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VAGINAL MICROBIOTA: CLINICAL SIGNIFICANCE AND MANAGEMENT STRATEGIES IN WOMEN WITH INTERMEDIATE NUGENT PROFILES (4–6)

Introduction. A Nugent score of 4–6 is not diagnostic for bacterial vaginosis (BV) but reflects vaginal microbiota instability and may indicate an unfavorable prognosis. Molecular studies show that BV-related microbial patterns occur even at intermediate morphotypes, highlighting the need for careful evaluation.

Aim. To summarise current data on the vaginal microbiome at Nugent scores 4–6, determine the clinical significance of this intermediate range, and outline possible management algorithms for patients with a borderline microbiological profile.

Materials and methods. This review is based on a structured analysis of 78 publications retrieved from PubMed, Scopus, Web of Science, and Google Scholar (2000–2025), including clinical studies, molecular microbiome analyses, and meta-analyses focused on women with intermediate Nugent scores (4–6).

A systematic search strategy with explicit inclusion and exclusion criteria was applied. Included studies: peer-reviewed clinical, molecular, or microbiome analyses with reported Nugent 4–6 data. Excluded: non-peer-reviewed sources, conference abstracts, studies without Nugent stratification.

Results. Intermediate scores are linked to reduced *Lactobacillus crispatus* and *L. jensenii*, predominance of *L. iners*, and moderate presence of anaerobes such as *Gardnerella vaginalis* and *Atopobium vaginae*. This pattern corresponds to community state type IV (CST-IV), associated with higher risks of BV, recurrent infections, and adverse reproductive outcomes. Symptoms, elevated pH, pregnancy, or immunosuppression justify treatment, while asymptomatic women with normal pH may be observed.

Conclusions. These conclusions are based on a synthesis of peer-reviewed scientific literature covering clinical, molecular and microbiome studies published between 2000 and 2025.

Data from Gram staining, qPCR, 16S rRNA sequencing, and CST classification support molecular diagnostics and differentiated therapy. Combined regimens using probiotics, antimicrobials, or integrated strategies help stabilise the microbiota and prevent dysbiosis. An intermediate Nugent score should be regarded as a marker of microbial imbalance requiring individualised management and further research toward personalised, biomarker-based care

Key words: Nugent 4–6, vaginal microbiota, *Lactobacillus iners*, bacterial vaginosis, management strategy, CST-IV, probiotics.

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ВАГІНАЛЬНА МІКРОБІОТА: КЛІНІЧНЕ ЗНАЧЕННЯ ТА СТРАТЕГІЇ ВЕДЕННЯ ЖІНОК ІЗ ПРОМІЖНИМ NUGENT-ПРОФІЛЕМ (4–6)

Вступ. Бал за шкалою Nugent 4–6 не є діагностичним для бактеріального вагінозу (БВ), але відображає нестабільність вагінальної мікробіоти та може свідчити про несприятливий прогноз. Молекулярні дослідження показують, що мікробні патерни, пов'язані з БВ, зустрічаються навіть при проміжних морфотипах, що підкреслює необхідність ретельної оцінки.

Мета. Узагальнити поточні дані про вагінальний мікробіом за шкалою Nugent 4–6, визначити клінічне значення цього проміжного діапазону та окреслити можливі алгоритми ведення пацієнтів з пограничним мікробіологічним профілем.

Матеріали та методи. Огляд ґрунтується на аналізі 78 наукових публікацій (2000–2025), відібраних у базах PubMed, Scopus, Web of Science та Google Scholar, що містили дані щодо жінок із проміжними показниками Nugent (4–6). Було застосовано систематичну пошукову стратегію з чіткими критеріями включення та виключення. Включено рецензовані клінічні, молекулярні та мікробіомні дослідження з показниками Nugent 4–6. Виключено нерецензовані джерела, тези конференцій та роботи без стратифікації за Nugent.

Результати. Проміжні бали пов'язані зі зниженим вмістом *Lactobacillus crispatus* та *L. jensenii*, переважанням *L. iners* та помірною присутністю анаеробів, таких як *Gardnerella vaginalis* та *Atopobium vaginae*. Цей патерн відповідає стану спільноти IV типу (CST-IV), пов'язаному з вищим ризиком БВ, рецидивуючих інфекцій та несприятливих репродуктивних наслідків. Симптоми, підвищений pH, вагітність або імуносупресія виправдовують лікування, тоді як можуть спостерігатися безсимптомні жінки з нормальним pH.

Висновки. Наведені висновки ґрунтуються на узагальненні рецензованих наукових джерел, що охоплюють клінічні, молекулярні та мікробіомні дослідження за 2000–2025 рр.

Дані фарбування за Грамом, кПЛР, секвенування 16S рРНК та класифікації CST підтверджують молекулярну діагностику та диференційовану терапію. Комбіновані схеми лікування з використанням пробіотиків, антимікробних препаратів або інтегрованих стратегій допомагають стабілізувати мікробіоту та запобігти дисбактеріозу. Проміжний бал за шкалою Nugent слід розглядати як маркер мікробного дисбалансу, що вимагає індивідуалізованого лікування та подальших досліджень у напрямку персоналізованого догляду на основі біомаркерів.

Ключові слова: Nugent 4–6, вагінальна мікробіота, *Lactobacillus iners*, бактеріальний вагіноз, стратегія лікування, CST-IV, пробіотики.

Introduction. The vaginal microbiota profile is a key component of a woman's reproductive health and overall well-being. A balanced vaginal ecosystem plays a crucial role in maintaining the natural defense mechanisms of the genital tract, protecting against infections, and ensuring optimal reproductive outcomes. The vaginal microbiota is formed as a dynamic and self-regulating system that changes throughout a woman's life under the influence of multiple endogenous and exogenous factors, including hormonal fluctuations, sexual activity, hygiene habits, diet, use of antibiotics and contraceptives, as well as the general immune status [1].

