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Intestinal dysbiosis during pregnancy: the norm or pathology?

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BACKGROUND: An interest in the study of intestinal microflora has grown among scientists in recent years. This is due to the active development of molecular genetic techniques. The obvious importance of gut microbiota for pregnancy has been established in some scientific works; however, the number of studies devoted to this issue is small.

AIM: This study was aimed to assess the qualitative and quantitative composition of the intestinal microflora in pregnant women.

MATERIALS AND METHODS: The study involved 200 women aged 18 to 43 years in pregnancy from six to 22 weeks. A qualitative and quantitative analysis of the intestinal and vaginal microbiota was performed by real-time PCR.

RESULTS: Intestinal dysbacteriosis was detected in 100% of the examined pregnant women. Grade I was detected in 64.5% (n = 129), grade II in 26.5% (n = 53), and grade III in 9% (n = 18) of cases. A decrease in the concentrations of resident bacteria was noted in all pregnant women; in addition, in women with moderate and severe dysbacteriosis, opportunistic microorganisms (*Clostridium difficile*, *Enterobacter* spp., *Streptococcus* spp., and *Campylobacter* spp.) were detected in quantities exceeding the formally permissible values. The analysis of the course of pregnancies showed that grade I and grade II intestinal dysbacteriosis is a risk factor for early pregnancy complications (OR = 0.2, p = 0.00), thus confirming the role of intestinal microbiocenosis in miscarriage.

CONCLUSIONS: Pregnancy is a predisposing factor for changes in the intestinal microflora, as evidenced by the detection of intestinal dysbiosis in 100% of pregnant women in the main and control study groups. Considering that the majority of women with a normal pregnancy were diagnosed with grade I intestinal dysbiosis, it can be assumed that this degree of dysbiosis is the norm of pregnancy. Thus, the identification of moderate or severe intestinal dysbiosis should be associated with complications of early pregnancy.

Keywords: intestinal dysbiosis; intestinal microflora; pregnancy; miscarriage.

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Дисбактериоз кишечника во время беременности: норма или патология?

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Обоснование. В последние годы среди ученых значительно вырос интерес к исследованию микрофлоры кишечника, что связано с активным развитием молекулярно-генетических методов диагностики. В некоторых научных работах была определена значимость кишечной микробиоты в поддержании гестационного процесса, но количество исследований, посвященных данной проблеме, невелико.

Цель — оценить качественный и количественный состав микрофлоры кишечника у беременных.

Материалы и методы. В исследовании участвовали 200 женщин в возрасте от 18 до 43 лет на сроке беременности от 6 до 22 нед. Всем беременным проводили качественную и количественную оценку состояния микрофлоры кишечника и влагалища методом полимеразной цепной реакции в режиме реального времени.

Результаты. Дисбактериоз кишечника выявлен у 100 % обследованных беременных, при этом в 64,5 % (n = 129) случаев нарушения соответствовали I степени дисбактериоза, в 26,5 % (n = 53) — II степени и в 9 % (n = 18) — III степени. Отмечено снижение интенсивности колонизации толстой кишки резидентной микрофлорой у всех беременных; кроме того, у женщин с умеренным и тяжелым дисбактериозом выявлены условно-патогенные микроорганизмы *Clostridium difficile*, *Enterobacter* spp., *Streptococcus* spp. и *Campylobacter* spp. в количествах, превышающих формально допустимые значения. Анализ течения беременностей показал, что дисбактериоз кишечника II или III степени является фактором риска осложненного течения беременности на ранних сроках (ОШ = 0,2; p = 0,00), что доказывает роль кишечного микробиоценоза в невынашивании беременности.

Заключение. Беременность служит предрасполагающим фактором к изменению микрофлоры кишечника, о чем свидетельствует выявление дисбактериоза кишечника у 100 % беременных. Принимая во внимание тот факт, что у большинства женщин с нормально протекающей беременностью был диагностирован дисбактериоз кишечника I степени, можно предположить, что данная степень нарушения микробиоценоза является нормой беременности. Умеренный или тяжелый дисбактериоз кишечника ассоциируется с осложненным течением беременности на ранних сроках.

Ключевые слова: дисбактериоз кишечника; микрофлора кишечника; беременность; невынашивание беременности; нарушение микрофлоры.

