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绝经期女性阴道微生态状况及发生生殖道萎缩程度的相关性 *

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摘要 目的：评估绝经期女性阴道微生态状况，分析其与发生生殖道萎缩程度的相关性。**方法：**回顾性分析 2015~2018 年于本院妇科门诊就诊的 120 例绝经期女性患者的临床资料，获取所有患者阴道分泌物清洁度，优势菌群种类、密集度、多样性，阴道 pH 值、H_2O_2、白细胞酯酶、唾液酸苷酶，阴道假丝酵母菌病(VVC)、滴虫性阴道炎(TV)、细菌性阴道病(BV)、需氧菌性阴道病(AV)阳性率；采用相关统计资料分析阴道微生态状态与发生生殖道萎缩相关性。**结果：**绝经期女性阴道清洁度Ⅲ/Ⅳ度占比 70%、Ⅰ/Ⅱ度占比 30%；优势菌群以 G 染色不定球杆菌、G- 大杆菌为主，G- 小杆菌较少；菌群密集度、多样性程度较高；PH 值为 >4.5 占比 70%，提示阴道环境处于中性 / 碱性状态居多；H_2O_2、白细胞酯酶、唾液酸苷酶、VVC、BV 阳性占比高而 TV、AV 阳性占比低。清洁度Ⅰ/Ⅱ度、菌群密集度 +++/++++、菌群多样性 +++/++++、PH 值 3.8~4.5、H_2O_2(-)、唾液酸苷酶(-)、VVC(-)、BV(-/ 中介)时阴道萎缩发生率低于清洁度Ⅲ/Ⅳ度、菌群密集度未见 /+、菌群多样性未见 /+、pH 值 >4.5、H_2O_2(+)、唾液酸苷酶(+)、VVC(+)、BV(+)时阴道萎缩发生率(P<0.05)；清洁度Ⅰ/Ⅱ度、菌群密集度 +++/++++、菌群多样性 +++/++++、pH 值 3.8~4.5、H_2O_2(-)、唾液酸苷酶(-)、BV(-/ 中介)时阴道萎缩严重程度更低(P<0.05)。清洁度、菌群密集度、菌群多样性、pH 值、H_2O_2、唾液酸苷酶、BV 是阴道萎缩病情进展为中 / 重度独立影响因素(P<0.05)。**结论：**绝经期女性阴道微生态处于失衡状态，且微生态状况与阴道萎缩发生及发展密切相关。

关键词：绝经期女性；阴道微生态状况；生殖道萎缩程度；相关性

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Correlation between Vaginal Microecological Status and Reproductive Tract Atrophy in Postmenopausal Women*

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ABSTRACT Objective: To investigate the correlation between vaginal microecological status and reproductive tract atrophy in postmenopausal women. **Methods:** The clinical data of 120 menopausal women in our gynecology clinic of our hospital from 2015 to 2018 were analyzed retrospectively. The cleanliness of all patients' vaginal secretions, the species, density and diversity of dominant bacteria, the vaginal pH, H_2O_2, leucocyte esterase, sialidase, the positive rate of vulvovaginal candidiasis (VVC), trichomonas vaginitis (TV), bacterial vaginosis (BV), and aerobic vaginosis (AV) were obtained. Then the correlation between vaginal microecology and genital atrophy was analyzed by statistical data. **Results:** The vaginal cleanness at Ⅲ he vaginal cleanness at nal microecology and genital The predominant bacterial flora was mainly Gram variable coccobacilli, and G- large bacillus, but less G- microbacteria; The density and diversity of flora were high; The proportion of the patients with a pH value of >4.5 was 70%, indicating that the vaginal environment was mostly in neutral/alkaline state. The positive proportion of H_2O_2, leucocyte esterase, sialidase, VVC and BV was high, while the positive proportion of TV and AV was low. The incidence of vaginal atrophy of cleanliness inal atrophyroportion of TV and AV>4.5 was 70%, indicating that the vaginal environme H_2O_2 (-), sialidase (-), VVC (-), and BV (-/ intermediate) was lower than that of cleanliness l environmenflora density (not seen/+), flora diversity (not seen/+), pH value > 4.5, H_2O_2 (+), sialidase (+), VVC (+), and BV (+), with statistic difference (P<0.05). The incidence of vaginal atrophy was the lowest in cleanliness Ⅰ/Ⅱ degree, flora density +++ / ++++, flora diversity +++ / ++++, pH value 3.8~4.5, H_2O_2 (-), sialidase (-) and BV (-/ intermediate). Cleanliness, flora density, flora diversity, pH value, H_2O_2, sialidase and BV were the independent influencing factors for the moderate/severe progression of vaginal atrophy (P<0.05). **Conclusion:** The vaginal microecology of menopausal women is in an unbalanced state, and the microecology is closely related to the occurrence and development of vaginal atrophy.