In a healthy state, the vaginal environment is predominantly colonized by *Lactobacillus* species, which maintain an acidic pH (~3.8–4.5) through production of lactic acid, hydrogen peroxide, and bacteriocins. These metabolites inhibit the growth of opportunistic and pathogenic microorganisms. Among the *Lactobacillus species*, *L. crispatus*, *L. jensenii* and *L. gasseri* are considered the most favourable due to their strong adherence to epithelial cells, ability to form biofilms, and stable acidogenic potential [2]. Conversely, the dominance of L. iners, although taxonomically classified within the *Lactobacillus* genus, is associated with an unstable microbiota and a higher likelihood of transition to dysbiosis [3]. This paradoxical behaviour of *L. iners* highlights the complexity of microbial interactions and the importance of molecular diagnostic approaches for accurate microbiome profiling.

Traditional diagnostic methods of vaginal microbiota disturbances remain largely based on the Nugent scoring system, developed in 1991, which quantifies Gram-stained smears according to the relative abundance of morphotypes representing lactobacilli, *Gardnerella vaginalis*, and *Mobiluncus spp*. [4]. While this method is simple, inexpensive, and widely used in both clinical and research settings, it provides only a semi-quantitative assessment of bacterial morphology rather than the specific species composition. The total score stratifies samples into three main categories: normal biota (0–3), intermediate biota (4–6), and bacterial vaginosis (7–10). However, the so-called "intermediate" or "grey zone" (scores 4–6) poses significant challenges for clinical interpretation.

The intermediate Nugent category reflects a transitional microbiological state that may represent either a mild shift within the normal microbiota or an early phase of dysbiosis. Some women with intermediate scores remain asymptomatic and maintain microbial stability over time, while others experience a gradual depletion of lactobacilli followed by colonization by anaerobic bacteria, ultimately progressing to bacterial vaginosis (BV) [5]. The variability in clinical outcomes suggests that the intermediate Nugent group is highly heterogeneous, encompassing several microbiological and immunological sub-types.

Recent advances in next-generation sequencing (NGS) and metagenomic analyses have allowed more detailed characterisation of the vaginal microbiome and revealed that intermediate Nugent scores correspond to a wide range of bacterial community states. According to the community state type (CST) classification proposed by Ravel et al., normal vaginal microbiota can be divided into distinct clusters dominated by specific *Lactobacillus* species (CST I –; CST II – *L. gasseri*; CST III – *L. iners*; CST V – *L. jensenii*) and one polymicrobial cluster (CST IV) dominated by anaerobic species such as *Gardnerella*, *Atopobium*, *Prevotella*, and *Sneathia*. Intermediate Nugent scores often correspond to CST III and IV-A, reflecting microbiomes in transition [6].

On the species level, it has been consistently observed that *L. crispatus* dominance is associated with reduced risk of BV, lower abundance of pathogens and viral coinfections. For example, a large cohort study showed that the presence of *L. crispatus* was significantly associated with fewer occurrences of *G. vaginalis*, *Fannyhessea vaginae* and high-risk HPV subtypes (OR < 1) whereas *L. iners* was associated with a higher frequency of bacterial pathogens and dysbiosis-related taxa [7].

Genomic analysis of lactobacilli shows that *L. crispatus* strains are enriched for functions related to plasma membrane integrity, biosurfactant production, hydrogen-peroxide synthesis, and iron sequestration, which may underpin their dominant beneficial role [2].

Meanwhile, *L. jensenii* and *L. gasseri* have functional capacities for adherence, aggregation, exopolysaccharide synthesis and bacteriocin production, but their protective impact appears somewhat less stable than that of *L. crispatus* [8]. The evidence suggests that not all lactobacilli are equal when it comes to vaginal health, and the presence of *L. iners* may reflect a vulnerable state rather than a stable protective one [8].

From an immunological perspective, lactobacilli play a role beyond acidification: they modulate local immune responses. For instance, in cell culture models, *L. crispatus* and *L. jensenii* significantly reduce production of pro-inflammatory cytokines IL-6 and TNF-α in response to TLR2/6 or TLR3 stimulation, whereas *L. iners*, unlike *L. crispatus*, may actually enhance expression of TLR downstream signalling molecules and pro-inflammatory

cytokines [9]. These findings lend mechanistic support to the notion that L. crispatus-dominated microbiomes are immunologically stable, while *L. iners*-dominated microbiomes may carry higher risk of inflammation and dysbiosis.

Given the increasing frequency of excessive or unjustified use of antimicrobial therapy in gynecological practice, the issue of accurate differentiation of normobiota and dysbiosis becomes particularly relevant. Over-use of antibiotics may disrupt the microbial homeostasis, reduce beneficial lactobacilli populations, and predispose to recurrence of BV or other genital-tract infections. Meanwhile, under-treatment or mis-classification of borderline cases may lead to untreated subclinical inflammation, adverse pregnancy outcomes, and increased susceptibility to sexually transmitted infections (STIs) [10]. Therefore, understanding the biological and clinical meaning of Nugent 4–6 is essential for developing evidence-based, personalised management strategies.

The clinical significance of an intermediate Nugent score (4–6) deserves special emphasis. In study of vaginal microbiota among women, species-level analysis showed that in the normal-biota group (*Lactobacillu*s index > 70 %) L. crispatus predominated, while *L. iners* predominated in moderate and pronounced dysbiosis groups; the ratio index of *L. crispatus/L. iners* changed nearly 4-fold from 0.7 in normobiota to 2.7 in pronounced dysbiosis [11]. This suggests that microbial composition even within intermediate scores may vary substantially and could have predictive value for progression to BV. Another study reported that in women with asymptomatic moderate vaginal dysbiosis, *L. iners* dominated in 49.5 % of symptomatic patients versus 20.5 % of asymptomatic ones ($p = 0.002$). In molecular profiling of women with BV, *L. gasseri* and *L. jensenii* were detected less frequently, and the communities dominated by *L. gasseri* exhibited a slightly higher pH (~4.4) compared to *L. crispatus* (~4.0) and *L. jensenii* (~4.2) dominated communities [12].

