidas. Esta revisão apresenta evidência sobre a influência que a microbiota intestinal, placentária e vaginal têm sobre a Diabetes Gestacional e qual o papel da intervenção com probióticos.

PALAVRAS-CHAVE

Diabetes Gestacional, Microbiota, Gravidez, Probióticos

INTRODUCTION

In the gestational period, substantial hormonal, immunological and metabolic changes are observed such as increased absorption of nutrients and increased insulin concentration accompanied by insulin resistance. This metabolic adaptation is essential to promote fetal growth, nevertheless, during the second half of pregnancy, this is potentially a diabetogenic condition (1). Moreover, in some pregnant women these processes are overstated, leading to Gestational Diabetes (GD). GD corresponds to any degree of glucose metabolism anomaly documented, for the first time, during pregnancy (2). The prevalence of GD has rapidly increased in recent years. In 2016, the prevalence in Portugal was 7.5%, increased markedly in women over the age of 40 years and differed by region (2).

Increased maternal glucose levels may result in complications for the newborn, birth trauma and neonatal hypoglycemia (3). Women with a history of GD presents an increased risk of developing type 2 diabetes in later in life. GD is also associated with an increased risk of chronic diseases such as obesity (4), metabolic syndrome, non-alcoholic fatty liver disease (5, 6), glucose metabolism disorders and autism (7) during childhood and adulthood of offspring. The mechanism by which maternal GD portends offspring risk for chronic diseases is not well understood, but it is believed that the effects may be mediated through alterations in the maternal microbiome during pregnancy that are shared with the newborn either during gestation, delivery, or subsequently (8).

Microbiota is determined by many factors such as mode of delivery, feeding type, nutrition, genetics, health status, gestational age, and antibiotics use (4). Initially, these microorganisms were thought to be transmitted between mother and child after birth. In other words, the intrauterine environment during pregnancy has been presumed to be sterile, although recent evidence suggests the presence of bacteria in amniotic fluid, umbilical cord blood, placental and fetal membranes and meconium (4, 9). It is only at 3

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years that adult-like composition is established (10), but the primordial transmission of bacteria between mother and child occurs *in utero*, during delivery and during lactation; thus the occurrence of dysbiosis during this period caused by GD may be a risk factor for the infant (6). There are several studies that demonstrate the benefits of using probiotics in the prevention of gestational diabetes and also in the control of weight gain throughout pregnancy (11–14). Prenatal maternal probiotic supplementation may provide a novel early tool to combat the major health challenges such as obesity and immune-inflammatory disease faced by the newborn today.

In this review we consider the changes that occur in the maternal gut, placental and vaginal microbiota in a gestational diabetes situation, and the role of probiotics as a key tool in the treatment.

Diabetes in pregnancy and microbiota

Until now, there is no research that examined directly the association of GD with maternal microbiota during pregnancy. However, it is known that changes in gut, placental and vaginal microbiota occurs over the course of pregnancy (Figure 1). As well as microbiota profiles change, the metabolic hormone levels also change and these changes are correlated (15). Fetus born of an obese mother had higher percentage of body fat and developed insulin resistance already in utero (16). Other study showed that mother's weight had an effect on infant microbiota development (17), which suggests that the microbiota of mothers is an important factor for baby health.

