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Research Article

Vaginal Microbiota Towards Cervical Intraepithelial Neoplasia (CIN) Screening Test. An Analytic Review

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Running Title

Vaginal Microbiota Implication as Cervical Intraepithelial Neoplasia (CIN) Primary Screening Test

Abstract

Background: Vaginal microbiota has recently come to light as a new promising indicator of intraepithelial neoplasia. Bacterial dysbiosis appears to initiate a cytological pathway favorable to cancerous alterations. Therefore, the present systematic review was performed with the purpose of particularizing the microorganisms most often involved, the relevance with HPV infection, as well as microbiome's impact on precancerous alterations.

Methods: Following assiduous research up to August 2022 of the Pubmed and Cochrane databases inserting the terms 'vaginal microbiota AND dysplasia OR cervical intraepithelial neoplasia, a total of 10 articles were selected. Studies with clearly defined objectives and studied microorganisms were included. Exclusion criteria was a population number less than 20 people.

Results: An HPV infection bears a positive correlation with an abundance of Gartenella and Prevotella colonies and a negative one with Lactobacillus. Lactobacillus seems to have a protective role against HPV. Subsequently a Lactobacillus-depleted microbiota has proven to facilitate the progression of CIN severity.

Conclusion: Our findings suggest a strong bond between vaginal microbial population, predisposed for CIN development. Moreover, it presents a plethora of other clinical possibilities which favor the use of vaginal microbiota as a screening tool.

Keywords: *Vaginal Microbiota; Cervical Intraepithelial Neoplasia (CIN), Human Papillomavirus (HPV); Lactobacillus Spp; Persistent Vaginal Infection; Carcinogenic Factors.*

Introduction

Cervical dysplasia is characterized by the abnormal growth of cells on the surface of the cervix. This allows the entrance into the cervical tissue of human papillomavirus (HPV), which accounts for approximately 90% of cervical cancer cases. [1]

An estimated 500 000 people are diagnosed with cervical cancer yearly worldwide. Risk factors include HPV or herpes infection, immunodeficiency, smoking, age, oral contraceptives, socioeconomic factors, and exposure to diethylstilbestrol (DES). As far as age is concerned, the risk of developing cervical cancer peaks during the late teens and mid-30s and remains stable, requiring regular check-ups. [2]

HPV alone seems to be responsible for a high percentage of cases of cervical dysplasia. In Greece, the incidence of HPV infection is up to 50%, with the vaccination coverage remaining low up to the present date. [3]

Intestinal metaplasia affects the glandular epithelium of the endocervix. It is a metaplastic precursor of cervical cancer with the first case reported in 1965. Possible mechanisms are either a preexisting heteroplastic or metaplastic mucosa that precedes the development of neoplasia or metaplastic changes coinciding with the malignant transformation. [4]

Approximately 30 types of HPV are known to affect the genital tract, 15 of which are characterized as 'high-risk' and are associated with high-grade lesions and invasive cervical cancer. Of those, HPV16 and HPV18 cause the vast majority of squamous cell carcinomas and adenocarcinomas. Another 11 types, classified as 'low-risk', result in genital warts and benign cervical lesions. [Table 1] [5]

HPV alone is not likely to induce cancer, as genetic and epigenetic alterations are also required. Its mechanism of action results from the role of E6 and E7 oncogenic proteins in regulating the cell cycle, specifically apoptosis. The disruption of E2 protein's mechanism follows, which normally suppresses the E6 and E7. Lastly, immune evasion is promoted through the expression of the E5 oncogene. A combination of the above-mentioned pathways results in carcinogenesis. [6]

The two main types of dysplasia are Low-grade Squamous Intraepithelial lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL), which are potential precancerous states. [Figure 1] [Table 2] [7]

Figure 1: Cervical infiltration staging.