Thus, while the Nugent scale remains a useful clinical tool, it lacks sensitivity in differentiating true health from early transition states of dysbiosis. The overlap of intermediate scores with CST III and IV community-types, plus the heterogeneity of lactobacilli species functions, means that women in the 4–6 range may represent: (a) a stable but non-optimal flora, (b) a transitional flora heading toward dysbiosis, or (c) a recovering biota post-intervention. Clinical management must weigh these possibilities, especially with respect to symptoms, risk factors (e.g., pregnancy, STIs), and local immunological markers.

Given this complexity, management algorithms for patients with a "borderline" microbiological profile (i.e., Nugent 4–6) should integrate multiple layers of information: microscopic score, species-level microbiome data (if available), host immune/inflammatory markers, patient symptoms and risk context (e.g., desire for pregnancy, recurrent infections). For example, in patients with Nugent score of 5, dominance of *L. crispatus* might suggest a near-normobiotic state that may simply be watched, whereas dominance of *L. iners* or detection of anaerobic bacteria at low levels could prompt closer follow-up, probiotic intervention or even targeted antibiotic therapy.

From the prophylaxis standpoint, formulation of probiotic therapies (or vaginal microbiome restorative therapies) increasingly relies on the specific selection of lactobacilli strains adapted to local populations. The pangenomic analysis of *L. crispatus*, *L. gasseri*, *L. jensenii* and *L. iners* across countries showed that *L. crispatus* has greater gene-gain capacity and functional attributes conducive to vaginal homeostasis, and that *L. gasseri* and *L. jensenii* show population-specific gene-cluster adaptation (iron chelation, bacteriocin synthesis) that may influence their protective efficacy in various ethnic groups [2]. This indicates that "one size fits all" probiotic approaches may be suboptimal and that region-specific candidate strains should be considered.

In parallel, emerging molecular diagnostics allow high-throughput 16S rRNA sequencing and metabolomics profiling of vaginal samples, which reveal that metabolite signatures such as 2-hydroxyisovalerate and gamma-hydroxybutyrate (GHB) correlate with high bacterial diversity and BV status, offering biomarkers beyond microscopy [13]. Such approaches may help stratify women with Nugent 4–6 into those at low risk vs. high risk of progression.

Clinically, the differentiation between a stable intermediate microbiota and subclinical BV has significant implications. Over-diagnosis of dysbiosis in women with transient or benign microbiome alterations can lead to unnecessary antimicrobial treatments, which paradoxically may further disrupt microbial balance and predispose to recurrent infections. Conversely, underestimation of a developing dysbiotic state may result in untreated inflammation, adverse pregnancy outcomes, and increased susceptibility to STIs.

Therefore, the aim of this work is to systematise current data on the structure of the vaginal microbiome corresponding to Nugent scores 4–6, to determine the clinical significance of this intermediate range, and to generalise possible algorithms for the management of patients with a borderline microbiological profile.

Materials and methods. The materials for this work were data from modern scientific publications devoted to the peculiarities of the vaginal microbiota of women with a Nugent score of 4–6, including morphotypic, cultural and molecular studies of the composition of the microbial biocenosis. The works included in the analysis investigated aspects of the species structure of the vaginal microbiome, the role of dominant lactobacilli, the ratio of anaerobic taxa and CST patterns within the Nugent-intermediate profile. The test objects of the analyzed studies were vaginal swab samples collected from patients of reproductive age with various clinical symptoms, with their subsequent study by Gram staining according to the Nugent standard, 16S rRNA sequencing or multiplex PCR. In a number of studies, qPCR systems validated for *Lactobacillus iners*, *Gardnerella vaginalis*, *Atopobium vaginae* and other key species were used to quantitatively assess the bacterial load. To assess the clinical feasibility of interventions, the results of the use of probiotics, acid environment regulators, antibacterial therapy, as well as the dynamic indicators of the Nugent score during observation were analyzed. All quantitative data presented in

the analyzed publications were subject to statistical processing in accordance with accepted standards, with an indication of the level of reliability.

Results. Among the analyzed cohort (n = 240), the distribution of Nugent scores was as follows: normal biota (0–3) – 42,9 %, intermediate (4–6) – 31,7 %, and bacterial vaginosis (≥ 7) – 25,4 %. Women in the intermediate group had a mean vaginal pH of 4,7 ± 0,3, compared with 4,2 ± 0,2 in the normal group and 5,3 ± 0.4 in the BV group (ANOVA, $p < 0,001$). The mean age did not differ significantly between groups (31,2 ± 5,9 years, $p > 0,05$) [5].

Patients with a Nugent score of 4–6 is traditionally categorized as having an intermediate microbiological status, making it difficult to interpret the results in a definitive manner. This Nugent interval is not a stable state, but rather reflects a transitional phase between the eubiosis of a healthy vaginal environment and the dysbiosis of bacterial vaginosis (BV). In a healthy woman of reproductive age, the vaginal microbiome is typically dominated by *Lactobacillus crispatus*, *Lactobacillus jensenii*, and less commonly *L. gasseri* or *L. iners*, which maintain a low pH (<4,5) by producing lactic acid, hydrogen peroxide, and other antimicrobial metabolites [5].

At Nugent score of 4–6 demonstrated a pronounced reduction in classical lactobacilli morphotypes, while exhibiting increased presence of Gardnerella vaginalis, Atopobium vaginae, and Mobiluncus spp. compared to the control group ($p < 0,05$). The frequency of detection of key microorganisms across Nugent categories is presented in Table 1.

In such a microbiological environment, *Lactobacillus iners* is often found, which is a facultative symbiont and has an ambivalent role – on the one hand, it is able to maintain pH at a level close to physiological, but on the other hand, it poorly protects the epithelium and coexists with BV-associated species [10, 14].

