论著·临床研究

宫颈功能不全患者阴道菌群的分布特征及妊娠结局

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［摘要］**目的**·探讨宫颈功能不全（cervical incompetence，CIC）患者的阴道菌群分布特点，以及异常阴道菌群CIC患者行宫颈环扎术对妊娠结局的影响。**方法**·纳入2016年1月—2020年12月在苏州大学附属第二医院妇产科就诊的1 261例妊娠期女性，根据诊断分为宫颈功能不全组（CIC组）及正常妊娠组（NP组），其中CIC组又随机分为宫颈环扎组（CIC-C组）以及期待组（CIC-E组），同时进行阴道分泌物培养，通过阴道菌群的结果，CIC-C组及CIC-E组进一步分为正常阴道菌群环扎组（CIC-C-N组）及期待组（CIC-E-N组）和异常阴道菌群环扎组（CIC-C-A组）及期待组（CIC-E-A组），随访对比妊娠结局。组间比较使用t检验、χ^2检验或单因素方差分析。P<0.05为差异有统计学意义。**结果**·1 261份阴道分泌物标本中，异常病原菌阳性率为22.0%（277/1 261）。CIC患者异常菌群阳性率（32.9%，229/696）明显高于NP组（8.5%，48/565）。CIC患者检出菌群23种，NP组检出菌群9种。CIC-C组、CIC-E组及NP组的足月产率比较，差异具有统计学意义（P=0.000）。阴道菌群异常的CIC患者中，CIC-E-A组的足月产率明显低于CIC-C-A组（61.84% *vs* 77.78%，P=0.011），妊娠期并发症发生率明显高于CIC-C-A组（22.37% *vs* 9.15%，P=0.006），差异均具有统计学意义。**结论**·CIC患者与正常妊娠女性的阴道菌群的分布及多样性存在差异。异常阴道菌群CIC患者行宫颈环扎术可改善妊娠结局。

［关键词］阴道菌群；宫颈功能不全；宫颈环扎；围产结局；早产率
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Distribution characteristics of vaginal flora and pregnancy outcomes in cervical incompetence patients

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[Abstract] **Objective**·To investigate the distribution characteristics of vaginal flora in patients with cervical incompetence (CIC), and the effect of cervical cerclage on pregnancy outcome in patients with CIC with abnormal vaginal flora. **Methods**·A total of 1 261 pregnant women participated in the study. According to the diagnosis, they were divided into cervical incompetence group (CIC group) and normal pregnancy group (NP group). The CIC group patients randomly received cervical cerclage (CIC-C group) or expectation therapy (CIC-E group). Vaginal secretion samples of the patients in the groups were collected and analyzed in the laboratory. Meanwhile, through the results of vaginal flora, the CIC-C group and CIC-E group were further divided into normal vaginal flora groups (CIC-C-N group and CIC-E-N group) and abnormal vaginal flora groups (CIC-C-A group and CIC-E-A group). All groups were processed accordingly and analyzed on pregnancy outcomes. *T*-test and Chi-squared test were used for comparison between the groups, and One-way ANOVA was used for comparison among the three groups. Statistical significance was accepted at a value of P<0.05. **Results**·Among 1 261 vaginal secretion specimens, the positive rate of pathogenic bacteria was 22.0% (277/1 261). The pathogen detection rates in the CIC group and NP group were 32.9% (229/696) and 8.5% (48/565). Twenty-three types of vaginal flora were detected in the CIC group, and 9 were detected in the NP group. The proportions of women who had term birth were 75.94% in the CIC-C group, 70.03% in the CIC-E group, and 87.79% in the NP group (P=0.000). Compared with the CIC-C-A group, the CIC-E-A group had a lower term delivery rate (61.84% *vs* 77.78%, P=0.011) and a higher incidence of pregnancy complications (22.37% *vs* 9.15%, P=0.006). **Conclusion**·There are differences in the distribution and diversity of vaginal flora between CIC patients and normal pregnant women. Cervical cerclage can improve pregnancy outcomes in CIC patients with abnormal vaginal flora.