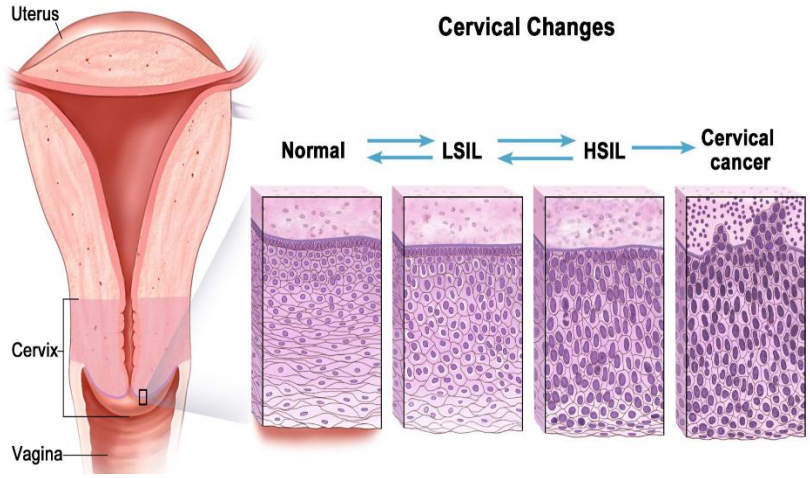

Table 1: Clinical depiction of HPV infiltration.

Disease	HPV type
Plantar warts	**1, 2,** 4, 63
Common warts	**2, 1, 7,** 4, 26, 27, 29, 41, 57, 65, 77, 1, 3, 4, 10, 28
Flat warts	**3, 10,** 26, 27, 28, 38, 41, 49, 75, 76
Other cutaneous lesions (e.g., epidermoid cysts, laryngeal carcinoma)	6, 11, 16, 30, 33, 36, 37, 38, 41, 48, 60, 72, 73
Epidermodysplasia verruciformis	**2, 3, 10, 5, 8, 9, 12, 14, 15, 17,** 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 50
Recurrent respiratory papillomatosis	**6, 11**
Focal epithelial hyperplasia of Heck	**13, 32**
Conjunctival papillomas/carcinomas	**6, 11, 16**
Condyloma acuminata (genital warts)	**6, 11,** 30, 42, 43, 45, 51, 54, 55, 70
Cervical intraepithelial neoplasia	
Unspecified	30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
Low risk	**6, 11,** 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 74
High risk	**16, 18,** 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
Cervical carcinoma	**16, 18,** 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70

The grade of dysplasia is determined by the percentage of dysplastic cells in the cervical epithelium. Thus, the lower ⅓ or less of the epithelium corresponds to low-grade or Cervical Intraepithelial Neoplasia (CIN) 1, while the invasion of the 2/3 of the epithelium corresponds to high-grade or CIN-2 and in situ to CIN-3. As the basement membrane is going to be penetrated, dysplasia depicts malignant infiltration. [8]

The primary screening method includes a Pap smear, colposcopy and potential cervical biopsy. The newest screening guidelines introduce the idea of cervical cancer testing to all patients with a cervix aged from 25 to 65, with either an HPV test done every 5 years, a combination of HPV and Papanicolaou smear testing every 5 years, or a Pap test alone every 3 years. [9]Routine vaccination against HPV is recommended for both sexes at the age of 11 or 12 years and includes two doses given 6 to 12 months apart. Vaccination after the age of 26 is not normally recommended, with the final decision based on a thorough discussion with a clinician.

Three types of vaccines are currently available. The bivalent Cervix is given in two doses six months apart for people aged 9 to 14 years and in three doses for people aged 15 and above. The quadrivalent Gardasil is administered in three doses at 0, 2 and 6 months. Lastly, the 9-valent Gardasil is given to patients from 9 through 14 years in either two or three doses apart, starting at 0, 6, 12 or 1, 2, 6 months respectively. Patients from 15 through 45 years receive a regimen of three doses and intervals of 0, 2 and 6 months. [10]

Table 2: Cervical infiltration cytological and histological classification.