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ЭКО•ВЕКТОР

BACKGROUND

In recent years, interest in the study of intestinal microflora has grown significantly among scientists. Thus, by searching for "gut microbiota" on the PubMed information resource, only 13 articles dated 2001 can be found; by 2015, the number of articles increased to 253. In 2020, 9453 articles were published. This increasing trend is due to the active development of molecular genetic diagnostic methods, such as chromatography, real-time polymerase chain reaction (PCR), sequencing, and metagenomics [1, 2]. Every day, new data on the relationship of changes in the qualitative and quantitative composition of the microflora with the pathology of the gastrointestinal tract, diseases of the cardiovascular system, metabolic disorders (obesity, type 2 diabetes mellitus), and allergic (atopic dermatitis and bronchial asthma) and autoimmune diseases (type 1 diabetes mellitus, celiac disease, and inflammatory bowel disease) are found [3–7].

A number of similar studies have been conducted among pregnant women. For example, D. Zhang (2015) [8] indicated that the intestinal microflora undergoes significant changes during pregnancy, and some studies aimed to maintain the normal course of the gestational period. During pregnancy, the total bacterial mass in the intestinal biotope increases significantly, and the species composition of microorganisms and their metabolic potential are transformed [9].

However, exogenous and endogenous factors can lead to a significant imbalance in the intestinal microbiota composition, which contributes to the maladjustment of the female body and cause complications such as spontaneous abortion, preeclampsia, preterm childbirth, and intrauterine growth retardation [10–22].

Thus, at present, studying the intestinal microflora in pregnant women is important to determine the changes that fit into the concept of "pregnancy norm" and to identify disorders associated with a complicated course of the gestational period, which requires active therapeutic and preventive measures.

This work aimed to assess the qualitative and quantitative composition of the intestinal microflora in pregnant women.

MATERIALS AND METHODS

This study included 200 pregnant women aged 18 to 43 years (mean age 29 ± 5 years) at a gestational age of 6 to 22 weeks, who were under follow-up or treated in the clinic of obstetrics and gynecology of the S.M. Kirov Military Medical Academy.

The exclusion criteria in the selection of subjects were pregnancy resulting from the use of assisted reproductive technologies; multifetal pregnancy; and pregnancy associated with confirmed genetic, anatomical, endocrine, immunological, thrombophilic, and infectious risk factors for miscarriage, acute inflammatory diseases, and exacerbation of extragenital pathology.

Pregnant women were examined in accordance with the requirements of the order of the Ministry of Health of the Russian Federation (MH RF) dated November 1, 2012, No. 572n (as amended on January 12, 2016). In addition, qualitative and quantitative analysis of the microbiocenosis of the rectum and vagina was performed using real-time PCR. The Femoflor-16 test system (DNA-technology, Moscow) was used to determine vaginal microflora. Moreover, a comprehensive study was performed using a set of oligonucleotide probes to determine *Bacteroides* spp., *Parabacteroides* spp., *Prevotella* spp. (type *Bacteroidetes*), *Faecalibacterium prausnitzi*, *Bifidobacterium* spp., *Lactobacillus* spp., *Blautia* spp., *Akkermansia* spp., *Enterococcus* spp., *Fusobacterium nucleatum*, *Clostridium difficile*, bacteria of the *Campylobacteriacae* family, *Enterobacter* spp., *Streptococcus* spp., *Pseudomonas* spp., and *Staphylococcus* spp. and to assess the state of intestinal microbiocenosis.

The range of reference values for the concentration of microorganisms in the colon for real-time PCR (Table 1) was collected from the operating instructions for the Colonoflor test system (RF, registration certificate No. RZN 2019/9479).