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[Key words] vaginal flora; cervical incompetence (CIC); cervical cerclage; perinatal outcomes; preterm birth rate

宫颈功能不全（cervical incompetence，CIC）是指妊娠中期宫颈在无宫缩或分娩发动的情况下，无法保留其正常的形态及功能直至妊娠足月，表现为无痛性宫口扩张导致胎儿娩出[1]。CIC是导致晚期自然流产和早产的主要原因之一，发病率为0.1%~2.0%，流产可反复发生，在孕16~28周的复发性流产中占15.0%左右[2]。早产（preterm birth，PTB）是一种常见的产科疾病，是造成新生儿死亡和严重并发症的主要因素。CIC因素约占所有晚期流产和PTB的8%[3]。在自发性早产（spontaneous preterm birth，sPTB）中，最常见发生的事件是宫颈的软化、缩短及扩张，也称为宫颈重塑。研究[4-6]也支持这种学说，即宫颈重塑而不是子宫收缩，可能是导致自发流产或早产的一连串事件的主要发起者。目前认为CIC的病因可能是宫颈过早成熟过程（process of premature cervical ripening），即由于亚临床感染、局部炎症、激素以及遗传等多个因素导致宫颈力学或完整性遭到破坏，启动“宫颈成熟过程”[7]。宫颈在孕期不仅起着承托作用，同时也有阻挡上行病原体的作用。

乳酸杆菌被公认为阴道的主要菌群，在维持阴道生态平衡的同时能限制其他病原体的生长。阴道pH值和雌激素被认为是维持阴道生态平衡和菌群结构的重要因素。在雌激素水平显著升高的妊娠期，因为糖原含量增加，会促进阴道菌群的生长和繁殖，更易出现阴道菌群失调。妊娠期最常见的阴道炎为外阴阴道假丝酵母菌病（vulvovaginal candidiasis，VVC）和细菌性阴道病（bacterial vaginosis，BV）。VVC是由条件致病菌假丝酵母过度生长造成的常见阴道炎之一。有研究表明BV也会增加不良妊娠结局的风险，可诱导宫颈胶原溶解，并通过增加促炎因子的分泌导致CIC[8]。然而也有证据表明BV并不是宫颈长度缩短的独立预测因子[9]。宫颈缩短、阴道菌群失调都是自发性早产的危险因素，它们之间是否有相互作用目前仍不明确。研究[10]提示孕期阴道菌群异常可能与宫颈缩短有关，而评估阴道菌群对CIC围产结局影响的数据目前仍然有限。宫颈环扎术对妊娠结局改善的影响有一定争议，这可能与研究选取的人群不同有关。本研究通过研究CIC患者的阴道菌群的分布特点，探讨宫颈环扎术对异常阴道菌群患者妊娠结局改善的影响。

1 对象与方法

1.1 研究对象

纳入2016年1月—2020年12月在苏州大学附属第二医院妇产科就诊的696例CIC患者，孕后行宫颈环扎术随访，并于孕12~14周采集阴道分泌物行分泌物培养。纳入标准：① 年龄28~44岁的单胎妊娠患者。② 孕中期经阴道超声检查宫颈长度≤25 mm。③ 孕中期查体发现宫颈扩张者。④ 无严重内外科合并症。排除标准：① 胎儿宫内死亡、胎儿畸形。② 临床资料不全者。③ 产前感染者。选择同期的565例健康孕妇作为对比，最终纳入1 261例妇女作为研究人群。

采用随机数字表，将CIC患者随机分为宫颈环扎（cervical incompetence cerclage，CIC-C）组及期待（cervical incompetence expectation therapy，CIC-E）组。在阴道超声随访时，CIC-E组有5例患者出现宫颈进行性缩短，进行紧急宫颈环扎，此5例患者妊娠结局另行统计。最终CIC-C组患者共399例，期待疗法组共297例。按阴道菌群是否异常进行分层，最终分组结果为异常阴道菌群环扎组（CIC-C-A组，n=153），正常阴道菌群环扎组（CIC-C-N组，n=246）；异常阴道菌群期待组（CIC-E-A组，n=76），正常阴道菌群期待组（CIC-E-N组，n=221）。