Quantitative PCR (qPCR) analysis revealed that mean bacterial loads (log_{10} copies/mL) in the Nugent 4-6 group were: *L. crispatus* – 4.2 ± 0.8, *L. jensenii* – 3.8 ± 0.7, *L. iners* – 6.3 ± 1.1, *G. vaginalis* – 5.8 ± 0.9, *A. vaginae* – 4.9 ± 1.0. The *L. iners/L. crispatus* ratio correlated positively with pH (Spearman $r = 0.52$, $p < 0.01$) and with Nugent score ($r = 0.47$, $p = 0.012$).

Molecular profiles of the vaginal microbiome in patients with Nugent 4–6 often show a shift from CST-I (*L. crispatus*-dominated) or CST-V (*L. jensenii*-dominated) to CST-III (*L. iners*) or even CST-IV (anaerobic dominance) [6]. These transitions are often accompanied by decreased epithelial barrier function, increased pH, and latent immune activation, although symptoms may be absent. *G. vaginalis* and *A. vaginae* are found with moderate bacterial loads, which, in conditions of reduced lactobacilli, indicates an unstable microbiological state [15]. Studies based on qPCR and multiplex PCR confirm that in Nugent 4–6 there is a significant decrease in the quantitative content of *L. crispatus* and *L. jensenii* compared with healthy women, while the concentration of *L. iners*, *G. vaginalis*, and *M. hominis* increases [14]. In the study by Oliveira et al., the number of lactobacilli in Nugent 4–6 was shown to be statistically significantly lower than in Nugent 0–3 ($P < 0.05$), and the ratio of *G. vaginalis/Lactobacillus spp*. was significantly shifted towards the dominance of the former [16].

In addition, a meta-analysis of clinical trials has shown that Nugent 4–6 is associated with an increased risk of microbial instability, even in the absence of BV symptoms. In the three double-blind RCTs included in the meta-analysis by de Vrese et al., the mean Nugent score in the placebo group remained within the range of 4–6 with little change, while in the group taking the probiotic strains *L. crispatus, L. gasseri, L. jensenii* and *L. rhamnosus*, the Nugent score decreased significantly more often (OR = 3.9, 95% CI 1.7–9.0, $P = 0.001$). This suggests that even without clinical BV, this condition may be a target for intervention, especially in the context of reproductive planning [15].

So, CST classification demonstrated that 48% of intermediate samples corresponded to CST III (*L. iners*-dominant), 37% to CST IV (anaerobic type), and only 15% to CST I/V (L. crispatus or *L. jensenii* dominant) ($\chi^2 = 21.4$, $p < 0.001$) [14, 16].

Another evidence of the dynamic nature of Nugent 4–6 is the results of Lu et al., where microbiological markers were compared in three groups (healthy, BV, Nugent 4–6) [14]. Using machine learning algorithms, it was found that women with an intermediate microbiota have a variable microbiological portrait, but most often the proportion of *L. iners* in them is comparable or even exceeds the corresponding indicator in the BV group, while *L. crispatus* is practically absent. This fact indicates a distortion of the evolutionarily inherent profile of the vaginal biocenosis and the potential risk of its further destabilization. Pathophysiologically, such a configuration of the microbiota causes a decrease in lactic acid production, a decrease in

Table 1

Frequency of detection of microorganisms in Nugent groups 0–3, 4–6 and ≥7

Microorganism	Nugent 0–3 (%)	Nugent 4–6 (%)	Nugent ≥7 (%)	p value (vs 0–3)
Lactobacillus crispatus	78.4	22.5	5.6	<0.001
Lactobacillus jensenii	64.1	27.2	10.3	<0.001
Lactobacillus iners	25.7	63.2	72.8	0.002
Gardnerella vaginalis	10.3	58.9	91.1	<0.001
Atopobium vaginae	4.1	32.5	85.7	<0.001
Mycoplasma hominis	1.2	15.3	67.4	<0.001
Mobiluncus spp.	78.4	22.5	5.6	<0.001

Note: χ^2 test, data from Oliveira et al., 2018; Lu et al., 2024.

the redox potential of the vaginal environment, and a disruption of the mucin layer, which opens the gate for epithelial adhesion of pathogens. Furthermore, the presence of even moderate amounts of *A. vaginae* and *M. hominis* in combination with an altered microbial taxa balance can trigger low-level chronic inflammation involving Toll-like receptors, particularly TLR4 and NOD receptors [14].

Therefore, Nugent 4–6 should not be considered a variant of the norm, but rather a marker of microbiome instability. Its presence indicates a predisposition to develop BV in the future, and in combination with clinical symptoms, the need for careful monitoring or preventive therapy. Understanding the structural features of the microbiota in this interval is key to risk stratification and individualization of patient management.

The Nugent 4–6 score does not allow for an unequivocal diagnosis of bacterial vaginosis, but its clinical significance is not neutral. This condition should be considered as a potentially unstable microbiological profile that can either spontaneously normalize or transform into full-blown BV. Therefore, the clinical management of patients with an intermediate score should be based on a combination of history, symptoms, pH, reproductive status, and risk of complications. Several studies have shown that even in the absence of symptoms, women with Nugent 4–6 are at increased risk of developing urogenital infections, including BV, candidiasis, chlamydia, HPV-associated conditions, and pregnancy complications [15]. The physiological instability of the microbiota that characterizes this interval is due to the loss of the dominant role of *L. crispatus* and *L. jensenii*, with the simultaneous emergence of anaerobes or opportunistic taxa such as *G. vaginalis, A. vaginae, M. hominis* and *Mobiluncus spp*. [16]. In most cases, *L. iners* predominates, which, although it is a lactobacillus, exhibits limited antimicrobial activity, has a low ability to produce hydrogen peroxide, and easily coexists with BV-associated species [17]. Among symptomatic women with Nugent 4–6 (n = 76), 67% reported abnormal discharge, 42% odor, and 29% itching. Symptom intensity correlated with pH ($r = 0.41$, $p < 0.01$) and *A. vaginae* load (OR = 3.2; 95% CI 1.6–6.5; $p = 0.004$). Serum cytokine data available for 48 patients revealed elevated IL-6 (13.4 ± 2.5 pg/mL) and TNF-α (11.2 ± 3.0 pg/mL) compared with the normal group (8.1 ± 2.2 pg/mL and 6.7 ± 1.9 pg/mL, respectively; $p < 0.05$) [9, 17].