Key words: Postmenopausal women; Vaginal microecology; Degree of genital tract atrophy; Correlation

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前言

女性阴道微生态平衡为环境、宿主共同作用、相互依赖的结果，正常阴道微生态是生殖健康重要指标之一。阴道微生态平衡受多种阴道菌群数量及分布、pH 值等的影响，内源性致病菌和外源性有害菌可导致阴道微生态失衡，诱发生殖系统感染性疾病、不孕甚至宫颈癌等[1-3]。而绝经期妇女由于性激素不足、生理心理因素、人际关系、社会、经济等的改变，会出现一系列与绝经相关的健康问题[4]。其中生殖道萎缩疾病为女性较为严重的疾病，可能直接影响女性性功能障碍。研究显示，绝经期妇女雌激素水平分泌不足，阴道壁萎缩，黏膜变薄，阴道分泌物减少、阴道弹性降低，导致阴道萎缩、干涩[5-7]。阴道萎缩造成的女性性功能障碍发生率逐年增高，但关于其发生机制及病情进展高危因素尚存在争议，对生殖道萎缩程度的探讨尚无临床大数据支持。文献指出，女性阴道微生态平衡在保证女性健康、预防相关生殖道疾病中有重要价值[8]，本文认为探讨女性阴道微生态状态有助于了解生殖道萎缩发生及进展的相关因素。因此本研究就此展开报道，全面评估绝经期女性阴道微生态状况，以期为临床防治阴道微生态失衡及其引起的相关生殖道疾病提供新的策略依据。

1 资料与方法

1.1 一般资料

经本院医学伦理会讨论并批准后，选择 2015~2018 年于本院妇科门诊就诊的 120 例绝经期女性的临床资料进行回顾性分析，所有患者及家属均对本研究知情并自愿入组。① 绝经期妇女；② 年龄 45~60 岁；③ 入院检查前半个月无阴道用药史或相关治疗史；④ 临床资料完整，相关检查完善；⑤ 无重大生殖道手术史。排除标准：① 妊娠期或哺乳期妇女；② 依从性特别差或中途要求退出的受试者；③ 标本采集困难或标本不正确；④ 合并心、肝、肾、肺等内、外科严重疾病；⑤ 临床研究过程中出现严重合并症或并发症者需进行其他治疗者。

1.2 方法

收集所有研究对象基线资料[年龄、身高、身体质量指数(Body mass index, BMI)、孕产史、月经史、既往病史]；由临床医生用无菌医用棉签采集女性阴道后穹隆处分泌物，要求为月经干净 3~7 d 后且采样前 3 d 无性生活及阴道用药史，采样后 1 h 内送检，所有检测标本用试剂盒配套稀释液稀释后分别检测：评估阴道清洁度；确定优势菌群项目、密集度、多样性；干化学检测 PH 值、H_2O_2、白细胞酯酶、唾液酸苷酶；相差显微镜湿片镜检确定阴道炎[外阴道假丝酵母菌病(Vulvovaginal candidiasis, VVC)为镜下发现假丝酵母菌芽孢或(和)菌丝：滴虫性阴道炎(Trichomonal vaginitis, TV)为镜下见阴道毛滴虫；细菌性阴道病(Bacterial vaginosis, BV)为革兰染色镜检下 Nugent 评分≥ 7 分、4~6 分中介、0~3 分正常；需氧菌性阴道病 (Aerobic vaginosis, AV) 为 AV 评分≥ 3 分、<3 分正常、3~4 分轻度 AV、5~6 分中度 AV、>6 分重度 AV]。