1.2 方法

1.2.1 标本采集及培养 孕妇清洁外阴后，以无菌窥阴器暴露阴道及宫颈，用无菌拭子从阴道后穹窿处采集分泌物，迅速放入无菌试管，立即送往检验科化验并进行培养。CIC-C组患者均在术前采集标本。采集的标本接种在不同的琼脂培养基中。① 需氧培养哥伦比亚血琼脂培养基（批号20091206B；郑州奥博诊断有限公司），淋病奈瑟菌培养基（批号090919；上海科玛格微生物技术有限公司），巧克力琼脂培养基（批号20091221B；Autobio Diagnostics Co，LTD.）。琼脂培养基在35 ℃，5%CO_2条件下培养24~48 h。② 厌氧

培养哥伦比亚血琼脂培养基，35 ℃厌氧条件下，使用HHCP培养箱（230 V，型号：3111；美国赛默飞世尔科学公司）培养24~48 h。培养物通过标准生化试验鉴定。72 h后如果观察到每毫升培养物≥1 000个生物体（相当于1个菌落），则认为呈阳性，均做革兰染色。③ 假丝酵母菌培养：标本经革兰染色确认酵母样真菌后转种念珠菌显色培养基CHROMagar（批号090628；上海CHROMagar微生物技术有限公司），在37 ℃下培养24~48 h，采用YBC真菌鉴定卡（REF21343，YZB/UCIC0798-2005；bioMerieux，法国），使用VITEK2系统（法国bioMerieux）进行鉴定。④ 乳酸杆菌被认为是正常的阴道菌群。

1.2.2　手术方法　麻醉成功后，取膀胱截石位，导尿管排空膀胱，消毒阴道，阴道拉钩暴露宫颈及穹窿部分，采用双股强生不可吸收编织线（Ethibond Excel MB66），在宫颈内口水平连续缝扎，深度为肌层的2/3，宫颈阴道段小于2 cm者切开宫颈膀胱间隙，上推膀胱，下推宫颈直肠间隙。逆时针由5~6点方向进针4点方向出针；2点方向进针11点方向出针；10点方向进针8点方向出针；7点方向进针6点方向出针。然后打结于5~6点之间，留线尾5 cm。缝扎松紧度以宫颈口直径0.5 cm为宜。手术均由同一人操作，用时15~30 min。孕妇孕周为14~22周，术后予抗感染抑制宫缩治疗，孕37周左右拆除缝线。

1.2.3　期待疗法　嘱患者卧床休息，每2~3周门诊随访，经阴道超声和宫颈检查，记录宫颈长度。

1.3　统计学分析

采用SPSS 26.0统计学软件进行分析，定量资料采用$\bar{x}\pm s$表示。符合正态分布的连续性变量采用Student t检验进行比较；定性资料用频数（百分比）表示，组间比较采用χ^2检验；多组间比较采用单因素方差分析。P<0.05表示差异有统计学意义。

2　结果

2.1　CIC组及NP组临床资料比较

CIC组患者年龄18~44岁，平均年龄（31.32±3.2）岁，既往孕中期流产次数1~4次。正常妊娠组（normal pregnancy，NP组）年龄19~44岁，平均年龄（31.04±3.8）岁，无既往孕中期流产史。2组在年龄及取样孕周上比较差异无统计学意义，2组在流产史上比较差异有统计学意义（P=0.000）。

2.2　CIC组及NP组阴道菌群检出比较

2组阴道分泌物培养结果见表1。总病原体检出率为22.0%。CIC组、NP组的病原体检出率分别为32.9%（229/696）、8.5%（48/565），2组比较差异有统计学意义（P=0.000）。CIC组检出病原菌23种，NP组检出9种，CIC组5例有混合感染。