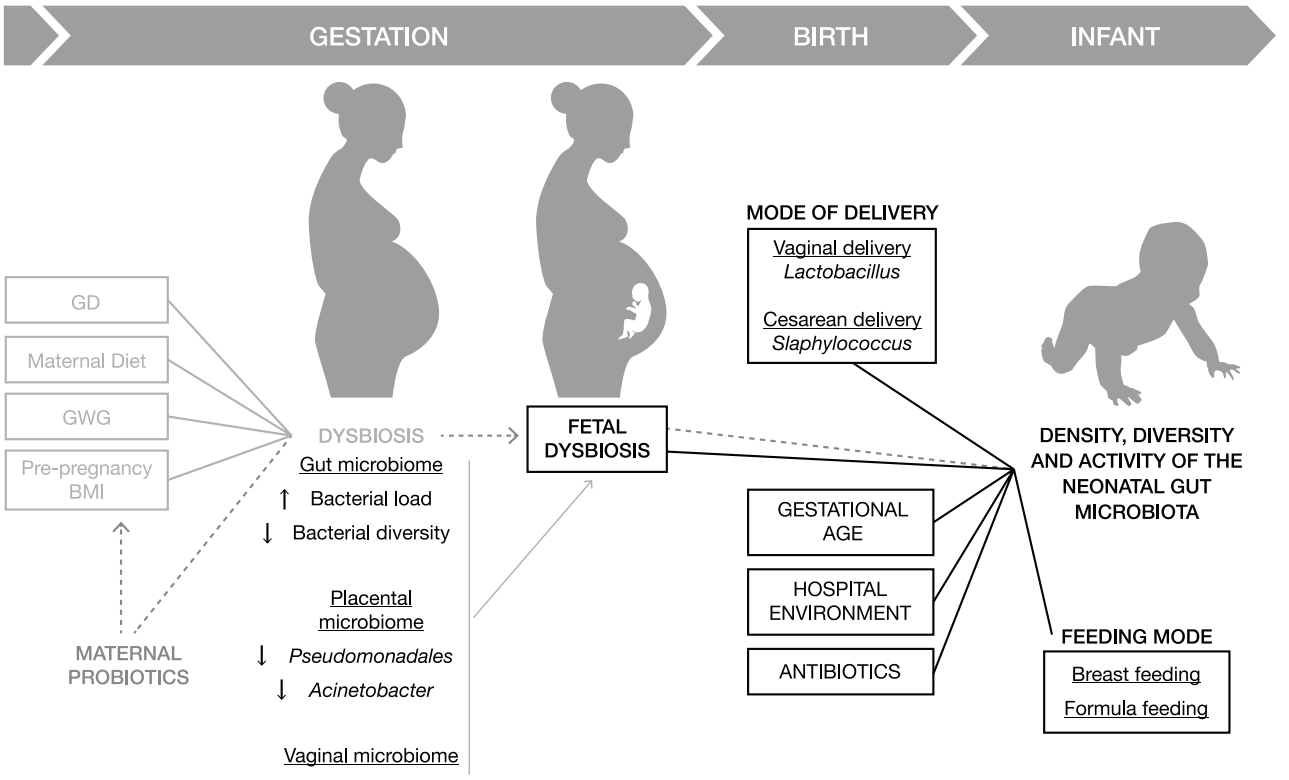
Gut microbiota

In the gut inhabits the largest microbiota at the human body. The colonization of commensal bacteria is essential to the biosynthesis of vitamins, release of gut hormones, maintenance of the gut barrier function (17), regulation of the immune system (8) and lipid metabolism (18) and control the energy extraction of non-digestible polysaccharides for the production of short chain fatty acids (SCFA), such as acetate, butyrate and propionate (19, 20). Gut microbiota also regulates the intercellular thigh junctions in the intestinal mucosa, in order to inhibit the absorption of endotoxins, like lipopolysaccharide (LPS), which have been positively correlated with obesity, inflammatory markers and abnormal glycemic levels (21). As well as circulating zonulin, a protein that influences intestinal barrier function, whose concentration is influenced by SCFA production, that is determined by gut microbiota composition, even as dietary intake of n-3 polyunsaturated fatty acids (PUFAs), fiber, and certain vitamins and minerals (22).

A strong influence between the gut microbiota composition and the pregnancy metabolism has been recently described (15). In fact, over the course of gestation profound changes have been shown (1): bacterial load increase in the gut (1, 23), the relative amount of lactic-acid producing bacteria increases (15) and bacterial diversity decrease with obesity and insulin resistance (24). A systematic review found that the maternal gut microbiota was associated with pre-pregnancy body mass index (BMI), gestational weight gain and GD (8). Insulin, c-peptide, insulin resistance index and fasting glucose were all significantly and positively correlated with increasing BMI and with specific bacteria. *Collinsella* (family *Coriobacteriaceae*, *phylum Actinobacteria*) showed a

Figure 1

Illustration of the main factors that shape the neonatal microbiota



Many metabolic changes occur during pregnancy: there is a normal increase in serum insulin concentration and an increase in insulin resistance that can lead to gestational diabetes (GD). GD and other determinants, such as the maternal diet, gestational weight gain (GWG), and pre-pregnancy body mass index (BMI) can lead to dysbiosis at level of the gut, placenta or vagina. Since the intrauterine environment is not sterile, the fetus will suffer with this dysbiosis that can strongly influence the density, diversity and activity of the neonatal gut microbiota. However, there are other factors that may still shape the neonatal microbiota, such as mode of delivery, gestational age, hospital environment, perinatal antibiotic exposure and feeding mode. The use of probiotics during pregnancy will improve not only the health status of the mother, but also improve the fetal microbiota and, consequently, the newborn health. Adapted from Soderborg et al.,2016 (6).