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
Pap-test	Bethesda System	CIN	WHO
Class I	Normal	Normal	Normal
Class II	ASCUS ASC-H	Atypia	Atypia
Class III	LSIL	CIN1 including flat condyloma	Koilocytosis
	HSIL	CIN2	Moderate dysplasia
	HSIL	CIN3	Severe dysplasia
Class IV	HSIL	CIN3	Carcinoma in situ
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

ASCUS: atypical squamous cell of undetermined significance, ASC-H: atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion, CIN: cervical intraepithelial neoplasia, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion.

The vaginal microbiota is composed of a plethora of microorganisms, of which Lactobacillus crispatus, L. jensenii, and L. gasseri are the main ones and commonly cohabit in an equilibrium. [Table 3]

Table 3: Vaginal microbiota classification.

Gram-positive aerotolerant anaerobes cocci and bacilli	*Lactobacillus* *Streptococcus*
Gram-positive facultative anaerobes cocci and bacilli	*Corynebacterium* *Gartenella* *Staphylococcus (*mainly *S.epidermidis)*
Gram-negative facultative anaerobes bacilli	*Escherichia* *Klebsiella* *Proteus*
Micoplasmas	*Mycoplasma (*especially *M.hominis)* *Ureaplasma*
Gram-positive strict anaerobes cocci and bacilli	*Atopobium* *Peptococcus* *Peptostreptococcus* *Clostridium* *Bifidobacterium* *Propionibacterium* *Eubacterium*
Gram-negative strict anaerobes bacilli	*Bacteroides* *Prevotella*

Their role is to protect the vaginal mucosa from harmful pathogens by producing antimicrobial substances, and co-aggregation with the pathogens thus eliciting a microbicidal effect as well as blocking the colonization of the vaginal epithelium by pathogens. [11]

In women of reproductive age, the pH of the lower vagina estimated around 4.5, a value determined by the lactic acid produced by Lactobacillus spp. that dominates the healthy vaginal microbiome. [12]

Aging, particularly after the age of 45, has proved to lead to an increase in vaginal pH, with menopause being another factor diminishing cervical acidity. [13]

Fluctuation in cervical microbiota's composition is induced mainly by the menstrual cycle status and sexual activity, with other still unknown factors certainly playing a role. [14]

Material and Methods

Search Strategy

An assiduous analysis was performed throughout Pubmed and Cochrane databases until September 2022, entering the term 'vaginal microbiota' and selecting clinical trials and randomized controlled trials. The following search was restricted to the last decade and the language to English. A total of 10 articles were selected (Table 4), based on the following inclusion criteria: (1) patients with no previous surgical intervention in the uterine cavity, (2) known HPV infection, (3) sexually active patients. Exclusion criteria reflect previous hysterectomy, sexual intercourse or douching the previous 48h prior to the sample taking, history of cervical or other lower genital cancer as well as destructive therapy of the cervix.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 9 Software. All statistical values were reported with 95% Confidence Intervals (CI), whereas statistically significant was interpreted as a p-value less than 0.05. Further subgroup analyses were focused on parameters such as the positive and negative impact of an HPV infection and a CIN progression on the vaginal microbiota.

Study Selection and Characteristics

The selected studies refer to a time frame between 2015 and 2022, with a population ranging from a minimum of 69 up to 448 women. Mean age was calculated at about 34.2 years. From the studied women, about 15.53% were current or past smokers with a history of more than 100 lifetime cigarettes and 45.28% used any of the following contraceptive methods: pill, injectable, condom.

Table 4: Study group's demographic characteristics.