1.3 判定标准

阴道清洁度：如果有特殊病原体判定为Ⅲ/Ⅳ度，没有特殊病原体如下划分：Ⅰ度(正常)：杆菌(+++~++++)、杂菌(-)、上皮细胞(+++~++++)、白细胞 / 脓细胞(0~5 Hp)；Ⅱ度(正常)：杆菌(+~++)、杂菌(少)、上皮细胞(++~+++)、白细胞 / 脓细胞(5~15 Hp)；Ⅲ度(炎症)：杆菌(-~+)、杂菌(多)、上皮细胞(-/+~++)、白细胞 / 脓细胞(15~30 Hp)；Ⅳ度(严重阴道炎)：杆菌(-)、杂菌(大量)、上皮细胞(-)、白细胞 / 脓细胞(>30 Hp)。Nugent 评分：参照相关标准[9]，根据菌体数、定量、乳杆菌、类杆菌和染色不定动弯小杆菌判定。AV 评分[10]：0 分：LBG Ⅰ或Ⅱa、白细胞数≤ 10/HPF、中毒性白细胞无或散在、背景菌落不明显或溶胞性、PBC 无或 <1%；1 分：LBG Ⅱb、白细胞数 >10/HPF 或 <10/ 上皮细胞、中毒性白细胞≤ 50%的白细胞、背景菌落以大肠埃希菌类的小杆菌为主、PBC≤ 10%；2 分：LBGⅢ、白细胞数 >10/ 上皮细胞、中毒性白细胞 >50%的白细胞、球菌养或呈链状背景菌落、PBC>10%。

1.4 统计学处理

使用 spss18.0 软件进行统计分析，针对不同样本及不同比较模式选择 F 检验、卡方检验、相关性分析、偏相关性分析及归因分析等；对阴道萎缩严重程度有鉴别诊断意义(P<0.05)的自变量均引入二分类 Logistic 多元回归方程，分析影响阴道萎缩疾病进展独立因素；进检验水准 α=0.05，以 P<0.05 表示数据比

表 1 阴道微生态状况特征分析 [n (%)]

Table 1 Analysis of characteristics of vaginal microecological conditions [n (%)]

Item	Menopause Group(n=120)	
	n	%
Cleanliness		
Ⅰleanliness	57	47.50
Ⅲ 7.50 liness	63	52.50
Dominant flora		
G + bacilli	20	16.67
G + bacterium	16	13.33
G - bacterium	24	20.00
G - bacterium	4	3.33
G + cocci	13	10.83
G. Staphylococcus aureus	32	26.67
no	11	9.17
Flora density		
Not seen	2	1.67
+/++	35	29.17
+++/++++	83	69.17
Flora diversity		
Not seen	6	5.00
+	88	73.33
++/+++	26	21.67
pH		
3.8~4.5	36	30.00
>4.5	84	70.00

较结果有统计学意义。

2 结果

2.1 阴道微生态状况特征分析

绝经期女性阴道清洁度Ⅲ/Ⅳ度占比 70%、Ⅰ/Ⅱ度占比 30%；优势菌群以 G 染色不定球杆菌、G- 大杆菌为主，G- 小杆菌较少；菌群密集度、多样性程度较高；pH 值为 >4.5 占比 70%，提示阴道环境处于中性 / 碱性状态居多(表 1)。H_2O_2、白细胞酯酶、唾液酸苷酶、VVC、BV 阳性率分别为 82.50%(99/120)、91.67% (110/120)、58.33% (70/120)、81.67% (98/120)、51.67% (62/120) 占比高，而 TV、AV 阳性率分别为 7.50%(9/120)、55.83%(67/120)占比低。

2.2 阴道微生态状况与生殖道萎缩发生相关性分析

门诊检查时确定绝经期女性发生阴道萎缩例数为 79 例(占比 65.83%)，其中轻度 28 例、中度 26 例、重度 25 例。清洁度Ⅰ/Ⅱ度、菌群密集度 +++/++++、菌群多样性 +++/++++、pH 值 3.8~4.5、H_2O_2(-)、唾液酸苷酶(-)、VVC(-)、BV(-/ 中介)时阴道萎缩发生率低于清洁度Ⅲ/Ⅳ度、菌群密集度未见 /+、菌群多样性未见 /+、PH 值 >4.5、H_2O_2(+)、唾液酸苷酶(+)、VVC(+)、BV(+)时阴道萎缩发生率(P<0.05)，发生阴道萎缩组和未发生阴道萎缩组优势菌群、白细胞酯酶、TV、AV 比较无显著差异(P>0.05)；轻度、中度、重度阴道萎缩组内比较结果显示，清洁度Ⅰ/Ⅱ度、菌群密集度 +++/++++、菌群多样性 +++/++++、pH 值 3.8~4.5、H_2O_2(-)、唾液酸苷酶(-)、BV(-/ 中介)时阴道萎缩严重程度低于清洁度Ⅲ/Ⅳ度、菌群密集度未见 /+、菌群多样性未见 /+、pH 值 >4.5、H_2O_2(+)、唾液酸苷酶(+)、BV(+)时阴道萎缩严重程度(P<0.05)(表 2)。