According to current studies, the structure of the vaginal microbiome in patients with a Nugent score of 4–6 demonstrates a high degree of variability, which complicates the clinical interpretation of this condition. The presence of reduced levels of *Lactobacillus crispatus* and *L. jensenii* is accompanied by a predominance of *Lactobacillus iners* or BV-associated anaerobes, such as *Gardnerella vaginalis* or *Atopobium vaginae*, which is characteristic of the CST-IV profile [18]. As Wang X. notes, it is precisely such changes in the microbial composition that are associated with an increased risk of developing symptomatic bacterial vaginosis, even if the Nugent score does not exceed 6 points. This confirms the importance of interpreting not only the morphotype, but also the clinical context, the pH of the environment and the patient's history [19].

It is known that *L. iners*, despite belonging to the genus *Lactobacillus*, has limited protective properties compared to *L. crispatus*, in particular with regard to the synthesis of lactic acid and bacteriocins [20]. Its presence is often a marker of instability or a transitional state of the microbiota. Therefore, Nugent 4–6 should not be considered as a definitively healthy state, but rather as a point of potential transition to dysbiosis. Bloom et al. indicate that *L. iners* has a dependence on exogenous cysteine, which may be therapeutically significant in attempts to regulate its population [21].

In clinical studies, oral probiotics containing *L. rhamnosus* GR 1 and *L. reuteri* RC 14 have been shown to improve Nugent scores, particularly in women with scores of 4-6, with a return to *L. crispatus* dominance [22, 23]. The efficacy of the interventions was particularly pronounced in patients with elevated pH and mild clinical manifestations. Marschalek et al. demonstrated that even in the setting of chemotherapy in women with cancer, probiotic intervention allowed for stabilization of the vaginal biota [24].

Clinical strategy in Nugent 4-6 cases should take into account individual characteristics, including reproductive status, pregnancy, symptoms, history of BV recurrence and sexually transmitted infections. In the presence of risk factors and clinical complaints, the use of probiotics, vaginal pH regulators or even short-term antimicrobial therapy is recommended. However, in asymptomatic women with physiological pH, a watchful waiting strategy with dynamic observation is advisable.

Modern approaches to diagnostics, in particular multiplex PCR and deep sequencing, have the potential to improve the stratification of microbiological variants within Nugent 4–6, which will allow to avoid overtreatment and at the same time not to miss clinically significant cases of initial dysbiosis [25]. Thus, Nugent 4-6 is a heterogeneous condition in terms of its microbial composition and clinical prognosis, which requires an individualized approach to management based on modern microbiological criteria.

Molecular studies, in particular using multiplex qPCR, allow to assess not only morphotypes, but also the actual bacterial load. For example, in the study of Cox C. et al., patients with Nugent 4–6 had mean values of *L. iners* and *G. vaginalis* loads higher than healthy subjects, but lower than in the group with BV, which supports the hypothesis of the transient nature of this condition. In addition, the authors found that with a stable pH <4.5 and a high proportion of *L. iners* without symptoms, it is possible to maintain conservative tactics, while with a pH >4.5 and clinical manifestations of vaginal discomfort, early intervention is recommended [26]. It is significant that according to the results of a systematic review by Yefet E. et al., 2019, three independent RCTs that evaluated the effect of oral probiotics (*L. crispatus, L. gasseri, L. jensenii, L. rhamnosus*) on the state of the microbiota showed a statistically significant decrease in the Nugent score in women with initial scores of 4–6 ($P < 0.01$) [27]. Among pregnant participants (n = 84), those with intermediate Nugent scores had a 2.3-fold increased risk of preterm birth (RR = 2.32; 95% CI 1.4-3.7; $p = 0.002$) and a

1.9-fold increased risk of low birth weight (RR = 1.86; 95% CI 1.1-3.1; p = 0.009) compared with women with Nugent 0–3 [28, 29]. Probiotic maintenance during pregnancy decreased recurrence of dysbiosis from 36% to 12% (p = 0.01) [27]. In two studies that assessed the rate of normalization of Nugent score to <4, the odds of improvement were almost four times higher in the probiotic group (OR = 3.9) compared with placebo [27]. This highlights the potential of non-hormonal interventions both in the prevention of BV and in stabilizing the vaginal microbial balance in the early stages of its disturbance.

A differentiated approach to the management of patients with Nugent 4–6 in the context of pregnancy or conception planning is particularly relevant. It is known that disruption of the vaginal microbiome is one of the independent predictors of preterm birth, low birth weight and chorioamnionitis. According to meta-analyses, even modest changes in the *Lactobacillus*/anaerobes ratio are associated with higher risk [28]. Therefore, active intervention is justified in patients with relevant risk factors or a history of miscarriage.

At the same time, it should be taken into account that Nugent 4-6 without symptoms and with normal pH may be a physiological variant or a consequence of transient changes (for example, in the phase of the menstrual cycle, after sexual intercourse or the use of antibiotics). In such conditions, dynamic observation and re-evaluation after 1–2 weeks are recommended before making a decision on therapy [24]. In a subgroup (n = 52) receiving combined therapy (metronidazole + probiotics), the mean Nugent score decreased from 5.1 ± 0.7 to 2.8 ± 0.6 (p < 0.001), with restoration of *L. crispatus* dominance in 64% of cases. By contrast, in women under observation alone, spontaneous normalization occurred in 33%, while 29% worsened to BV within 4 weeks (p = 0.02). These data confirm that targeted modulation of the microbiome can prevent progression and support eubiosis [23, 24].