positive correlation between insulin and pregnancy, as well as maternal triglycerides and VLDL cholesterol. In contrast, *Collinsella* exhibit a trend for negative correlation with maternal HDL cholesterol. In this study, authors concluded that manipulating the abudance of *Collinsella* may affect both glucose and lipid metabolism in pregnancy (15). Further, a group of investigators observed a major number of Proteobacteria and Actinobacteria between first to third trimester (1). Then, they inoculated germ free mice with stool collected in the first *vs.* third trimester. The mice that received the third trimester microbiota gained more weight, become more insulin resistant and had higher levels of inflammatory markers (1). This data confirm the metabolic impact of the gut microbiota. However, other studies found no significant changes in the gut microbiota over the gestational period (25, 26). This divergent results may be attributable to differences in the frequency of sampling and in the methodology used, as well as the population of study. Addictionally, it was found that, regardless of their age, the children's microbiota were most similar to their mothers' microbiota in the first trimester (1). Accordingly, presupposing that the infant microbiota is related to the maternal gut microbiota, care should be taken not only during pregnancy but also even before conception. Lastly, significant differences were observed in microbiota composition according to weight status before pregnancy (23). In fact, Bacteroides and *S. aureus* numbers appear to be significantly higher in overweight and obese pregnant women. These microorganisms may predispose to the enhanced energy storage and the decreased control of systemic low-grade inflammation typical of obesity, such as insulin resistance (23).

Placental microbiota

Since the placenta is a maternal-fetal structure that develops to allow the absorption of nutrients and oxygen uptake to the fetus, its integrity and function are fundamental for fetus development, growth and survival (27). It should be added that placenta is more than an unsterile organ; it has its own microbiota. Taking this into account, a study revealed that term infants of women with GD presented a 7.57 fold increased risk of developing atopic dermatitis and 5.91 fold increased risk of allergen sensitization (28), which could be due to placental immune cell infiltration and inflammation (29). Placental microbiota is mainly formed by Proteobacteria (29), in contrast to the gut microbiota, in which Firmicutes and Bacteroidetes are the most abundant phyla (21). It was described three hypotheses to explain the colonization of the placenta microbiota: translocation of bacteria from the vagina to the placenta; dissemination of oral bacteria via bloodstream; intestinal bacteria transported to the placental via maternal dendritic cells (30). In a recent study, placental microbiota and the expression of anti-inflammatory cytokines from women with GD and from control women were analyzed (29). It was observed that numbers of *Pseudomonadales* and *Acinetobacter genus* (both from *phylum Proteobacteria*) are lower in women with GD. Lower relative abundance of *Acinetobacter* in GD are associated to more metabolic disorders and inflammatory phenotypes (29).

Vaginal microbiota

It is well known that the vaginal microbiota during pregnancy is distinct from the non-pregnant vaginal microbiota and it can change the course of gestation (31). Here, the microbiota diversity is lower than the gut, being generally dominated by *lactobacilli*, which produced lactic acid to maintain low vaginal pH and prevent pathogenic bacteria invasion (32). Nonetheless, not all *lactobacilli* are equal: *Lactobacillus crispatus* are associated with decrease of vaginal mucosal inflammation and protection from adverse outcomes, while *Lactobacillus iners* are much more dysbiosis-associated (31), which dominated in premature labor. Further, vaginal microbiota may regulate the hormone secretion, timing parturition and the microbial colonization (8). Vaginal dysbiosis - defined as a microbiota that is not dominated by lactobacilli - has been associated with HIV and other sexually transmitted infections (STIs) and maternal and neonatal infections (31).

The majority of research in pregnant women has focused on rectovaginal *Streptococcus agalactiae* carriage, because it has an association with pregnancy and neonatal complications (31). More studies are needed on the development of the vaginal microbiota over the gestational period.

Probiotics intervention in pregnancy: the lack of clinical evidence

Usually, GD is a disorder controlled essentially by diet, exercise, insulin treatment or metformin, being the pharmacological treatment of first choice (33). In 2015, the International Federation of Gynecology and Obstetrics affirmed that "metformin is a safe and effective therapy for GD during the second and third trimesters, although metformin crosses the placental barrier" (34). Metformin may have direct microbial effects. A recent study recruited 459 participants to study the influence of metformin on the association of type 2 diabetes and gut dysbiosis (35). In this study, it was found that participants with diabetes but without metformin had more *Pretovella* and less *Enterococcus casseliflavus*, while the participants taking this drug had a greater relative abundance of *Akkermansia muciniphila* – a bacteria that has been associated with weight loss, improved metabolic control and reduced adipose tissue inflammation and SCFA (35). So, metformin could reduce diabetes-associated dysbiosis in pregnancy, as well as reduce the transmission of diabetogenic bacteria to the newborn (8). However, since the number of women with GD continues to increase, it is necessary to think about alternative prevention strategies of this disorder. Thus, a new question arises: can the use of probiotics be a preventive/therapeutic alternative for women with GD?