The degree of the intestinal microflora impairment was assessed in accordance with the classification approved by the order of the MH RF dated June 9, 2003, No. 231, considering the data of the working instructions for analysis of the colon microbiota by real-time PCR with fluorescence detection:

1) degree I (mild) manifested itself with the appearance of opportunistic microorganisms (OM) in an amount of less

Table 1. Reference intervals for the study of colonic microbiocenosis by real-time polymerase chain reaction

Parameter	Reference range, DNA copies/mL
Bacteroides spp.	10^9–10^{12}
Prevotella spp.	Up to 10^{11}
Akkermansia spp.	Up to 10^{11}
Faecalibacterium prausnitzi	10^8–10^{11}
Bacteroides spp. / *Faecalibacterium prausnitzi* ratio	0,01–100
Blautia spp.	10^8–10^{11}
Bifidobacterium spp.	10^9–10^{10}
Parabacteroides spp.	10^7–10^8
Lactobacillus spp.	10^7–10^8
Fusobacterium nucleatum	Not detected
Enterococcus spp.	Maximum 10^8
Clostridium difficile	Maximum 10^4
Enterobacter spp.	Maximum 10^4
Pseudomonas spp.	Maximum 10^4
Streptococcus spp.	Maximum 10^4
Staphylococcus spp.	Maximum 10^4
Campylobacter spp.	Maximum 10^4

than 10^4 DNA copies/mL associated with a deficiency of the normobiota representatives (decrease in the number of microorganisms by less than two orders of magnitude);
2) degree II (moderate) manifested itself with the OM in the amount greater than 10^4 but less than 10^6 DNA copies/mL with a deficiency of normobiota (decrease by less than two orders of magnitude);
3) degree III (severe) manifested itself with excessive growth of OM associations (>10^6 DNA copies/mL) with a pronounced deficiency of the normobiota (with a decrease by more than two orders of magnitude).

Statistical data analysis was performed using the IBM SPSS Statistics 22 software package (Armonk, NY, USA). We used the methods of variational statistics with a differentiated assessment of statistical analysis methods depending on the type of distribution of attributes in the samples. Differences were considered statistically significant when determining a 95% probability ($p < 0.05$).

RESULTS

When assessing the intestinal microflora by PCR, intestinal dysbiosis was detected in 100% of the examined pregnant women, whereas the disorders corresponded to degree I of dysbiosis in 64.5% ($n = 129$) of cases, degree II in 26.5% ($n = 53$) of cases, and degree III in 9% ($n = 18$) of cases. Female patients with intestinal dysbiosis were included in group 1, and pregnant women with moderate and severe intestinal dysbiosis were combined into group 2.

Table 2. Qualitative and quantitative composition of the intestinal microflora in pregnant women

Concentration of microorganisms. log10 DNA copies/mL (Me ± m)	Group 1	Group 2	*p*
Bacteroides spp.	6.6 ± 1.3	5.5 ± 2.0	0.03
Prevotella spp.	5.5 ± 2.0	5.0 ± 2.2	0.8
Akkermansia spp.	2.5 ± 2.0	2.5 ± 2.4	0.3
Faecalibacterium prausnitzi	5.8 ± 1.3	6.0 ± 2.0	0.4
Bacteroides spp. / *Faecalibacterium prausnitzi* ratio	1.13 ± 0.02	0.9 ± 0.01	0.1
Blautia spp.	5.8 ± 1.3	5.4 ± 1.9	0.6
Bifidobacterium spp.	6.7 ± 0.5	4.5 ± 2.8	0.001
Parabacteroides spp.	4.5 ± 0.9	4.7 ± 2.2	0.3
Lactobacillus spp.	6.1 ± 0.5	3.8 ± 2.1	0.00
Fusobacterium nucleatum	1.1 ± 1.7	2.2 ± 2.0	0.6
Enterococcus spp.	1.8 ± 1.8	4.0 ± 2.0	0.00
Clostridium difficile	1.9 ± 1.5	4.2 ± 2.0	0.00
Enterobacter spp.	2.1 ± 1.4	4.0 ± 2.3	0.002
Pseudomonas spp.	0.6 ± 0.7	1.2 ± 1.1	0.2
Streptococcus spp.	2.0 ± 1.4	4.9 ± 1.8	0.00
Staphylococcus spp.	1.6 ± 1.6	2.9 ± 1.4	0.012
Campylobacter spp.	1.4 ± 2.0	4.0 ± 0.8	0.026

When analyzing the qualitative and quantitative composition of the intestinal microflora (Table 2), a decrease in the intensity of colonization of the colon by the resident microflora was noted relative to the reference values in all pregnant women. The concentration of microorganisms such as *Bifidobacterium* spp., *Lactobacillus* spp., and *Bacteroides* spp. in pregnant women of group 2 was statistically and significantly lower than that of group 1.