Patients with a Nugent score of 4–6 constitute a clinically heterogeneous group in which the features of a healthy microbiota and initial signs of dysbiosis overlap. This determines the need to stratify management tactics depending on symptoms, physiological status, vaginal pH, reproductive goals and risk factors. In most cases, such a Nugent score is interpreted as an altered vaginal microbiota or an intermediate variant between normal and bacterial vaginosis (BV), but the border between a transient norm and the debut of pathology remains blurred [30].

Current clinical guidelines do not provide clear guidance on intervention for Nugent 4–6, so a personalized approach is key (Table 2).

Observation is advisable in the absence of symptoms of BV (abnormal discharge, itching, odor), a maintained pH ≤4.5 and a dominance of *Lactobacillus iners* without signs of anaerobic transformation. However, even in such cases, Nugent 4–6 can be unstable – up to 30% of women with this score demonstrate an increase in Nugent ≥7 within 2–3 weeks, especially if there is a history of BV or changes in the microbiota after antibiotic therapy [10].

Molecular methods, including multiplex PCR and 16S rRNA sequencing, allow better characterization of the microbiome composition in patients with Nugent 4-6, especially in cases of clinical ambiguity. For example, the presence of *Gardnerella vaginalis, Atopobium vaginae*, *Megasphaera spp., Mobiluncus spp*. in significant numbers indicates a BV-associated microbiome even with Nugent <7. Data from Lu S. et al., confirm that errors in identification are most frequent in the category of "altered biota" for both specialists and neural network models – this requires care in the clinical assessment of such results [14].

Interest in innovative digital tools is growing – neural networks, in particular CNN, demonstrate accuracy of up to 94% in predicting Nugent categories from Gram-stained images [30]. Their potential implementation in clinical practice will reduce the variability of diagnostics between specialists and provide standardized assessment of patients, especially in primary care settings or limited access to laboratories.

During a 3-month follow-up of women with Nugent 4-6 (n = 68), 28% progressed to ≥ 7, 55% reverted to ≤ 3, and 17% remained stable. The probability of progression was significantly higher when *L. iners* constituted > 60% of reads (p = 0.03). Logistic regression identified high vaginal pH (> 4.5) and prior antibiotic exposure as independent predictors of BV progression (OR = 2.8; 95% CI 1.3–5.9; p = 0.005) [14, 15].

When choosing a preventive tactic, the immunological reactivity of the mucosa, the level of lactic acid production and the ability of the microbiome to self-cleanse should be taken into account. The most justified is therapy with probiotics containing *Lactobacillus crispatus,*

Table 2

Tactics of managing patients with Nugent 4–6

Clinical conditions	Recommended tactics	Comments / Examples
Asymptomatic, pH ≤4.5, no risk factors	Dynamic observation	Repeat examination in 10–14 days
No symptoms but with risk factors (pregnancy, IVF, recurrent BV)	Preventive intervention	Oral probiotics (*L. crispatus, L. rhamnosus*) ± lactic acid
BV symptoms (discharge, odor, discomfort), pH >4.5	Active therapy	Metronidazole or clindamycin + probiotics
Immunosuppression, HIV, frequent relapses, CST-IV changes	Combination treatment	Antibacterials + long-term probiotic support
Suspicion of an alternative diagnosis (candidiasis, cytolysis)	Etiological treatment	Antifungals or other agents according to the clinic
Nugent's unstable results, microbiome unstable	Prevention + support	Probiotic courses, local pH normalization

L. rhamnosus and *L. gasseri*. Trials using these strains have shown a statistically significant reduction in Nugent scores in women with baseline values of 4–6 ($P < 0.01$) and an increase in the proportion of women with *L. crispatus* dominance after 14 days [15].

Data pooled from three randomized controlled trials (n = 486) demonstrated that oral probiotic therapy with *L. crispatus*, *L. rhamnosus*, *L. gasseri* and *L. jensenii* reduced mean Nugent score by 1.8 ± 0.6 points versus 0.3 ± 0.5 in placebo ($p < 0.001$). Normalization (Nugent ≤ 3) was achieved in 46% of the probiotic group compared with 12% in controls (OR = 3.9; 95% CI 1.7-9.0; $p < 0.01$). Women with baseline Nugent 4–6 and elevated pH benefited most, showing 68% reversion to normal microbiota after 2 weeks of supplementation [15, 22].

In addition to probiotics, topical lactic acid and glycogen-based products that promote colonization of eubiotic lactobacilli are considered in the arsenal of prophylaxis. Their use may be justified in cases after menstruation, sexual intercourse, or antibiotic therapy, when the vaginal biocenosis is particularly vulnerable to dysbiotic shifts. It is known that periodic disturbances of microbial homeostasis in the setting of Nugent 4-6 may be asymptomatic, but are associated with transient inflammatory changes that facilitate the penetration of STIs [17]

In women of reproductive age at risk of pregnancy loss or preparing for IVF, more aggressive management is advisable even with asymptomatic Nugent 4-6. Meta-analyses have shown that changes in the microbial profile below the diagnostic threshold for BV already increase the risk of chorioamnionitis and preterm labor [29]. In such situations, short courses of intravaginal agents with bacteriostatic activity, combined with subsequent probiotic support, may be justified. As we continue to analyze the management of patients with Nugent 4-6, it is important to focus on cases that require not only prevention but also active intervention. Although this range of scores is not diagnostic for BV, in the presence of clinical symptoms (abnormal discharge, amine odor, itching, burning sensation) and a disturbed pH (>4.5), Nugent 4-6 may reflect a subclinical or initial form of BV that deserves targeted therapy. In such cases, the use of short courses of metronidazole (oral or vaginal) or clindamycin, followed by probiotics, has been shown to be effective in restoring vaginal eubiosis and reducing the risk of relapse [14].

This tactic is confirmed by the study by Yefet E. et al., in which, when analyzing patients with Nugent 4-6 and symptoms of BV, in more than 70% of cases, the microbiological profile (based on mPCR results) corresponded to BV-associated CST-IV. This indicates the limitations of traditional cytological diagnosis and the need for clinical thinking when interpreting intermediate results. This is especially important in the context of the increasing frequency of recurrent BV, when each intermediate state can become the basis for a chronic course [27, 31].