表1　CIC组与NP组阴道菌群分布对比

Tab 1　Comparison of pathogen species between the CIC group and NP group

Flora	Vaginal flora/n (%)		χ^2	P value
	CIC group (n=696)	NP group (n=565)		
Enterococcus faecalis	11 (1.58)	3 (0.53)	3.131	0.077
Candida albicans	55 (7.90)	14 (2.48)	17.965	0.000
Candida tropicalis	6 (0.86)	8 (1.41)	4.905	0.027
Candida glabrata	33 (4.74)	10 (1.77)	8.402	0.004
Escherichia coli	21 (3.01)	2 (0.35)	12.455	0.000
Streptococcus agalactiae	11 (1.58)	5 (0.88)	1.203	0.273
Gardnerella vaginalis	48 (6.90)	7 (1.24)	24.353	0.000
Klebsiella pneumoniae	5 (0.71)	1 (0.18)	1.930	0.165
Staphylococcus aureus	5 (0.71)	0 (0)	4.082	0.044
Staphylococcus epidermidis	3 (0.43)	1 (0.18)	0.636	0.425
Streptococcus bovis	2 (0.29)	0 (0)	1.626	0.203
Acinetobacter baumannii	1 (0.14)	0 (0)	0.812	0.368
Proteus mirabilis	3 (0.43)	0 (0)	2.442	0.118
Haemophilus parainfluenzae	1 (0.14)	0 (0)	0.812	0.368
Enterobacter aerogenes	2 (0.29)	0 (0)	1.626	0.203
Hemophilus ducreyi	1 (0.14)	0 (0)	0.812	0.368
Streptococcus milleri	1 (0.14)	0 (0)	0.812	0.368
Neisseria subflava	1 (0.14)	0 (0)	0.812	0.368
Staphylococcus haemolyticus	2 (0.29)	0 (0)	1.626	0.203
Morganella morganii	2 (0.29)	0 (0)	1.626	0.203
Burkholderia cepacia	1 (0.14)	0 (0)	0.812	0.368
Pseudomonas aeruginosa	1 (0.14)	0 (0)	0.812	0.368
Enterobacter cloacae	1 (0.14)	0 (0)	0.812	0.368

2.3　CIC组及NP组的优势菌群比较

CIC组的优势菌群为白假丝酵母、阴道加德纳菌、光滑假丝酵母、大肠埃希菌和无乳链球菌。NP组的优势菌群为白假丝酵母、光滑假丝酵母、热带假丝酵母、阴道加德纳菌、无乳链球菌（表2）。

表2 CIC组及NP组的优势菌群比较

Tab 2 Comparison of dominant species between the CIC group and NP group

Top	Vaginal flora/*n* (%)			
	CIC group (*n*=696)		NP group (*n*=565)	
1	*Candida albicans*	55 (7.90)	*Candida albicans*	14 (2.48)
2	*Gardnerella vaginalis*	48 (6.90)	*Candida glabrata*	10 (1.77)
3	*Candida glabrata*	33 (4.74)	*Candida tropicalis*	8 (1.41)
4	*Escherichia coli*	21 (3.01)	*Gardnerella vaginalis*	7 (1.24)
5	*Streptococcus agalactiae*	11 (1.58)	*Streptococcus agalactiae*	5 (0.88)
Total percent		168 (24.13)		44 (7.78)

2.4 阴道菌群与妊娠结局的关系

CIC-C组、CIC-E组、NP组的流产率分别为8.52%、10.10%、5.49%，组间差异有统计学意义（*P*=0.034）。CIC-C组、CIC-E组、NP组妇女的早产率分别为15.54%、19.87%、6.72%，差异有统计学意义（*P*=0.000）。CIC-C组、CIC-E组、NP组妇女的足月产率分别为75.94%、70.03%、87.79%，差异有统计学意义（*P*=0.000）。3组的妊娠期并发症发生率差异有统计学意义（*P*=0.000）。3组在分娩孕周、活产率方面差异无统计学意义。见表3。

表3 CIC-C组、CIC-E组与NP组妊娠结局比较

Tab 3 Comparison of pregnancy outcomes among the CIC-C group, CIC-E group, and NP group