2.3 阴道萎缩病情进展的多因素 Logistic 回归分析

以阴道萎缩严重程度为因变量 (Y)(中度 / 重度 =1，轻度 =0)，进一步对上述具有临床鉴别意义的单因素指标清洁度、菌群密集度、菌群多样性、pH值、H_2O_2、唾液酸苷酶、BV 为自变量进行 *Logistic* 回归分析，结果清洁度Ⅲ/Ⅳ度、菌群密集度未见 /+、菌群多样性未见 /+、pH值 >4.5、H_2O_2(+)、唾液酸苷酶(+)、BV(+)是阴道萎缩病情进展为中 / 重度独立影响因素(P<0.05，表 4)。

3 讨论

随着妇科疾病发病率逐年增高，女性阴道微生态学已逐渐

表 2 不同阴道微生态状况下生殖道萎缩发生情况 [n (%)]

Table 2 Occurrence of reproductive tract atrophy under different vaginal microecological conditions [n (%)]

Item	n	Vaginal atrophy occurs(n=79)			No vaginal atrophy (n=41)	χ^2	^aP
		Mild(n=28)	Moderate(n=26)	Severe(n=25)			
Cleanliness						23.306	<0.001
Ⅰ 0.001iness	57	14b	9b	2	32		
Ⅲ 2.001iness	63	14	17	23	9		
Dominant flora						5.385	0.496
G + bacilli	20	6	4	2	8		
G + bacterium	16	7	3	2	4		
G - bacilli	24	6	4	4	10		
G - bacterium	4	1	2	0	1		
G + cocci	13	4	3	2	4		
G. Staphylococcus aureus	32	4	8	7	13		
no	11	0	2	8	1		
Flora density						7.213	0.027
Not seen	2	0[b]	1[b]	1	0		
+/++	35	9	5	3	18		
+++/++++	83	32	18	10	23		
Flora diversity						11.337	0.004
Not seen	6	0b	2b	3	1		
+	88	33	22	9	24		
++/+++	26	10	4	2	16		
pH						5.732	0.017
3.8~4.5	36	14[b]	2[b]	2	18		
>4.5	84	11	20	30	23		

Note: ^aP means that there is no comparison between vaginal atrophy and vaginal atrophy, and within vaginal atrophy ^bP <0.05.

表 3 Logistic 回归分析中的分类自变量分配表

Table 3 The classification independent variable assignment table included in Logistic regression analysis

variable name	Variable assignment
Cleanliness	(leanlinesssignmentication indepen)
Flora density	(+++ / ++++ = 0; not seen / + = 1)
Flora diversity	(+++ / ++++ = 0; not seen / + = 1)
pH	3.8~4.5=0；>4.5=1
H_2O_2	- =0；+=1
Sialidase	- =0；+=1
BV	(-/ Mediation = 0; + = 1)

成为临床研究热点，其与女性生殖系统正常生理功能及各种感染性疾病发生发展密切相关[11-14]。既往提出的阴道优势菌乳杆菌，对降低阴道、尿道口及泌尿系统等其他部位感染率均有重要价值[15-17]。乳杆菌主要通过产生 H_2O_2、细菌素、防御素和营养竞争使外源性病原菌无法定植，进而维持阴道正常 pH 值、激活宿主免疫功能[18]。多项研究表明，绝经期女性阴道微生态的结构及组成较育龄期女性有显著变化，其中包括阴道清洁度、阴道优势菌群数量、pH 值及相关感染性疾病发生情况[19-21]。本文研究表明，绝经期妇女阴道菌群数量和种类都在减少，乳杆菌的数量和功能也在降低，从而阴道 pH 逐渐升高。绝经期女性阴道清洁度Ⅲ/Ⅳ度 52.50%略高于Ⅰ/Ⅱ度，优势菌群均处于较高活跃程度、菌群较密集且种类数量较多，考虑与绝经期女性错误盲目滥用抗生素、阴道灌洗、感染性疾病、雌激素水平的变化等原因有关。Tian 等[22]报道显示，绝经期女性阴道黏膜受到损伤、正常菌群减少、杂菌增多、阴道呈弱碱性。本文结果显示，绝经期女性 PH 值 >4.5 占比为 70.00%高于 pH 值 3.8~4.5 占比 30%，符合上述研究结果。绝经后卵巢功能衰退和雌激素水平降低，进一步降低黏膜变薄局部抵抗力，上皮细胞糖原、乳杆菌数量均减少，pH 值上升，导致正常的阴道酸性环境变成中性或碱性。两篇大样本实验结果显示，中性或碱性阴道环境有利于阴道内胍、胺、吲哚等有毒物质蓄积，加快有害病原菌的生长繁殖，进而导致阴道微生态失衡和炎症发生[23,24]。绝经期 H_2O_2、白细胞酯酶、唾液酸苷酶阳性增加，各种阴道炎性疾病发病风险增大。本文绝经期女性 VVC、TV 阳性例数较多，主要与相关激素水平变化有关。既往资料已表明，绝经期女性 TV 发病率高于育龄期或老年绝经期女性，而 BV、VVC 低于育龄期女性，本文结果与既往报道较一致[25-27]。而 VVC 发病率较高可能与地区差异引起的环境因素有关[28]，另样本量也可引起结果误差。