Another category of patients who require active intervention in Nugent 4-6 are women with immunodeficiencies, in particular HIV-infected. In such patients, the risk of progression of vaginal dysbiosis to a pronounced clinical picture of BV is significantly higher, and changes in the microbiome may be part of a general immune dysfunction [32]. Here, even minimal disturbances in the microbiota can have systemic consequences, including an increased risk of viral shedding, increased inflammation, and increased susceptibility to co-infections.

There are also microbiological situations that at first glance correspond to Nugent 4-6, but have a non-anaerobic etiology, for example, changes on the background of vaginal candidiasis or nonspecific inflammation after mechanical or chemical stimuli. In such cases, the tactics depend not so much on the Nugent score, but on the dominant pathophysiological factor. In the study of Sethi S. et al. showed that up to 20% of women with Nugent 4-6 had concomitant candidiasis or cytolytic vaginosis. Such conditions do not require classical anti-BV treatment, but require differentiated therapy, which once again emphasizes the importance of a comprehensive approach [33].

Data from meta-analyses and clinical trials also indicate that in case of repeated return of Nugent 4-6 after normalization (i.e., repeated instability of the microbiome), it is advisable to use a combined strategy: initial sanitation with antiseptic or antibacterial agents, followed by a course of probiotics lasting at least 14 days and maintenance therapy in the form of periodic administration of probiotics or lactic acid for 1–3 menstrual cycles [18]. This approach demonstrates higher efficacy in preventing relapses than short-term therapy.

Special attention should be paid to scenarios where Nugent 4–6 is part of the Nugent score + AI diagnostic algorithm pair. Abou Chacra L. et al demonstrated that the combined use of deep neural networks and molecular profiling allows for more accurate discrimination of intermediate states than standard microscopy [34]. In the future, this may form the basis of an integrated model for the management of vaginal infections, where Nugent will not be the only criterion. In general, Nugent 4-6 is not a "gray" result that should be ignored, but a marker of microbial instability. Its management should be dynamic and flexible: from expectant tactics to aggressive treatment – depending on the clinical context. The introduction of personalized medicine in the field of intimate health, taking into account microbiological, immune and behavioral factors, allows preventing complications and preserving the reproductive health of women.

Discussion. The findings presented in this review confirm that the intermediate Nugent score (4-6) represents a clinically significant yet diagnostically ambiguous state of the vaginal microbiota. While it does not meet the criteria for bacterial vaginosis (BV), it reflects a measurable disruption of the normal Lactobacillus-dominated ecosystem. Several independent studies have corroborated that this range frequently corresponds to *Lactobacillus iners* – dominant or mixed anaerobic communities, known in the community state type (CST) framework as CST III or CST IV [6, 14]. The recognition of this intermediate condition is important not only for microbiological classification but also for clinical management, as it can predict instability of the vaginal environment and higher susceptibility to infections and reproductive complications.

Microbiome instability and transitional dynamics. The transitional nature of the Nugent 4–6 state is reflected in both taxonomic and functional shifts within the vaginal

microbiota. Studies employing metagenomic and qPCR approaches have shown that *L. crispatus* and *L. jensenii*, which ensure optimal acidification and protection of epithelial barriers, decline significantly in women within this range, while *L. iners*, *Gardnerella vaginalis* and *Atopobium vaginae* increase in prevalence [10, 16]. Such reorganization weakens the ecological resilience of the vaginal community, rendering it more susceptible to external stressors like antibiotic use, hormonal fluctuations, or sexual activity [20].

The molecular and metabolic properties of *L. iners* are particularly relevant. Its smaller genome and limited capacity for hydrogen peroxide and D-lactic acid production reduce its ability to suppress anaerobes, while its persistence in fluctuating conditions may indicate a "repair" phase following dysbiosis [21]. Comparative genomic studies show that *L. iners* depends on exogenous cysteine for growth and lacks several biosynthetic pathways characteristic of protective *L. crispatus* [2] (Bhattacharya et al., 2023). This may explain its frequent dominance in transitional microbiomes and its association with an increased risk of BV recurrence [19].

Clinical relevance and predictive potential. Multiple studies link intermediate Nugent scores to adverse reproductive outcomes. Leitich et al. demonstrated that even modest reductions in *Lactobacillus* abundance below the BV diagnostic threshold correlate with higher rates of preterm delivery [28]. Similarly, Skafte-Holm et al. reported that women undergoing IVF with intermediate dysbiosis had lower implantation and pregnancy success rates [12]. These findings suggest that the Nugent 4-6 condition should be viewed as an early warning sign of potential reproductive risk rather than a benign variant of normality.

The variability in outcomes among women with the same Nugent 4-6 score underscores the limitations of morphology-based diagnostics. Factors such as local pH, immune activation markers, and CST profile must be integrated for accurate risk stratification. França et al. demonstrated that intermediate dysbiosis is accompanied by low-grade mucosal inflammation and modulation of cytokine responses, especially reduced IL-10 and elevated IL-6 and TNF-α levels [17]. These subtle immunologic changes, although often subclinical, contribute to epithelial barrier weakening and facilitate pathogen adhesion.

Moreover, molecular and metabolomic studies identified metabolite signatures such as gamma-hydroxybutyrate and 2-hydroxyisovalerate, which are enriched in Nugent 4–6 and BV microbiomes [13]. These metabolic indicators could serve as non-morphological biomarkers for microbiome instability and help refine diagnostic algorithms beyond the Nugent score alone.

Diagnostic challenges and technological evolution. The intermediate Nugent range remains problematic for clinicians because the morphologic criteria fail to capture microbial diversity and functional variability. The introduction of multiplex PCR panels and artificial intelligence–based microscopy has markedly improved the precision of diagnosis [14, 30]. For example, Theiler et al. found that multiplex PCR outperformed Nugent scoring in identifying early dysbiotic states, particularly in asymptomatic women [25]. Similarly, Abou Chacra et al. demonstrated that mass-spectrometry-based profiling accurately differentiates transitional and BV-associated microbiomes, potentially eliminating the diagnostic "gray zone" [34].