Author	Year	Population nr.	Age (years)	Smoker n(%)	Contraceptive use n(%)	HPV without CINs n(%) or Normal group	LSIL n(%)	HSIL n(%)	ICC n(%)
Mitra et al. [27]	2015	169	31	41 (24.26)	63 (37.28)	20 (11.83)	52 (30.77)	92 (54.44)	5 (2.96)
Dareng et al. [28]	2016	278	36.05	8 (2.88)	62 (22.3)	NS	NS	NS	NS
van de Wijgert et al. [29]	2019	448	34	50 (11.16)	113 (25.2)	NS	NS	NS	NS
Usyk et al. [30]	2020	273	22.9	65 (23.8)	263 (96.33)	NS	NS	NS	NS
Chen et al. [31]	2020	229	45.26	NS	NS	78 (34.01)	51 (4.87)	23 (10.04)	9 (3.93)
Wu et al. [32]	2020	69	38.5	NS	NS	31 (44.93)	22 (31.88)	16 (23.19)	0 (0)
McKee et al. [33]	2020	109	26	NS	NS	55 (50.46)	45 (37.19)	6 (4.96)	3 (2.48)
Zhai et al. [34]	2021	168	41.19	NS	NS	58 (34.52)	32 (19.05)	40 (23.81)	38 (22.62)
Carter et al. [35]	2021	84	29	NS	NS	NS	NS	NS	NS
Lin et al. [36]	2022	448	38.05	NS	NS	NS	NS	NS	NS

CIN intraepithelial neoplasia, LSIL Low-grade squamous intraepithelial lesions, HSIL High-grade squamous intraepithelial lesions, ICC Invasive cervical cancer, NS not specified.

Results

HPV or possible precancerous lesions were not specified in five studies. The resulting data portrayed a total of 35.15% women either healthy or presenting an HPV infection without CIN, 24.75% women with low-grade squamous intraepithelial lesions, 23.89% with a high-grade squamous intraepithelial lesion and 6.4% women with invasive cervical cancer.

Lactobacillus and Gardnerella vaginalis are the most abundant microorganisms found in a healthy vagina. An HPV infection seems to increase Gardnerella and Prevotella abundance, while diminishing the number of Lactobacillus population. No statistically significant result could predict an association in the progression of CIN severity. [Table 5].

Discussion

We performed an analytic review of the current bibliography pertaining to the vaginal microbiota as a possible biomarker of intraepithelial neoplasia. Though a correlation between the type of prevailing vaginocervical micro-organisms and the development of precancerous lesions has been widely speculated, the up-to-date literature has not yet brought to light substantial evidence.

Our study deduces Lactobacillus as the most abundant vaginal microorganism, whose population significantly diminishes with an HPV infection. Similarly, Gartenella and Prevotella abundance is positively correlated with an HPV condition. Moreover, a Lactobacillus-depleted microbiota has proven to facilitate the progression of CIN severity.

Table 5: Vagina's microbial population.

Author	Year	Most abundant microorganism	Positive HPV impact on its abundance	Negative HPV impact on its abundance	Positive association with the progression of CIN severity	Negative association with the progression of CIN severity
Mitra et al. [27]	2015	*Lactobacillus spp.*	NS	*Lactobacillus crispatus, Lactobacillus jensenii*	*Lactobacillus-depleted, Sneathia sanguinegens, Anaerococcus tetradius, Peptostreptococcus anaerobius*	*Lactobacillus spp, Lactobacillus crispatus*
Dareng et al. [28]	2016	*L. iners, Atopobium vaginae, Gardnerella vaginalis, L. crispatus*	*Prevotella, Leptotrichia*	*Lactobacillus sp., L. crispatus, L. iners*	NS	NS
van de Wijgert et al. [29]	2019	*Lactobacillus iners*	NS	*Lactobacillus crispatus* or *jensenii*	NS	NS
Usyk et al. [30]	2020	*Lactobacillus, Gardnerella vaginalis*	*G. vaginalis*	*L. iners*	NS	NS
Chen et al. [31]	2020	*Lactobacillus, Firmicutes, Actinobacteria, Bacteroidetes, Fuso- bacteria, Proteobacteria*	*Prevotella, Bacillus, Anaerococcus, Sneathia, Megasphaera, Streptococcus and Anaerococcus, Bacteroidetes, Sneathia sanguinegens, Bifidobacterium unclassified, Candidatus Mycoplasma, Comamonadaceae, Veillonella montpellierensis, Faecalibacterium, Finegoldia unclassified, Fusobacterium mortiferum, Porphyromonas uenonis, Ralstonia pickettii, Fusobacteria, Proteobacteria, Sneathia sanguinegens, Bifidobacterium unclassified, Candidatus Mycoplasma, Comamonadaceae, Veillonella*	*Lactobacillus, Gardnerella, Atopobium*	*Bacillus, Anaerococcus*	*Gradnerella vaginalis*