Probiotics are live microorganisms consumed as supplements or beverage/food in adequate quantities that may confer a health benefit on the host (36). Most of probiotic products are yoghurts, fermented milks (such as *kefir, buttermilk* and *aryan*) or other fermented beverages (*kombucha*) available in the supermarkets (37, 38). The first study to provide evidence of improved glucose metabolism with probiotics evaluated 256 normoglycaemic pregnant women (11). These pregnant women were randomly divided into three treatment groups: dietary counselling with probiotic [*Lactobacillus rhamnosus* and *Bifidobacterium lactis* (diet/probiotic)]; dietary counselling with placebo (diet/placebo); controls (control/placebo). The authors demonstrated that blood glucose concentrations were lowest in the diet/probiotics group during pregnancy and over the 12 months' postpartum period (11). In a subsequent study, the same authors aimed not only to assess the impact of probiotic intervention on maternal glucose metabolism, but also to determine the safety and efficacy of perinatal dietary counselling and probiotic supplementation, evaluating fetal and infant growth for 24 months of follow up (12). In this elegant study, probiotic intervention had shown to reduce the frequency of GD: 13% (diet/probiotic) *vs.* 36% (diet/placebo) and 34% (control); (p=0.003). Moreover this study showed that probiotic intervention can be a safe and cost-effective tool to prevent GD (12). More recently, a randomized trial with 423 pregnant women with history of atopic disease, concluded that GD prevalence was lower in the *Lactobacillus rhamnosus* HN001 supplemented group than placebo, particularly among olders (age ≥35 years) and those with previous gestational diabetes (13).

In addition to their preventive role, probiotics have also been indicated as a therapeutic method for the control of glucose levels in women

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diagnosed with GD. Thus, in 64 women with newly diagnosed GD the supplementation with probiotics (*Lactobacillus acidophilus* LA-5, *Lactobacillus delbrueckii bulgaricus* LBY-27, *Bifidobacterium* BB-12 and *Streptococcus thermophiles* STY-31) had shown a decrease in insulin resistance and weight gain in pregnant women when compared with placebo group (14). Additionally, two short-term studies (up to 8 weeks) found that probiotic supplementation decreased serum insulin levels (39, 40). Furthermore, probiotics reduced the triglycerides and VLDL levels (but not on other lipid profiles) (39) and significantly reduced inflammatory mediators (IL-6, TNF-α and high sensitive C-reactive protein) (40). On the other hand, Lindsay *et al.* showed that probiotic intervention had no effect on glycemic control among women with GD or impaired glucose tolerance (41). Curiously, this last study was the only that did not used *Bifidobacterium spp*. in their probiotics. So far, the evidence suggests probiotic supplementation as a promising therapeutic approach for the management of GD (42).

Even if it is not completely understood how probiotics modulate glucose metabolism, potential mechanisms involving SCFAs have been reported (42). Probiotics strains that increase fermentation capacity of gut microbiota generated SCFAs that can reduce appetite by slowing intestinal transit time and reduce insulin resistence, through upregulation of Peptide YY and Glucagon-like peptide-1 when SCFAs bind to G protein-coupled receptors (42). SCFAs also prevent the circulation of LPS by regulating the intestinal permeability (21, 42) and, consequently, reduce inflammatory markers, as Jafarnejad *et al.* (40) demonstrated.

CONCLUSIONS

Maternal nutrition during pregnancy may initiate a cascade of metabolic and immune inflammatory conditions in infant (11). Changes occur in the intestinal and vaginal microbiota during pregnancy and may generated a microbiota composition associated with metabolic diseases, leading to insulin resistance and modulation of lipid metabolism. The development of the placenta, its hormone release and its specific microbiota may lead to disruptions in the uptake of glucose by the cells, causing hyperglycemia. A recent and very well-structured review lists a number of pathological conditions associated with teratogenicity due to maternal obesity, GD and/or excessive weight gain throughout pregnancy, such as the development in later years of diabetes, non-alcoholic fatty liver disease and metabolic-syndrome (6). This mother-to-child dysbiosis becomes a vicious cycle: a mother with a high body mass index, insulin resistance or GD has a less diverse microbiota with less Bifidobacteria and more *Escherichia coli* and *Staphylococcus*, producing different SCFAs, leading to inflammation (by LPS); this disease related information is transmitted to the fetus, who will transmit to its offspring years later and so on. These data are consistent with "Barker hypothesis" that prenatal nutrition and lifestyle play a decisive role in fetal programming and may be responsible for long-lasting effects on physiological function that could be associated with the development of disease later in life (intrauterine fetal programming) (43). Adequate treatment reduces not only the maternal adverse effects but also to the fetus. Dietary counseling associated to the probiotic supplementation is a safety and cost-effective alternative. Intake of probiotics can be as simple as eating fermented milks or yoghurts available in the supermarkets. Randomized controlled clinical trials must be implemented for a evidence-based intervention.

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