Item	Pregnancy outcome			*P* value
	CIC-C group (*n*=399)	CIC-E group (*n*=297)	NP group (*n*=565)	
Gestational weeks at delivery	36.1±5.2	35.3±4.5	37.3±3.5	0.362
Pregnancy loss/*n*(%)	34 (8.52)	30 (10.10)	31 (5.49)	0.034
Preterm birth/*n*(%)	62 (15.54)①	59 (19.87)①②	38 (6.72)	0.000
Term birth/*n*(%)	303 (75.94)①	208 (70.03)①③	496 (87.79)	0.000
Live birth/*n*(%)	371 (92.98)	273 (91.92)	534 (94.51)	0.315
Pregnancy complications/*n*(%)	26 (6.51)④	27 (9.09)①⑤	16 (2.83)	0.000
Puerperal infection/*n*(%)	5 (1.25)	5 (1.68)	3 (0.53)	0.245

Note: ①*P*=0.000, compared with the NP group; ②*P*=0.136, compared with the CIC-C group; ③*P*=0.080, compared with the CIC-C group; ④*P*=0.004, compared with the NP group; ⑤*P*=0.205, compared with the CIC-C group.

2.5 不同阴道菌群的CIC-C组与CIC-E组的妊娠结局对比

2组的妊娠结局见表4。在正常菌群条件下，2组的流产、早产、足月产、妊娠期并发症及新生儿结局比较差异无统计学意义。异常菌群条件下，CIC-E组的足月产率（61.84%）低于CIC-C组（77.78%），差异有统计学意义（*P*=0.011）；妊娠期并发症发生率CIC-E组较高（22.37% *vs* 9.15%，*P*=0.006）。

表4 不同阴道菌群的CIC-C组与CIC-E组妊娠结局比较

Tab 4 Comparison of pregnancy outcomes between the CIC-C group and CIC-E group with different vaginal florae

Outcome	Normal vaginal flora		*P* value	Abnormal vaginal flora		*P* value
	CIC-C-N group (*n*=246)	CIC-E-N group (*n*=221)		CIC-C-A group (*n*=153)	CIC-E-A group (*n*=76)	
Pregnancy loss/*n*(%)	25 (10.16)	21 (9.50)	0.812	9 (5.88)	9 (11.84)	0.116
Preterm birth/*n*(%)	37 (15.04)	29 (13.12)	0.553	25 (16.33)	20 (26.32)	0.074
Term birth/*n*(%)	184 (74.8)	171 (77.38)	0.516	119 (77.78)	47 (61.84)	0.011
Vaginal delivery/*n*(%)	112 (45.52)	97 (43.89)	0.722	70 (45.75)	33 (43.42)	0.738
Caesarean section/*n*(%)	109 (44.30)	103 (46.60)	0.619	74 (48.36)	34 (44.74)	0.604
Premature rupture of membrane/*n*(%)	5 (2.03)	4 (1.81)	0.864	4 (2.61)	1 (1.32)	0.529
Pregnancy complications/*n*(%)	12 (4.88)	10 (4.52)	0.440	14 (9.15)	17 (22.37)	0.006

Continued Tab

Outcome	Normal vaginal flora		*P* value	Abnormal vaginal flora		*P* value
	CIC-C-N group (*n*=246)	CIC-E-N group (*n*=221)		CIC-C-A group (*n*=153)	CIC-E-A group (*n*=76)	
Chorioamnionitis/*n*(%)	1 (0.41)	2 (0.90)	0.266	3 (1.96)	4 (5.26)	0.173
Puerperal infection/*n*(%)	2 (0.81)	2 (0.90)	0.569	3 (1.96)	3 (3.95)	0.378
Asphyxia neonatorum/*n*(%)	4 (1.62)	2 (0.90)	0.812	2 (1.31)	2 (2.63)	0.473
Small for gestational age/*n*(%)	27 (10.98)	28 (12.67)	0.572	22 (14.38)	13 (17.1)	0.591

3　讨论

本研究旨在研究分析CIC患者阴道菌群分布特点及妊娠结局，通过对比分析CIC患者和正常妊娠妇女的阴道菌群分布，确定在存在异常菌群的情况下，何种治疗方式更有利于妊娠结局。