Changes in the intestinal microflora in pregnant women of group 2 were also characterized by the detection of opportunistic *Clostridium difficile*, *Enterobacter* spp., *Streptococcus* spp., and *Campylobacter* spp. in amounts exceeding the permissible values. In particular, statistically significant intergroup differences were found in *Staphylococcus* spp. and *Enterococcus* spp. (Figure).

Gastroenterological complaints were analyzed to clarify the clinical manifestations of intestinal dysbiosis. Bloating was reported in 40% ($n = 80$) of cases, stool disorders such as constipation and diarrhea in 80% ($n = 160$) and 20% ($n = 40$) of cases, respectively, nausea in 33% ($n = 66$) of cases, and epigastric burning in 7% ($n = 14$) of cases. Notably, all complaints were nonspecific, which occurred with the same incidence, regardless of the degree of the intestinal microflora disorder.

When identifying possible factors contributing to the disruption of the intestinal microflora, female patients with a history of chronic diseases of the gastrointestinal tract had a high probability of moderate and severe intestinal dysbiosis during pregnancy (overall Mantel–Haenszel odds ratio [OR] was 4.1, with 95% confidence interval of 1.5 to 11.9, $p = 0.007$). Thus, the gastrointestinal tract pathology was detected in 25.5% ($n = 51$) of women. Chronic gastritis (30 female patients), irritable bowel syndrome ($n = 18$), and chronic gastroduodenitis ($n = 17$) predominated in the structure of gastroenterological pathology in pregnant women. Gastroesophageal reflux disease, functional disorder of the biliary tract, duodenal ulcer, and chronic pancreatitis were less commonly observed.

Based on the study of the vaginal microflora by real-time PCR, normocenosis was noted in 73% ($n = 146$) of cases, and dysbiotic changes were recorded in 27% ($n = 54$) of cases. Degree I dysbiosis was diagnosed in 17.5% ($n = 35$) of cases, and degree II dysbiosis was diagnosed in 9.5% ($n = 19$) of cases. In pregnant women with vaginal dysbiosis, obligate anaerobes (*Gardnerella vaginalis*, *Atopobium vaginae*, *Prevotella bivia*, *Eubacterium* spp., *Megasphaera* spp.) dominated in 60% of cases, and facultative anaerobic bacteria (family *Enterobacteriaceae*, *Streptococcus* spp., and *Staphylococcus* spp.) were registered in 30% of cases. Furthermore, mixed flora was detected in the remaining 10% of cases.

When conducting a comparative analysis of vaginal and intestinal biotopes, an association of vaginal dysbiosis with

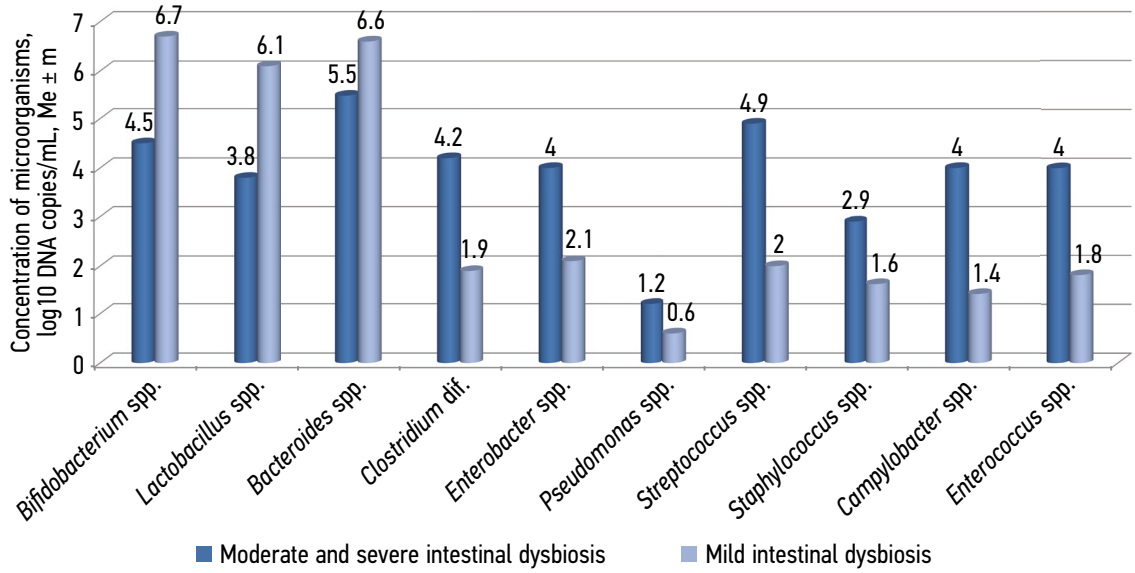

Figure. Comparative diagram of the content of significant microorganisms in the intestines of pregnant women examined