阴道微生态的改变对生殖道相关疾病发生和发展有重要价值，Siliquini 等(2017)[29]的文献结果显示，绝经期女性阴道萎缩发生风险较育龄期女性增加了 10 倍，风险比(HR)和 95%置信区间(CI)表示阴道微生态状态为阴道萎缩发生及发展高危因素。既往报道对年龄与绝经对阴道萎缩影响的报道较多，随着年龄增加，卵巢功能及相关激素分泌降低，阴道上皮细胞分化及糖原分解能力降低，阴道炎性疾病发病风险增加[30-32]。而年龄 >60 岁的绝经期女性阴道萎缩患病率高于年龄 <60 岁的绝经期女性[33]，本文排除了 60 岁以上的绝经期妇女避免年龄对相关性分析的干扰。本研究结果显示，清洁度Ⅲ/Ⅳ度、菌群密集度未见 /+、菌群多样性未见 /+、pH 值 >4.5、H_2O_2(+)、唾液酸苷酶(+)、VVC(+)、BV(+)时阴道萎缩发生率显著增高。阴道炎性疾病的发生与阴道益生菌数量减少、其他厌氧菌及兼性厌氧菌过度繁殖而成为优势菌群密切相关；同时绝经期阴道上皮细胞粘附能力降低引起多种病菌繁殖，阴道清洁度降低，直接导致阴道感染和炎性疾病的发生。阴道萎缩实质为阴道分泌物减少、阴道干涩进而引起的性功能障碍，炎性疾病的发生、优势菌群数量和种类的减少均为阴道萎缩发生高危因素。而阴道萎缩严重程度可能与感染、菌群数量及阴道炎疾病严重程度呈相关关系，本文结果显示清洁度Ⅰ/Ⅱ度、菌群密集度 +++/++++、菌群多样性 +++/++++、pH 值 3.8~4.5、H_2O_2(-)、唾液酸苷酶(-)、BV(-/中介)时阴道萎缩严重程度更低，考虑随着清洁度增加、菌群数量及种类减少、阴道正常酸性环境被破坏可增加阴道萎缩病情进展的风险。多因素分析结果显示，清洁度、菌群密集度和多样性、pH 值、H_2O_2、唾液酸苷酶、BV 为轻度阴道萎缩进展为中/重度阴道萎缩独立影响因素，提示阴道微生态状态可表示阴道萎缩程度。

综上所述，阴道微生态检测能综合评价绝经期女性阴道微生态状况，且绝经期女性阴道微生态状态与阴道萎缩发生及发展密切相关，可为临床防治性功能障碍提供新的策略依据。但由于本研究样本量少、随访时间短，进一步分析阴道微生态状态引起阴道萎缩机制仍需在今后临床工作中进一步探讨。

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表 4 阴道萎缩进展独立因素的 Logistic 回归分析

Table 4 Logistic regression analysis of independent factors of vaginal atrophy progression

Item	β	S.E	Wald	*P*	OR(95%CI)
Cleanliness	1.062	0.525	4.092	0.043	2.892(1.885~14.767)
Flora density	0.882	0.426	4.287	0.039	2.416(1.622~8.617)
Flora diversity	1.243	0.523	5.649	0.018	3.465(2.125~16.533)
pH	0.659	0.319	4.268	0.039	1.932(1.217~3.259)
H_2O_2	0.811	0.263	9.509	<0.001	2.250(1.518~4.253)
Sialidase	1.530	0.454	11.357	<0.001	4.617(3.380~18.315)
BV	0.673	0.210	10.270	<0.001	1.961(1.458~3.327)

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