宫颈功能不全的病因尚不明确。目前有研究[11-12]认为导致宫颈重塑的病因是感染，动物实验也证实了感染因素是过早宫颈重塑的触发器。新兴的阴道微生物组的研究领域也开始积极探索导致宫颈重塑的因素[13-14]。阴道微环境平衡打破以及炎症的存在会导致宫颈发生变化，白细胞介素6（interleukin 6，*IL-6*）与甘露糖结合凝集素2（mannose binding lectin 2，*MBL-2*）基因单核苷酸的多态性在CIC患者中表达增多[15]。有研究[16]发现，宫颈缩短的患者宫颈黏液中IL-8升高，与早产风险增加有关。关于CIC和羊膜腔内感染（intra-amniotic infection）的研究[17]发现，抗生素治疗后，超过60%的患者治疗成功与羊膜腔内感染的解决有关。报道称，8%~52%的CIC患者发生了羊膜腔内感染[18]，而没有羊膜腔内感染的患者妊娠结局更好[19]。

宫颈长度在妊娠14~28周内通常稳定。有学者提出流产或早产病史的孕妇，宫颈长度的缩短一般发生在孕20周前，因此我们在孕12~14周进行取样。此时阴道菌群可能已存在不同，但宫颈长度并未明显改变。这预示着阴道菌群可能对后续宫颈的重塑软化产生不同的影响。一项研究[20]表明，惰性乳酸杆菌可以破坏宫颈上皮屏障，可能在宫颈重塑中发挥作用。另一项研究[21]表明，阴道微生物群中乳酸杆菌相对丰度降低与宫颈过早扩张有关。在一项前瞻性病例对照研究中，发现菌群状态类型（community state type，CST）IV的特点是严格和兼性厌氧菌的多样性和乳酸杆菌的稀少，与短宫颈的概率增加有关[10]。本研究显示，CIC组的病原体检出率和病原体种类明显高于NP组，且2组的前5种优势菌群也不同，进一步表明阴道菌群异常可能与宫颈早熟有关。有研究[22]表明，阴道加德纳菌会刺激绒毛膜产生IL-1β、TNF-α、IL-6等。CIC患者阴道加德纳菌占比高达6.90%。本研究还发现5例合并感染的CIC患者。这5例患者均接受了宫颈环扎术，其中2例术后流产；1例在27^{+5}周流产，新生儿体质量为1 kg；另2例早产。表明合并感染对妊娠结局有较大影响。

宫颈环扎术是一种广泛使用的预防早产的临床策略。它可以降低有自发性早产史或宫颈长度过短的妇女早产发生的风险[3,23]。宫颈环扎术通过提供机械支持并用缝线封闭宫颈内口，手术采用双股针的编织缝合线，具有高抗拉强度。同一手术指征下，CIC患者进行了随机分组，未考虑阴道菌群分布差异，因此CIC-C组与CIC-E组的菌群分布可能对妊娠结局产生影响。在考虑阴道菌群的基础上，与CIC-E-A组相比，CIC-C-A组的足月产率和妊娠期并发症的发生率差异有统计学意义，表明异常菌群CIC患者的宫颈环扎术可能提高足月产率，降低妊娠期并发症的发生。因此，我们建议在手术指征的考量上，加上阴道菌群的培养与鉴定[24]。CIC组的病原体检出率更高，但没有足够的证据证明病原体与CIC的致病机制有关。既往研究大多关注致病菌的识别与妊娠结局的关联，缺乏对CIC这一特殊人群的菌群构成分析。本研究重点关注了CIC这一特殊人群的菌群分布。本研究亦有缺陷，环扎术前术后的菌群未进行对比，今后要扩大样本量进一步进行明确。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

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《赫尔辛基宣言》的条例进行。

All the protocols in this study were approved by the Ethics Committee of Second Affiliated Hospital of Soochow University (Document No: JD-LK-2018-030-03), and all the protocols were carried out by following the guidelines of *Declaration of Helsinki*.

作者贡献/Authors' Contributions

李雪参与试验设计，研究实施及论文撰写；张弘参与试验设计及论文修改；肖伊参与研究实施及数据整理。所有作者均阅读并同意了最终稿件的提交。

The study was designed by LI Xue and ZHANG Hong. The manuscript was drafted and revised by LI Xue and ZHANG Hong. The research implementation and data analysis were carried out by XIAO Yi. All the authors have read the last version of paper and consented for submission.

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