Table 3. Statistically significant correlations between vaginal and intestinal microflora

Intestinal microflora (*r*)	Vaginal microflora (*r*)						
	***Gardnerella vaginalis, Prevotella bivia, Porphyromonas* spp.**	***Atopobium vaginae***	***Sneathia* spp., *Leptotrichia* spp., *Fusobacterium* spp.**	**Family *Enterobacteriaceae***	***Eubacterium* spp.**	***Streptococcus* spp.**	***Peptostreptococcus* spp.**
Lactobacillus spp.						–0.5	
Akkermansia spp.			–1			–0.6	
Pseudomonas spp.							0.5
Staphylococcus spp.	0.5	0.46	0.5	0.42	0.45	0.6	0.4
Clostridium difficile		0.4				0.6	
Campylobacter spp.		0.77					

intestinal dysbiosis was revealed (Spearman correlation coefficient [*r*] was 0.4, $p = 0.04$). Thus, a high level of clinically significant OM in the vaginal biotope was revealed against the deficit of normoflora and a high concentration of OM in intestinal biocenosis (Table 3).

Statistically significant relationships were established between *Lactobacillus* spp. in the intestine and *Streptococcus* spp. in the vagina with a negative moderate relationship ($r = –0.5$, $p = 0.04$), between *Akkermansia* spp. in the intestine and *Streptococcus* spp. in the vagina with a negative moderate relationship ($r = –0.6$, $p = 0.02$), and between *Akkermansia* spp. in the intestine and *Sneathia* spp./*Leptotrichia* spp./*Fusobacterium* spp. in the vagina with a negative strong relationship ($r = –1$, $p < 0.001$). A positive moderate relationship was found among OM, namely, *Pseudomonas* spp. in the intestine and *Peptostreptococcus* spp. in the vagina ($r = 0.5$, $p < 0.05$); *Staphylococcus* spp. in the intestine and microorganisms of the *Enterobacteriaceae* family ($r = 0.42$, $p = 0.02$); *Streptococcus* spp. ($r = 0.6$, $p = 0.004$), *Gardnerella vaginalis*/*Prevotella bivia*/*Porphyromonas* spp. ($r = 0.5$, $p = 0.003$), *Peptostreptococcus* spp. ($r = 0.4$, $p = 0.01$), *Atopobium vaginae* ($r = 0.46$, $p = 0.04$), *Sneathia* spp./*Leptotrichia* spp./*Fusobacterium* spp. ($r = 0.5$, $p = 0.02$), and *Eubacterium* spp. ($r = 0.45$, $p = 0.01$) in the vagina; *Clostridium difficile* in the intestine and *Streptococcus* spp. (r = 0.6, $p = 0.001$); and *Atopobium vaginae* ($r = 0.4$, $p = 0.049$) in the vagina. A positive strong relationship was also found between *Campylobacter* spp. in the intestine and *Atopobium vaginae* ($r = 0.77$, $p = 0.046$). These results indicated the existence of a relationship between the qualitative and quantitative composition of the intestinal and vaginal biotopes in female patients.

Analysis of the course of pregnancies showed that in 74 female patients (37%), complicated spontaneous miscarriage occurred during the gestational period in 52 women (70.2%) of group 2 and 22 (29.8%) women of group 1, which was a statistically significant intergroup difference ($p = 0.00$). Thus, moderate or severe intestinal dysbiosis is a risk factor for complicated pregnancy in the early stages (OR = 0.2, 95% confidence interval 0.08–0.5, $p = 0.00$), which indicates the role of intestinal microbiocenosis in miscarriage disorders.