			montpellierensis, Faecalibacterium, Finegoldia, Fusobacterium mortiferum, Porphyromonas uenonis, Ralstonia pickettii			
Wu et al. [32]	2020	*Lactobacillus*	NS	NS	NS	*Peptostreptococcaceae, Pseudomonadales*
McKee et al. [33]	2020	*Gardnerella vaginalis, L. iners, L. crispatus*	*Gardnerella vaginalis*	*Lactobacillus spp., L. iners, L. gasseri.*		
Zhai et al. [34]	2021	*Lactobacillus (Firmicutes), Gardnerella (Actinobacteria)*	*Gardnerella, Prevotella*	*Lactobacillus, Ignatzschineria*	*Gardnerella and Prevotella*	*Lactobacillus, Ignatzschineria*
Carter et al. [35]	2021	*L. iners, Gardnerella*	NS	*Lactobacillus crispatus*	NS	NS
Lin et al. [36]	2022	*Lactobacillus, Firmicutes*	*Gardnerella, Prevotella, Actinobacteria, Bacteroides*	*Firmicutes*	NS	NS

These findings support the idea of further development of existing vaginal microbiome screening tests, which offer promising diagnostic and therapeutic possibilities. Thus, vaginal microbiota componency could be used as a biomarker in screening the general population for CIN or its predisposure. [15]

Further possibilities would be suppressing certain pathogen microorganisms that favor precancerous lesions but also further infections, such as bacterial vaginosis and other relevant infectious entities. [16]

A special focus could be placed on vaginal microbiome transplantations as a possible preventive or therapeutic method against CIN lesions. [17]

Microbial dysbiosis is associated with unfavorable obstetric outcomes and complications. Specifically, it increases the risk of spontaneous preterm birth. Early vaginal cultures have been suggested as a predictor factor of a pregnancy's outcome. A microbiota-based diagnosis and therapy is therefore encouraged for further studies. [18]

Furthermore, we propose that the association between vaginal microbiota and reproductive health, particularly infertility among women, should be analyzed extensively. Hong, X. et al. suggests a negative correlation between a Lactobacillus rich vaginal microbiota and female infertility. [19]

Skafte-Holm et al. indicates a negative impact of vaginal dysbiosis on pregnancy rates per embryo transfer in in vitro fertilization (IVF). [20]

The vaginal microbiota could be also studied as a tool to predict IVF success. Koedooder et al. suggests a division into favorable and unfavorable microbiome profiles of the vaginal microbiota, with specific characteristic and microbial populations of each. [21]

As estrogen is regulated by the gut microbiota through secretion of β-glucuronidase, it subsequently impacts the vaginal microbiome. Thus, it safe to admit that further studies of the gut microbiome would have a strong impact on understanding and modulating the vaginal microbiota. [22]

Limitations

The current study has several limitations. The scarceness of up-to-date evidenced-based literature could potentially lead to biased results. Parameters such as onset of sexual activity, number of sexual partners, HPV vaccination, safe sexual practices and genetics influence the outcome. Thus, we propose further studies of vaginal microbiota focusing on detailed characteristics of the studies arms and their more accurate comparison.

Disclosure of Interest

All authors declare any financial interest with respect to this manuscript.

Conclusion and Take-away message

Vaginal microbiota seems to be the cornerstone for future studies of the female reproductive tract. As opposed to the uterine microbiota, its sample extraction is non-invasive, cheaper, less time-consuming and with significantly less discomfort for the patient. Its connection to the diagnosis and therapy of infections, cancerous lesions, as well as fertility and pregnancy outcome, sets a promising tone for the contemporary researcher and clinician.

It consists without doubt a significant role towards potential screening test of CIN (cervical intraepithelial neoplasia), especially in reproductive ages. Multidisciplinary approach seems mandatory, in order to establish proper diagnosis and therapeutic mapping.

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