Artificial intelligence–driven models can further standardize Nugent interpretation. Convolutional neural networks trained on digital microscopy images have achieved up to 94% accuracy in distinguishing Nugent categories [30]. When combined with molecular and metabolic data, such systems could revolutionize clinical diagnostics by providing automated, multi-parameter classification of vaginal microbiota states.

Therapeutic implications and probiotic evidence. From a therapeutic perspective, managing Nugent 4–6 requires balancing under- and over-treatment. Observational data indicate that approximately one-third of women with this score progress to BV within two to three weeks, particularly when symptoms or pH > 4.5 are present [10]. Therefore, risk-based stratification is recommended.

Probiotic interventions have demonstrated the most consistent benefit in this population. A meta-analysis by de Vrese et al. showed that oral administration of *L. crispatus*, *L. rhamnosus*, *L. gasseri* and *L. jensenii* significantly reduced Nugent scores compared to placebo (OR = 3.9, $p < 0.01$) [15]. Subsequent randomized trials confirmed that *L. crispatus* restoration correlates with improved epithelial integrity and lower recurrence rates [22, 23]. Importantly, these benefits extend to women with subclinical dysbiosis, supporting early intervention strategies.

Marschalek et al. demonstrated that even in women undergoing chemotherapy – a group with impaired immunity – oral probiotics stabilized the vaginal biota and prevented dysbiosis progression [24]. Similarly, Yefet et al. showed that probiotic supplementation during pregnancy reduced the incidence of both BV and vulvovaginal candidiasis [27]. These findings support incorporating probiotics into prophylactic and adjunctive therapy for intermediate Nugent scores, particularly in high-risk settings.

Nonetheless, not all probiotic formulations are equally effective. Comparative genomic analyses reveal that *L. crispatus* strains exhibit superior adhesion, biosurfactant production, and bacteriocin synthesis relative to *L. gasseri* or *L. iners* [2]. Thus, strain-specific selection is critical for designing targeted therapies, and region-specific adaptation may further optimize efficacy.

Risk-based management algorithms. Clinical algorithms for Nugent 4–6 should integrate microbiological data with patient-specific risk factors. In asymptomatic women with physiological pH ≤ 4.5 and *L. iners* predominance, observation with re-evaluation in 10–14 days may suffice. However, women with high pH, recurrent BV, pregnancy, or immunocompromise require preventive or active treatment [28, 32].

Empirical regimens combining short courses of metronidazole or clindamycin with subsequent probiotic therapy have shown good outcomes in reducing BV recurrence [31]. The use of topical lactic acid or glycogen-based formulations can support restoration of acidic pH and enhance *Lactobacillus* recolonization [35].

Emerging evidence also supports the use of personalized microbiome restoration therapies. By sequencing an

individual's baseline CST profile, clinicians may soon predict the optimal probiotic or antimicrobial combination. As Bhattacharya et al. and Ottinger et al. note, the future of vaginal microbiota management lies in precision medicine – tailoring interventions to microbial genomics, host immunity, and lifestyle context [2, 23].

Future perspectives. Despite major progress, several gaps remain. The molecular determinants that govern the transition from Nugent 4–6 to BV are incompletely understood. Prospective longitudinal studies are needed to define the temporal stability of intermediate microbiomes and to identify predictive biomarkers. Moreover, current clinical trials often lack standardized endpoints, making cross-study comparison difficult. Integration of metagenomic sequencing, immune profiling, and metabolomics could enable creation of predictive models for early dysbiosis detection.

Another promising avenue involves the use of synthetic or bio-engineered probiotic consortia. Engineered *Lactobacillus* strains with enhanced lactic acid or hydrogen peroxide production could potentially outcompete anaerobes and restore long-term stability [23]. Meanwhile, AI-driven analysis of microbiome data could facilitate automated monitoring, flagging women whose microbiota trajectory suggests risk of BV progression.

In summary, the intermediate Nugent score is neither a benign finding nor a definitive disease marker but an early indicator of microbiome instability. Recognizing its dynamic nature and integrating molecular, immunological, and clinical dimensions are key to personalized management.

Conclusions. These conclusions are based on a synthesis of peer-reviewed scientific literature covering clinical, molecular and microbiome studies published between 2000 and 2025.

The assessment of the vaginal microbiome according to the Nugent scale within 4–6 points demonstrate a borderline microbiological state, which is accompanied by a decrease in the dominance of classical lactobacilli and an increase in the presence of opportunistic anaerobes. Analysis of the structure of such microbiota indicates the potential instability of the biocenosis and the likelihood of its progression to bacterial vaginosis. It has been established that Nugent 4–6 is often associated with a CST-IV profile, characterized by a low content of *L. crispatus* and a predominance of *L. iners* or gardnerella. Given this, the interpretation of intermediate results should not be carried out in isolation, but taking into account clinical symptoms, pH level, risk factors and history. The results of generalized studies confirm the feasibility of observation only in cases of asymptomatic course and preserved acidity. The presence of symptoms or reproductively significant conditions warrants prophylactic or therapeutic interventions, including the use of probiotic strains of *L. crispatus*, pH regulators, or short courses of antimicrobials. Clinical trial data demonstrate the effectiveness of such strategies in stabilizing the microbiome and reducing the risk of relapse. Experience with the implementation of personalized management algorithms demonstrates the importance of an individual approach in the assessment of Nugent 4–6. The determination of tactics should be based on microbiological and clinical parameters, as well as the reproductive goals of the patient. In the future, the integration of molecular methods, including qPCR and deep sequencing, as well as artificial intelligence into diagnostics, may improve the stratification of such cases. Thus, Nugent 4–6 is an indicator of a disturbance in the microbial balance, which requires careful clinical assessment and informed decisions about management tactics.

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