DISCUSSION

Our data confirm the results of a number of scientific works. Therefore, M.N. Gapon et al. (2016) established intestinal dysbiosis in all pregnant women [23]. According to I.S. Polischuk et al. (2016), intestinal microbiocenosis in pregnant women was characterized by a low level of bifidobacteria and a high level of OM, among which bacteria of the genus *Clostridium*, *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Proteus*, atypical Escherichia, and Enterococci were most common [24].

B.T. Seytkhanova (2014) reported that 48.6% of pregnant women were diagnosed with changes in the intestinal microbiocenosis, as shown by the decrease in the concentration of the main components of the protective flora (lacto- and bifidobacteria) and a high concentration of OM. Degree I intestinal dysbiosis was detected in 23.5% of pregnant women, degree II in 60.8% of cases, and degree III in 15.7% of cases. Bacterial vaginosis was revealed in pregnant women with moderate and severe degrees of intestinal dysbiosis [25], which also correlates with the data of our work. Similar results on the relationship between vaginal and intestinal microbiocenoses were obtained in a number of other works [26–29].

S.A. Karpeev [30] determined that diseases of the digestive system, such as chronic gastritis, gastroesophageal reflux disease, irritable bowel syndrome with a predominance of constipation, or diarrhea, lead to disruption of the intestinal microflora, which are associated with the risk of recurrent miscarriage.

A number of scientific papers confirm the pathological effect of dysbiotic changes in the intestinal microflora on the course of pregnancy.

T.N. Savchenko et al. (2013) analyzed the microbiocenosis of the digestive tract in female patients with miscarriage, of which dysbiosis was diagnosed in 84% of pregnant women with clinical manifestations of an onset of miscarriage (subgroup 1), in 95.7% of female patients with terminated pregnancy (subgroup 2), and in 55% of healthy pregnant women (comparison group). Degree III intestinal dysbiosis in subgroups 1 and 2 was recorded significantly more often ($p < 0.05$) than in the comparison group (corresponding indicators were 25.3%, 34.1%, and 5.0%) [31].

Carla R. Taddei et al. (2018) showed that the occurrence or exacerbation of obstetric and/or systemic diseases in pregnant women was associated with low microbial diversity; an increase in the number of pathogenic representatives of the *Firmicutes* and *Proteobacteria phyla* types; and a decrease in eubiotic bacteria, such as *Bifidobacterium*, *Faecalibacterium*, and *Akkermansia*, in the intestinal microbiota [18]. The work of M.E. Baldassarre et al. (2019) showed that intestinal dysbiosis was associated with a high risk of miscarriage, preterm birth, and adverse outcomes of prematurity in a newborn as feeding intolerance, necrotizing enterocolitis, and late sepsis [21]. N.N. Rukhlyada et al. (2020) indicated that intestinal dysbiosis was associated with a complicated course of pregnancy [22].

Thus, in case of a history of gastrointestinal pathology or if dysbiotic changes in the vaginal microflora are detected, the study of intestinal microbiocenosis is recommended for women in the early stages of pregnancy or women who are planning pregnancy. Correction of the intestinal microflora can contribute to the physiological course of pregnancy in the early stages.

CONCLUSIONS

1. Pregnancy is a factor predisposing to changes in the intestinal microflora, as evidenced by the detection of intestinal dysbiosis in 100% of pregnant women. Most female patients with normal pregnancies are diagnosed with degree I intestinal dysbiosis; thus, this degree of microbiocenosis disorder is the norm of pregnancy. Moderate or severe intestinal dysbiosis is associated with a complicated course of early pregnancy (OR = 0.2, $p = 0.00$).
2. Changes in the vaginal biotope are associated with disorders in the intestinal microflora, whereas the degree of dysbiotic changes in the vaginal microflora is directly proportional to the degree of intestinal dysbiosis ($r = 0.4$, $p = 0.04$).
3. Intestinal dysbiosis during pregnancy is characterized by an asymptomatic course; all complaints of a gastroenterological nature were nonspecific, with the same incidence in pregnant women with degree I dysbiosis and in the case of moderate and severe dysbiosis.
4. Chronic diseases of the digestive system in history contribute to significant disorders of the intestinal microflora during pregnancy (OR = 4.1, $p = 0.007$).

ADDITIONAL INFORMATION

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